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NNT : 050 2021

Documents de Synthèse des Titres et Travaux
Pour l'obtention du diplôme D'Habilitation à Diriger les Recherches
Présentés au sein de
L'UNIVERSITE CLAUDE BERNARD – LYON 1

Soutenue publiquement le 17/11/2021, par
Brahim HARBAOUI

Rigidité artérielle, physiologie et pertinence des actes en cardiologie interventionnelle

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Devant le jury composé de :
M. le Pr Eric VanBelle, rapporteur
M. le Pr Patrick Ohlmann, rapporteur
M. le Pr Guillaume Cayla, rapporteur
Me le Pr Hélène Eltchaninoff, examinateur
M. le Pr Pierre Lantelme, examinateur
M. Le Pr Hervé Liebgott, examinateur

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Table des Matières

1/ Curriculum vitae

Etat civil

Nom : HARBAOUI

Prénom : Brahim

Date et lieu de naissance : 10 Novembre 1981, à Oullins (Rhône)

Nationalité : Française

Statut familial : Marié, 3 enfants de 1, 5 et 9 ans

Situation professionnelle actuelle (hospitalière et universitaire)

Praticien Hospitalier Universitaire (nommé en Mai 2016)

UFR de médecine Lyon Sud, Université Claude Bernard Lyon I

Hospices Civils de Lyon

Fédération de cardiologie Croix-Rousse Lyon Sud,
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Directeur : Olivier Boeuf

Appartenance à l'équipe 2 « Ultrasons » (Responsable d'équipe : Hervé Liebgott)

4

Liste des diplômes

Thèse de Doctorat d'Université
Ecole doctorale Inter Disciplinaire Sciences Santé (Université Claude Bernard Lyon I)
Titre : Rigidité Vasculaire en cardiologie interventionnelle
Soutenue le 4 décembre 2017 à Lyon

Thèse de Doctorat de Médecine
Université Claude Bernard Lyon I
Titre : Place de la stratégie de reperfusion à minima MIMI dans la prise en charge de l'infarctus du myocarde.
Mention : félicitations du Jury
Soutenue le 11 octobre 2011 à Lyon

Spécialité reconnue par l'Ordre des Médecins : Cardiologie et maladies vasculaires
Numéro d'inscription au tableau de l'Ordre des Médecins du Rhône : 22616
N° RPPS : 10100294775

Diplôme d'Etudes Spécialisées (DES) de **Cardiologie et maladies vasculaires**
Université Claude Bernard Lyon I.
Titre du Mémoire : Stenting différé dans l'infarctus du myocarde
Date d'obtention : 11 octobre 2011

Master 2 : Régulation Cardiovasculaire Métabolique et Nutritionnelle
Université Claude Bernard Lyon I
Titre du mémoire : Mise au point d'une technique de mesure de la vitesse de l'onde de pouls coronaire
Mention assez-bien, 1 brevet déposé
Date de soutenance : 18 juin 2013 à Lyon

AEU Simulation en Santé
Université Claude Bernard Lyon 1
Date : 2021

Diplôme Universitaire de Pédagogie Médicale, 2017-2018
Mémoire : Création d'un e-learning d'échocardiographie destiné aux médecins urgentistes
Université Claude Bernard Lyon I
Date : 2008-2010

Diplôme Inter Universitaire : Cardiologie interventionnelle
Titre du Mémoire : Utilisation du ballon actif en pratique
Université Paris V
Date : 2011-2013

Diplôme Inter Universitaire : Echocardiographie
Université Claude Bernard Lyon I
Date : 2008-2010

Diplôme Inter Universitaire : Urgences et soins intensifs cardiologiques
Titre du Mémoire : Les pseudoanévrysmes du ventricule gauche
Université Claude Bernard Lyon I
Date : 2010

Baccalauréat série S, spécialité mathématiques
Lycée Antoine de Saint Exupery, Lyon
Année d'obtention : 2000
Académie de Lyon
Mention assez bien

E- Liste des fonctions antérieures

2016- **Praticien Hospitalier Universitaire**
UFR de médecine Lyon Sud, Université Claude Bernard Lyon I
Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Service de Cardiologie
Date de Nomination : 1er mai 2016

2013-2016 **Chef de Clinique des Universités, Assistant des Hôpitaux**
Période du 1/11/2013 au 31/10/2015
UFR de médecine Lyon Sud, Université Claude Bernard Lyon I
Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Service de Cardiologie

2014-2015 **Activité d'intérêt général au CH de Vienne**

2011-2013 **Praticien Hospitalier Contractuel**
Période du 1/11/2011 au 31/10/2013
UFR de médecine Lyon Sud, Université Claude Bernard Lyon I
Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Service de Cardiologie

2007-2012 **Interne des Hospices Civils de Lyon**
Examen Classant National 2007
Rang de classement : 178 ème /5565
Choix de la subdivision de Lyon, Spécialités Médicale,
Internat dans les services de Cardiologie du GHN et du GHE, de réanimation de l'hôpital Nord-Ouest et Bourg en Bresse

2001-2007 **Premier et deuxième cycle des études médicales**
UFR de Médecine Lyon Nord, Université Claude Bernard Lyon I
(septembre 2001 – octobre 2007)
Concours de PCEM1, Rang de classement : 28ème
Remplacements Aide-Soignant pendant l'externat (Week-end et nuit)
Hôpital Louis Pradel, HCL

F- Liste des fonctions administratives nationales :

Fonctions administratives universitaires locales

Depuis 2017, Responsable de l'Enseignement de la cardiologie au sein du DES de médecine d'urgence (Mission confiée par le Pr Tazarourte), UFR de médecine Lyon Sud depuis la création de ce DES

Depuis 2019, Co-responsable avec le Pr Bernard Pierre de l'enseignement de l'ECG par simulation aux étudiants de FASM2, UFR de médecine Lyon Sud, Pôle Lyon Sud de Simulation en Santé (PL3S) (Coordination des enseignements par le Dr Coury-Lucas)

Fonctions administratives hospitalières locales

2019-2020, Membre du groupe de travail « Attractivité des carrières Hospitalo-Universitaire »**,** sur proposition du CCEM

2018-2021, Membre de la CME, représentant du collège des personnels temporaires et non titulaires CCA, AH, AHU et PHU

2021-, Responsable d'Unité Fonctionnelle Cardiologie interventionnelle, Hôpital de la Croix-Rousse

2013-, Responsable d'Unité Fonctionnelle 24132 Unité de Soins Intensifs Cardiologiques, Hôpital de la Croix-Rousse

2013-, Membre du comité médical du GCS de cardiologie interventionnelle Croix-Rousse Villefranche sur Saône

Autres fonctions administratives nationales

Membre du conseil médical du GRCI (Groupe de Réflexion en Cardiologie interventionnelle) 2019https://www.grci.fr/Media/1903F_GRCI2019_Catalogue_A5_WEB.pdf

G- Prix, distinctions honorifiques

2021 Prix du Meilleur mémoire du DU de cardiologie interventionnelle du Dr Marc Bonnet (encadrement)

2019 3ème prix de la meilleure communication orale
Congrès international Endovascular Cardiac Complications ECC,
Lausanne, Suisse

2018 Bourse de financement de l'étude COREYE « Can we predict COronary Resistance By EYE examination ? » attribuée par la Fédération Française de Cardiologie dans le cadre des bourses de recherche « Foudon »
Investigateur principal : **248.491 Euros**

2017 Bourse de mobilité attribuée par la Fédération Française de Cardiologie
Mobilité à Lausanne, Suisse
Montant obtenu : **35.000 Euros**

2017 1er prix de la compétition jeune chercheur, section recherche clinique,
Journées Européennes de la Société Française de Cardiologie

2017 Bourse de recherche, « Intérêt pronostique de la combinaison de biomarqueurs biologiques, vasculaires échographiques et ECG dans l'évaluation du risque de mortalité dans l'hypertension artérielle. » attribuée par la Fédération Française de Cardiologie.
Co-investigateur principal avec Pr Pierre-Yves Courand
Montant obtenu : **35.000 Euros**

H-Appartenance à des sociétés Savantes, Médicales ou Scientifiques

- Membre de la Société Française de Cardiologie

- Membre de l'European Society of Cardiology

- Membre du conseil médical du Groupe Athérome et Cardiologie Interventionnelle (GACI)

- Membre du groupe USIC (Unité de Soins Intensifs Cardiologiques) de la Société Française de Cardiologie

- Membre du groupe Valvulopathies de la Société Française de Cardiologie

- Membre du conseil scientifique du réseau régional des urgences RESCUE depuis 2013

2/ ACTIVITES DE RECHERCHE

A-Liste des publications

Liste des publications

Publications originales articles (n=48)

1. Courand PY, Dauphin R, Rouvière O, Paget V, Khettab F, Bergerot C, Harbaoui B, G. Bricca G, Fauvel JP, Lantelme P. Renal denervation for treating hypertension: experience at the University Hospital in Lyon. Ann Cardiol Angeiol (Paris). 2014; 63(3):183-8.
2. Courand PY, Feugier P, Workineh S, Harbaoui B, Bricca G, Lantelme P.Baroreceptor stimulation for resistant hypertension: first implantation in France and literature review.Arch Cardiovasc Dis. 2014 Dec;107(12):690-6.
3. Harbaoui B, Courand PY, Charles P, Dauphin R, Boussel L, Jegaden O, Dubreuil O, De Gevigney G, Lantelme P. Aortic Calcifications Present the Next Challenge for the Heart After TAVR. J Am Coll Cardiol. 2015 Mar 17; 65(10) :1058-60.
4. Lantelme P, Harbaoui B, Courand PY. Resistant hypertension and carotid baroreceptors stimulation. Presse Med. 2015 Jul-Aug;44(7-8):730-6
5. Courand PY, Grandjean A, Charles P, Paget V, Khettab F, Bricca G, Boussel L, Lantelme P, Harbaoui B. R wave in aVL lead is a robust index of left ventricular hypertrophy: a cardiac MRI study. Am J Hypertens. 2015 Aug;28(8):1038-48
6. Harbaoui B, Courand PY, Milon H, Fauvel JP, Khettab F, Mechtouff L, Casser E, Girerd N, Lantelme P.Association of various blood pressure variables and vascular phenotypes with coronary, stroke and renal deaths: potential implications for prevention. Atherosclerosis. 2015 Nov;243(1):161-8.
7. Harbaoui B, Courand PY, Besnard C, Dauphin R, Cassar E, Lantelme P. Deferred vs immediate stenting in ST elevation myocardial infarction: potential interest in selected patients. Presse Med. 2015 Nov;44(11):e331-9.
8. Berge C, Courand PY, Harbaoui B, Paget V, Khettab F, Bricca G, Fauvel JP, Lantelme P. Decrceased plasma prorenin levels in primary aldosteronism: potential diagnostics implications. J Hypertens. 2015; 33(1):118-25.
9. Harbaoui B, Montoy M, Charles P, Boussel L, Liebgott H, Girerd N, Courand PY, Lantelme P. Aorta calcification burden: Towards an integrative predictor of cardiac outcome after transcatheter aortic valve implantation. Atherosclerosis. 2016 Jan 11;246:161-168.
10. Harbaoui B, Courand PY, Defforges A, Khettab F, Milon H, Girerd N, Lantelme P. Cumulative effects of several target organ damages in risk assessment in hypertension. Am J Hypertens. 2016 Feb;29(2):234-44.
11. Courand PY, Harbaoui B, Serraille M, Berge C, Lantelme P. Ruling out white coat hypertension with NT-proBNP: A new paradigm away from blood pressure assessment. Int J Cardiol. 2016 Jan 9;207:57-58.
12. Mohkam K, Fanget F, Darnis B, Harbaoui B, Rode A, Charpiat B, Ducerf C, Mabrut JY.Use of Systemic Vasodilators for the Management of Doppler Ultrasound Arterial Abnormalities After Orthotopic Liver Transplantation. Transplantation. 2016Dec;100(12):2671-2681.
13. Courand PY, Harbaoui B, Grandjean A, Charles P, Paget V, Boussel L, Lantelme P.Significance of different ECG indices for left ventricle enlargement and systolic dysfunction assessment: A cardiac MRI study. Int J Cardiol. 2016 Aug 1; 216:114-7. doi: 10.1016/j.ijcard.2016.04.157.
14. Courand PY, Serraille M, Girerd N, Demarquay G, Milon H, Lantelme P, Harbaoui B. The Paradoxical Significance of Headache in Hypertension. Am J Hypertens. 2016
15. Courand PY, Lesiuk C, Milon H, Defforges A, Fouque D, Harbaoui B, Lantelme P. Association between protein intake and mortality in hypertensive patients without chronic kidney disease in the OLDHTA Cohort. Hypertension. 2016Jun; 67(6):1142-9.
16. Souteyrand G, Valladier M, Amabile N, Derimay F, Harbaoui B, Leddet P, Barnay P, Malcles G, Mulliez A, Berry C, Eschalier R, Combaret N, Motreff P. Diagnosis and Management of Spontaneously Recanalized Coronary Thrombus Guided by Optical Coherence Tomography - Lessons From the French "Lotus Root" Registry. Circ J. 2018 Feb 23;82(3):783-790.

17. Harbaoui B, Courand PY, Cividjian A, Lantelme P. Development of Coronary Pulse Wave Velocity: New Pathophysiological Insight Into Coronary Artery Disease. J Am Heart Assoc 2017 Feb 2;6(2):e004981.
18. Harbaoui B, Emsellem P, Cassar E, Besnard C, Dauphin R, Motreff P, Courand PY, Lantelme P. Primary angioplasty: Effect of deferred stenting on stent size. Arch Cardiovasc Dis. 2017 Apr;110(4):206-213.
19. Courand PY, Harbaoui B, Bècle C, Mouly-Bertin C, Lantelme P. Plasma NT-proBNP mirrors the deleterious cardiovascular and renal continuum in hypertension. Eur J Prev Cardiol. 2017 Mar;24(5):452-459.
20. FRANCE TAVI Investigators. Temporal Trends in Transcatheter Aortic Valve Replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol. 2017 Jul 4;70(1):42-55.
21. Fournier S, Iten L, Marques-Vidal P, Boulat O, Bardy D, Beggah A, Calderara R, Morawiec B, Lauriers N, Monney P, Iglesias JF, Pascale P, Harbaoui B, Eeckhout E, Muller O. Circadian rhythm of blood cardiac troponin T concentration. Clin Res Cardiol. 2017
22. Ouzir N, Basarab A, Liebgott H, Harbaoui B, Tourneret JY. Motion Estimation in Echocardiography Using Sparse Representation and Dictionary Learning. IEEE Trans Image Process. 2018 Jan.;27(1):64-77.
23. Courand PY, Harbaoui B, Fay H, Grandjean A, Milon H, Lantelme P. Aortic atherosclerosis is a key modulator of the prognostic value of postural blood pressure changes. Atherosclerosis. 2018 Jan;268:108-116.
24. Fournier S, Guenat F, Fournier A, Alberio L, Bonny O, Bertaggia Calderara D, Bardy D, Lauriers N, Harbaoui B, Monney P, Pascale P, Eeckhout E, Muller O. Circadian variation of ticagrelor-induced platelet inhibition in healthy adulty. Eur Heart J Cardiovasc Pharmacother. 2018 Jan 23.
25. Courand PY, Harbaoui B, Fay H, Grandjean A, Milon H, LantelmeP. Aortic atherosclerosis is a key modulator of the prognostic value of postural blood change. Atherosclerosis 2018
26. Harbaoui B, Nanchen D, Lantelme P, Gencer B, Heg D, Klingenderg R, Raber L, Carballo D, Matter CM, Windecker S, Mach F, Rodondi N, Eeckhout E, Monney P, Antiochos P, Fournier S, Luscher T, Muller O. Prognostic value of pulse pressure after an acute coronary syndrome. Atherosclerosis 2018 Jan;268:108-116.
27. Masci PG, Pavon AG, Muller O, Iglesias JF, VincentiG, Harbaoui B, Eeckhout E, Schwitter J. Relationship between CMR-derived parameters of ischemia reperfusion injury and the timing of CMR after reperfused ST-segment elevation myocardial infarction. J Cardiovasc Magn Reson 2018 Jul 23;20(1):50.
28. Muller O, Fournier S, Pilgrim T, Heg D, Noble S, Jeger R, Toggweiler S, Taramasso M, Windecker S, Stortecky S. Local Versus General Anesthesia for Transcatheter Aortic Valve Replacement: A SwissTAVI Registry Analysis; SwissTAVI Investigators (collaborator). JACC Cardiovasc Interv. 2019 Sep 23;12(18):1874-1876.
29. Lantelme P, Eltchaninoff, Rabilloud M, Souteyrand G, Dupré M, Spaziano M, Bonnet M, Becle C, Riche B, Boussel L, Lefèvre T, Harbaoui B Development of a Risk Score Based on Aortic Calcification to Predict 1-year Mortality After TAVR. JACC Cardiovasular Img 2019 Jan;12(1):123-132
30. Harbaoui B, Durand E, Dupré M, Rabilloud M, Souteyrand G, Courand PY, Boussel L, Lefevre T, Eltchaninoff H, Lantelme P. Significance of the CAPRI risk score to predict heart failure hospitalization post-TAVI: The CAPRI-HF study. Int J Cardiol. 2019 Dec 1;296:98-102.
31. Garcia D, Harbaoui B, Van de Hoef T, Meuwissen M, Nijjer S, Davies J, Piek JJ, Lantelme P. Relationship between FFR, CFR and coronary microvascular resistance. Plos One 2019 Jan 7;14(1):e0208612
32. Grandjean A, Courand PY, Mouly-Bertin C, Berge C, Langevin F, Harbaoui B, Garcia D, Lantelme P. Risk stratification in hypertension: NT-proBNP and R wave in aVL lead combination better than echocardiographic left ventricular mass. J Hypertens. 2020 Jan;38(1):65-72.
33. Lantelme P, Lacour T, Bisson A, Herbert J, Ivanes F, Bourguignon T, Quilliet L, Angoulvant D, Harbaoui B, Babuty D, Etienne CS, Deharo P, Bernard A, Fauchier L. Futility Risk Model for Predicting Outcome After Transcatheter Aortic Valve Implantation. Am J Cardiol. 2020 Jun 7:S0002-9149(20)30554-3.
34. Cividjian A, Harbaoui B, Chambonnet C, Bonnet JM, Paquet C, Courand PY, Lantelme P.Comprehensive assessment of coronary pulse wave velocity in anesthetized pigs. Physiol Rep. 2020 May;8(9):e14424.
35. Bècle C, Riche B, Rabilloud M, Souteyrand G, Eltchaninoff H, Lefèvre T, Harbaoui B, Lantelme P. Role for Vascular Factors in Long-Term Outcomes After Transcatheter Aortic Valve Implantation. Am J Cardiol. 2020 Jun 15;125(12):1884-1889.
36. Meier D, Fournier S, Masci PG, Eeckhout E, Antiochos P, Tzimas G, Stoyanov N, Muenkaew M, Monney P, Schwitter J, Muller O, Harbaoui B. Impact of manual thrombectomy on microvascular obstruction in STEMI patients. Catheter Cardiovasc Interv. 2020 Apr 11. doi: 10.1002/ccd.28907.
37. Lantelme P, Couray Targe S, Metral P, Bochaton T, Ranc S, Le Bourhis M, Lecoanet A, Courand PY, Harbaoui B. Worrying decrease in hospital admissions for myocardial infarction during theCOVID-19 pandemic. Archives of cardiovascular Diseases Arch Cardiovasc Dis. 2020 Jun 25:S1875-2136(20)30130-

3.

38. Jolicœur M, Dendukuri N, Belisle P, Range G, Souteyrand G, Bouisset F, Zemour G, Delarche N, Harbaoui B, Schampaert E, Kouz S, Cayla G, Roubille F, Boueri Z, Mansour S, Marcaggi X, Tardif JC, McGillion M, Tanguay JF, Brophy J, Woong Yu C, Berry C, Carrick D, Høfsten D, Engstrøm T, Kober L, Kelbæk H, Belle L Immediate vs. Delayed Stenting in ST-Elevation Myocardial Infarction: Rationale and Design of the International PRIMACY Bayesian Randomized Controlled Trial. Canadian Journal of Cardiology in press DOI:https://doi.org/10.1016/j.cjca.2020.01.019
39. Courand PY, Kochly F, Haddad C, Harbaoui B, Lantelme P. Therapeutic management and outcome of nonagenarians admitted to an intensive care unit for an acute coronary syndrome as compared to octogenarians Archives of cardiovascular Diseases Arch Cardiovasc Dis. 2020 in press
40. Hamandi M, Amiens P , Grayburn PA, Al-Azizi K , van Zyl J, Lanfear AT, Rabilloud R , Riche B, Gopal A, Szerlip MA, Potluri S, DiMaio JM , Mack MJ, Harbaoui B, Lantelme P Usefulness of Thoracic Aortic Calcium to Predict 1-Year Mortality After Transcatheter Aortic Valve Implantation Am J Cardiol. 2021 Feb 1;140:103-109.
41. Combaret N, Gerbaud E, Dérimay F, Souteyrand G, Cassagnes L, Bouajila B, Berrandou T, Rangé G, Meneveau N, Harbaoui B, Lattuca B, Bouatia-Naji N, Motreff P. National French registry of spontaneous coronary artery dissections: prevalence of fibromuscular dysplasia and genetic analyses. EuroIntervention. 2021 Aug 27;17(6):508-515.
42. Haddad C, Courand PY, Berge B, Harbaoui B, Lantelme P. Impact of cortisol on blood pressure and hypertension-mediated organ damage in hypertensive patients. J Hypertens. 2021 Jul 1;39(7):1412-1420.
43. Courand PY, Lenoir J, Grandjean A, Garcia D, Harbaoui B, Lantelme P SCORE underestimates cardiovascular mortality in hypertension: insight from the OLD-HTA and NEW-HTA Lyon cohorts. Eur J Prev Cardiol. 2021 Jan 18;zwaa163
44. Lantelme P, Bisson A, Lacour T, Herbert J, Ivanes F, Bourguignon T, Angoulvant D, Harbaoui B, Bonnet M, Babuty B, Saint Etienne C, Deharo P, Fauchier L Timing of Coronary Revascularization and Transcatheter Aortic Valve Replacement: An Observational Nationwide Cohort Analysis. JACC Cardiovasc Interv. 2021 Feb 22;14(4):484-486.
45. Harbaoui B, Ghigo N, Boussel L, Liebgott H, Souteyrand G, Durand E, Eltchaninoff H, Lefevre T, Courand PY, Lantelme P. Prognostic significance of vascular and valvular calcifications in low- and high-gradient aortic stenosis. Eur Heart J Cardiovasc Imaging. 2021 Mar 8;jeab039.
46. Peter E, Fraison JB, Harbaoui B, Kone Paut I, Dauphin C, Gomard-Mennesson E, Hervier B, De Boysson H, Varron L, Keraen J, Pugnet P, Gobert D, Bachmeyer C, Humbert S, Landron C, Roblot P, Cathébras P, Gerfaud-Valentin M, Weber W, Jamilloux Y, Fain O, Seve P. Cardiovascular outcome in adult-onset Kawasaki disease Autoimmun Rev. 2021 Sep;20(9):102886.
47. Investigator Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction N Engl J Med. 2021 Jul 22;385(4):297-308.
48. Lantelme P, Moulayat C, Courand PY, Mouly-Bertin C, Debouzy-Berge C, Rial MO, Iwaz J, Harbaoui B, Riche B, Rabilloud M Gain in net survival from hypertension control over the last half-century. Eur J Prev Cardiol. 2021 Jul 16;zwab094.

Publications autres

- **Cas cliniques** (n=12)

49. Harbaoui B, Finet G, Rioufol G. Spontaneous dissecting coronary haematoma with and without intimal tear. Arch Cardiovasc Dis. 2014 Dec; 107(12): 697-700.
50. Courand PY, Harbaoui B, Marchal FX, Martin X, Bricca G, Lantelme P. Uncommon secondary hypertension. Presse Med. 2015 Sep;44(9):976-8.
51. Harbaoui B, Courand PY, Schmitt Z, Farhat F, Dauphin R, Lantelme P. Early Edwards SAPIEN Valve Degeneration After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2016 Jan 25;9(2):198-9.
52. Montoy M, Courand PY, Fareh S, Farhat F, Lantelme P, Harbaoui B. Uncommon complication of myocardial infarction revealed by sustained ventricular tachycardia. Presse Med. 2016 Feb;45(2):276-8..
53. Saison J, Harbaoui B, Bouchiat C, Pozzi M, Ferry T.Unexpected severe native aortic subacute endocarditis due to Bartonella quintana in a 40-year-old woman with good socioeconomic condition.BMJ Case Rep. 2016 Sep 20;2016. pii: bcr2016216355.

10

54. Trans-oesophageal echocardiography for acute systemic embolism: Check the heart don't forget the aorta. Descaillot L, Lantelme P, Harbaoui B. Presse Med. 2017 Sep;46(9):874-876.
55. Tzimas G, Eeckhout E, Antiochos P, Roguelov C, Fournier S, Harbaoui B, Monney P, Muller O. Percutaneous Valvular Closure Followed by TAV-in-TAV Intervention during a Single Procedure in order to Treat a Severe Paravalvular Leak after Performing TAVI in a Bicuspid Aortic Stenosis Case Rep Cardiol. 2019 Apr 15;2019:4825607.
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- **Lettres, correspondances (n=11)**

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- **Editorial (n=1)**

72. Harbaoui B, Muller O. Quantification of Absolute Coronary Blood Flow and Microvascular Resistance. Circ Cardiovasc Interv 2017 Oct;10(10):e005916.

- **Article de Revue (n=4)**

11

73. Delahaye F, Harbaoui B, Cart Regal V, De Gevigney G. Recommendations on prophylaxis for infective endocarditis: Dramatic changes over the past seven years Archives of cardiovascular diseases; 2009, vol. 102, no3, pp. 233-245.
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1. Courand PY, Grandjean A, Charles P, Paget V, Harbaoui B, Boussel L, Bricca G, Lantelme P. R wave in aVL lead is a sufficient ECG index to detect left ventricular hypertrophy in women and in patients without heart failure. 24th European Meeting on hypertension and cardiovascular protection. Athens, June 13-16th 2014.
2. Courand PY, Paget V, Berge C, Grandjean A, Khettab F, Harbaoui B, Bricca G, Lantelme P. The dynamic response of NT-proBNP to circadian rhythm is related to cardiovascular remodelling. 24th European Meeting on hypertension and cardiovascular protection. Athens, June 13-16th 2014.
3. Courand PY, Fay H, Harbaoui B, Khettab F, Fauvel JP, Bricca G, Milon H, Lantelme P. Influence of aortic atherosclerosis on the prognostic value of postural blood pressure changes. 25th European Meeting on hypertension and cardiovascular protection. Milan, June 12-15th 2015.
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7. Courand PY, Harbaoui B, Rial MO, Mouly-Bertin C, Lantelme P. Plasma NT-proBNP mirrors the deleterious cardiovascular continuum in hypertension. 26th European Meeting on hypertension and cardiovascular protection. Paris, June 10-13rd 2016
8. Harbaoui B, Courand PY, Cividjian A, Lantelme P. Coronary Pulse Wave Velocity: insight from a first routine assessment in humans. European Society of Cardiology congress, Rome, 2016
9. Serraille M, Courand PY, Girerd N, Demarquay G, Milon H, Harbaoui B, Lantelme P. The paradoxical significance of headache in hypertension. 26th European Meeting on hypertension and cardiovascular protection. Paris, June 10-13rd 2016
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15. Schiele F, Puymirat E, Chatot M, Isaaz K, Farah F, Harbaoui B, Plastaras P, Ducrocq G, Ferrières J, Simon T, Nicolas Meneveau N, Danchin N. THE COMPASS CRITERIA APPLIED TO A REAL LIFE POPULATION FROM THE FAST-MI 2005 AND 2010 REGISTRIES. American College of Cardiology Congress, 2018. Journal of the American College of Cardiology, Volume 71, Issue 11 Supplement, March 2018
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19. Duband B, Harbaoui B, Becle C, Souteyrand G, Courand PY, Eltchaninoff H, Boussel L, Durand E, Lefevre T, Motreff P, Lantelme P. Mitral annular calcification volume predicts one year cardiovascular mortality after transcatheter aortic valve implantation. European Society of Cardiology congress, Paris, 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz747.0128, https://doi.org/10.1093/eurheartj/ehz747.0128
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21. Harbaoui B, G Souteyrand, T Lefevre, H Liebgott, PY Courand, E Durand, C Becle, H Eltchaninoff, P Lantelme Respective pronostic value of the valvular aortic calcifications and the thoracic aorta calcifications in patients with and without low gradient aortic stenosis after TAVI. European Society of Cardiology congress, Paris, 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz747.0503, https://doi.org/10.1093/eurheartj/ehz747.0503
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24. Grandjean A, Courand PY, Charles P, Paget V, Harbaoui B, Khettab F, Bricca G, Boussel L, Lantelme P. Significance of different ECG indices for left ventricular enlargement assessment: a cardiac MRI study.

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25. Courand PY, Grandjean A, Harbaoui B, Charles P, Paget V, Khettab F, Bricca G, Boussel L, Lantelme P. R wave in AVL lead is a robust index of left ventricular hypertrophy: a cardiac MRI study. Journées. Européennes de la Société Française de Cardiologie 2015. Archives of Cardiovascular Diseases Supplements
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https://doi.org/10.1016/j.acvdsp.2018.10.027
29. Good F, Harbaoui B, Bonnefoy-Cudraz E, El Khoury C, Bochaton T. Early discharge strategy after a ST-segment elevation myocardial infarction: safety assessment at one-year follow-up - Journées Européennes de la Société Française de Cardiologie 2018. Archives of Cardiovascular Diseases Supplements Doi : 10.1016/S1878-6480(17)30104-0
30. Harbaoui B, Cividjian A, Courand PY, Lantelme P. Coronary pulse wave velocity, a biomechanistic marker of vulnerable vessel vulnerability: towards plaque rupture prediction. 27ème Journées Européennes de la Société Française de Cardiologie, 11-14 Janvier 2017
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32. M. Dupré M, B. Harbaoui B, E. Durand E, J. Dacher JN, L. Boussel L, E. Davila E, H. Eltchaninoff H, P. Lantelme P.Thoracic aorta calcifications and TAVI: evaluation of automatic measurements and prognostic value on the cohort of Rouen –Le Printemps de la Cardiologie 2017, Nantes
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33. Descaillot L, Harbaoui B, Emsellem P, Besnard C, Dauphin R, Mouly Bertin C, Courand PY, Charles P, LantelmeP. Use of intra-aortic balloon pump in cardiogenic shock: Evidence-based or experience-based? Insights from a historical, real life comparison Journées Européennes de la Société Française de Cardiologie, 2018, Paris
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34. Delmas C, Puymirat E, Leurent G, Manzo-Silberman S, Elbaz M, Levy B, Morel O, Aissaoui N, Chevalier S, Vanzetto G, Harbaoui B, Champion S, Ternacle J, Bonello L, Combaret N, Gerbaud E, Lamblin N, Bonnefoy E, Roubille F. Early predictive factors of 30-days mortality in cardiogenic shock: An analysis of the FRENSHOCK multicenter prospective registry. Journées Européennes de la Société Française de Cardiologie, 2018, Paris. Archives of Cardiovascular Diseases Supplements Volume 11, Issue 1, January 2019, Page 145
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38. Harbaoui B, Souteyrand G, Lefevre T, Durand E, Liebgott H, Rabilloud M, Boussel L, Ghigo N, Bonnet Low gradient aortic stenosis and TAVI: The differential prognostic value of valvular and aortic calcifications may traduce a particular pathophysiology - Journées Européennes de la Société Française de Cardiologie, 2020, Paris
https://doi.org/10.1016/j.acvdsp.2019.09.168
39. Courand PY, Lenoir J, Milon H, B. Harbaoui B, Serraille M, Pernet K, Berge C, Lantelme P. Prognostic value of SCORE in hypertensive patients referred to a tertiary centre: Insight from the OLD-HTA Lyon Cohort – Journées Européennes de la Société Française de Cardiologie, 2020, Paris
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40. Duband B, Harbaoui B, Becle C, Souteyrand G, Courand PY, Eltchaninoff H, Durand E, Boussel L, Lefevre T, Motreff P, Lantelme P. Mitral annular calcification volume predicts one year all-cause mortality after transcatheter aortic-valve implantation Journées Européennes de la Société Française de Cardiologie, 2020, Paris –
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41. Bècle C, Riche B, Rabilloud M, Eltchaninoff H, Souteyrand G, Dupré M, Bonnet M, Durand E, Boussel L, Lefevre T, Courand PY, Harbaoui B, Lantelme P. Long-term outcome after TAVI: The valve is cured but the vessels remain harmful! - Journées Européennes de la Société Française de Cardiologie, 2020, Paris
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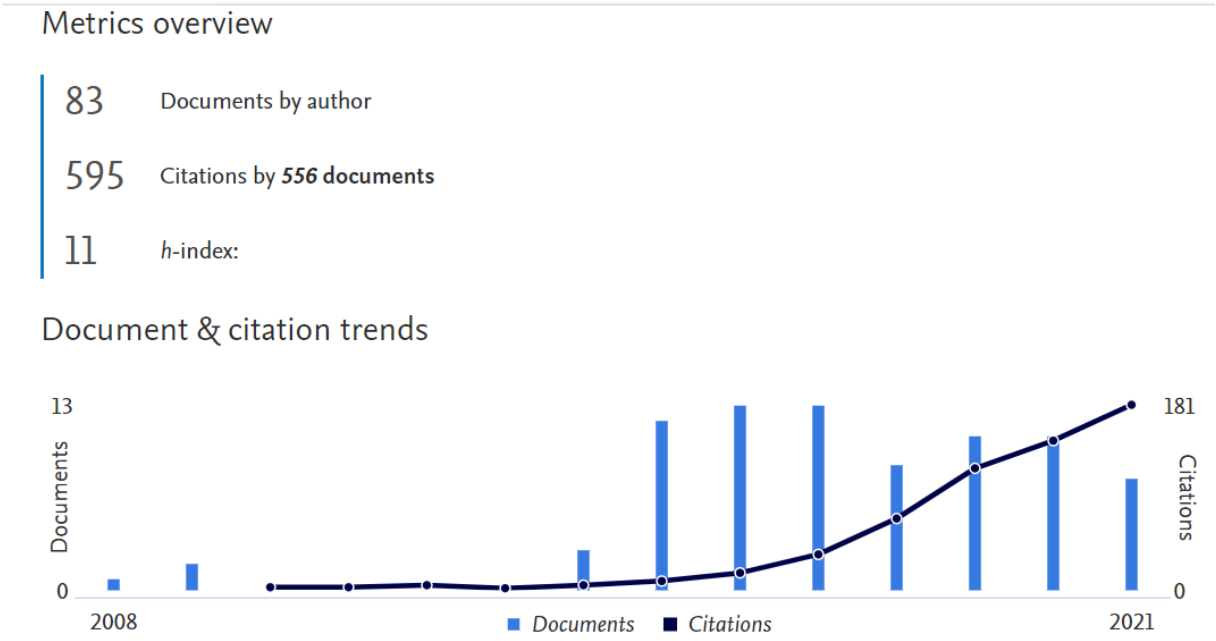
Synthèse des publications originales

Années	Nom de la revue	Facteur d'impact	Nombre total de publications					
			1ère position	2ème position	Autre position	Avant dernière position	Dernière position	Nb total des publications pour un même journal
2021	NEJM	91.2			1inv			1
2015, 2017, 2019	Journal of American College of Cardiology (JACC)	18.6	1		2			3
2019	JACC cardiovascular Imaging	10.97					1	1
2019, 2020, 2021	JACC cardiovascular Intervention	9.55			3			3
2021	Auto Immun Reviews	7.76			1			1
2016	Hypertension	7.01				1		1
2021	European Journal of cardiovascular imaging	6.87	1					1
2018	IEEE Trans Image Process	6.79				1		1
2018	European Heart journal cardiovascular Pharmacology	6.72			1			1
2021	Eurointervention	6.54			1			1
2017, 2021	European Journal of Preventive Cardiology	5.64		1	2			3
2020	Canadian Journal of Cardiology	5.59			1			1
2018	Journal of cardiovascular magnetic resonance	5.07			1			1
2017	Clinical Research Cardiology	4.9			1			1
2016	Transplantation	4.7			1			1
2017	Journal of the American Heart Association	4.66	1					1
2016, 2018	Atherosclerosis	4.25	3	1				4
2015, 2019	Journal of Hypertension	4.2			3	1		4
2018	European Radiolology	4.02			1			1

15

2016, 2019	International journal of Cardiology	3.47	1	2				3
2018	Circulation Journal	3.02			1			1
2020	American Journal of Cardiology	2.84			1	1		2
2019	Plos One	2.77		1				1
2020	Catheter cardiovascular Interventions	2.55					1	1
2015, 2016	American Journal of Cardiology	2.53	1				2	3
2009,2014 2017,2020	Archives of Cardiovascular Disease	2.27	1	1	2		1	4
2020	Physiological Reports	2.13		1				1
2015	La Presse Medicale	1.07	1	1				2
2014, 2019	Annales de Cardiologie et Angeiologie	0.3			1		1	2
2019	Bulletin du cancer				1			
TOTAL			**10**	**8**	**25**	**4**	**6**	**53**

Facteur H : 11 selon SCOPUS au 01/10/2021



16

C- Liste des conférences sur invitation

- **Conférences internationales**

1. TAVI procedural complications, Endovascular Cardiac Complications, ECC 2019, Lausanne (Suisse), http://ecc-conference.com/2019-Lausanne/Scientific_Program/index.php
2. Trouble shooting in STEMI: a step-by-step guide to primary PCI. Euro PCR 2017, Paris https://www.pcronline.com/Courses/EuroPCR/Programme/2017/Scientific-programme
3. A PCI complications showcase: how would you prevent it? How would you solve it? Euro PCR 2017, Paris https://www.pcronline.com/Courses/EuroPCR/Programme/2017/Scientific-programme
4. Learning how to perform a transfemoral TAVI procedure, Euro PCR 2018, Paris https://www.pcronline.com/Courses/EuroPCR/Programme/2018/Course-Programme
5. When a nightmare comes true, there is no time for dreaming-Managing coronary perforations, Euro PCR 2018, Paris https://www.pcronline.com/Courses/EuroPCR/Programme/2018/Course-Programme
6. Advanced Physiology Course, Assessment of coronary physiology in patients with Aortic stenosis? Lyon, 28/09/2018 https://simpleeducation.co/moments/915/preview
7. Advanced Physiology Course, FFR and IFR discordance, Paris, 22/06/2018 https://simpleeducation.co/moments/911/preview

En qualité de Modérateur

1. Coronary pci complications, Endovascular Cardiac Complications, ECC juin 2017 Lausanne http://ecc-conference.com/2017-Lausanne/Directors_Faculty/index.php
2. Modération de session poster « Machin learning » TCT San Diego (Etats Unis), 2018
3. International Session: Hemodynamic functional assessment of coronary stenosis in daily practice Presented by Groupe Atherome et Cardiologie Interventionnelle (GACI) and Colegio Argentino de Cardioangiólogos Intervencionistas (CACI), TCT San Diego (Etats Unis), 2018 http://www.caci.org.ar/post/2018-SanDiego

- **Conférences nationales**

1. Pseudoanevrysme du ventricule gauche compliquant un SCA ST-. Journées de cardiologie Rhone-Alpes-Auvergne, Chamonix, février 2011

2. Spasme coronaire réfractaire sous methergin, séminaire du DIU de cardiologie interventionnelle, mars 2012, Paris

3. L'infarctus du Myocarde ST+ : les dernières recommandations européennes ont elles modifié nos pratiques ? 3ème journée nationale du GACI, mars 2013, Paris

4. Le rotablator, indications en routine ? La croix Rousse en live, 2013, Lyon

5. Symposium HTA Rhône-Alpes : Compliance des artères coronaires: le chaînon manquant? », 5 juin 2015, Voiron

6. Rigidité Aortique et TAVI : Printemps de la Cardiologie, 7-9 avril 2016, Dijon
7. Invitation à participer à la compétition jeune chercheur (obtention du 1er prix) Coronary pulse wave velocity Journées Européennes de la Société Française de cardiologie, Janvier 2017, Paris.
8. Comment la physiologie coronaire peut nous aider pour la revascularisation ? - GRCI 2018, Paris https://www.grci.fr/Media/grci_2018_catalogue.pdf
9. IFR ou FFR : Quel examen pour quelle lésion ? TUC GACI 2019, Paris 2019 https://tuconline.org/document/programmeTGG2019.pdf
10. Comment la physiologie coronaire peut nous aider pour la revascularisation ? Congrès du Groupe de Réflexion en cardiologie interventionnelle (GRCI), Paris, 2018 https://www.grci.fr/Media/grci_2018_catalogue.pdf

17

11. Biarritz, APPAC 2019 : Faut-il faire de la FFR dans les pontages aorto-coronaires ? https://www.appac.fr/archives/2019
12. Calcifications de l'aorte et score de risque TAVI - GRCI 2019, Paris https://www.grci.fr/programme-2019
13. Optimisation de l'angioplastie complexe par l'imagerie TUC-GACI 2021, Paris

En qualité de modérateur

1. Commentaires de procédures en live, La Croix Rousse en Live 2012, Lyon
2. Commentaires de procédures en live La Croix Rousse en Live 2013, Lyon
3. Session commune avec le Swiss Working Group for Interventional Cardiology. Congrès du Groupe de Réflexion en cardiologie interventionnelle (GRCI), 2018, Paris https://www.grci.fr/Media/grci_2018_catalogue.pdf
4. Les syndromes coronaires chroniques, Congrès du Groupe de Réflexion en cardiologie interventionnelle (GRCI), 2019, Paris https://www.grci.fr/programme-2019

D- Essais clinique et Cohortes

Implication dans des contrats de recherche

Investigateur principal et Start up i-COR technologies

Investigateur principal	
2018	BOURSE DE RECHERCHE FEDERATION FRANCAISE DE CARDIOLOGIE 2018 Etude COREYE (Can we predict COronary Resistance by EYE examination?) Promoteur : Hospices Civils de Lyon **Investigateur principal** responsable : B. Harbaoui (code promoteur 69HCL18_0301) https://clinicaltrials.gov/show/NCT03739073 Montant obtenu : **248.491 Euros**
2017	BOURSE DE RECHERCHE FEDERATION FRANCAISE DE CARDIOLOGIE Intérêt pronostique de la combinaison de biomarqueurs biologiques, vasculaires échographiques et électro cardiographiques dans l'évaluation du risque de mortalité dans l'hypertension artérielle. **Co-investigateur principal** avec le Pr Pierre-Yves Courand Montant obtenu : **35.000 Euros**
Levées de fonds Start-up i-COR technologies	
2020	Bourse BPI France French Tech « Deep-Tech » 2020 **90.000 Euros**
2020	Bourse Pack Ambition Recherche 2020 **198.493 Euros**

Investigateur associé

- ***Etude internationale***
  Etude PRIMACY Primary Reperfusion Secondary Stenting Trial
  Inclusion de 12 patients**, 15.500 euros** à la DRCI
  Promoteur : CH d'Annecy et Institut de Montréal
  Rôle du Candidat : Investigateur principal pour Lyon
  https://clinicaltrials.gov/show/NCT01542385
  Etude multicentrique Internationale, protocole publié dans Canadian Journal of Cardiology

18

- ***PHRC nationaux***

FUTURE
Promoteur : Hospices Civils de Lyon
Rôle du Candidat : Investigateur principal pour Lyon Croix Rousse
Etude multicentrique nationale

DISCO
Promoteur : CHU de Clermont Ferrand
Rôle du Candidat : Investigateur principal pour Lyon
Etude multicentrique nationale

FRENSHOCK
Promoteur : CHU de Toulouse
Rôle du Candidat : Investigateur principal pour Lyon
Etude multicentrique nationale

EVAOLD
Essai comparatif randomisé multicentrique national
Promoteur : CHU de Grenoble
Rôle du Candidat : Investigateur principal pour Lyon

Etude FLOWER-MI
Promoteur : Assistance Public des Hôpitaux de Paris
Rôle du Candidat : Investigateur principal pour Lyon

- ***Cohortes nationales***

FASTMI
Registre Français des infarctus du myocarde
Promoteur : Société Française de Cardiologie
Investigateur associé

FRANCETAVI
Base de données Française des TAVI
Promoteur : HAS
Investigateur associé

FRANCE2
Base de données Française des TAVI
Promoteur : HAS
Investigateur associé

- ***Etude à promotion industrielle***

Source 3 Observational Study to Evaluate Safety and Performance of SAPIEN 3 THV System in Real Life Practice.
Etude de registre, valve TAVI Edwards Sapien XT
Investigateur principal pour la Croix-Rousse

19

E- Reviewer/comité éditorial pour des journaux

Lecteur pour :

- Circulation
- Circulation Cardiovascular interventions
- Circulation cardiovascular quality and outcome
- American Heart Journal
- American Journal of Cardiology
- Medicine journal

F- Encadrements

Encadrement d'étudiants en master et thèse d'université

Master 1

Année	*Nom de l'étudiant*	*Titre du mémoire*	*Pourcentage encadrement*
2019	Emma Hantute	« Machin Learning » corrélation des dimensions artérielles pulmonaires sur les scanners pré-TAVI et valeurs des pressions artérielles pulmonaires échographiques Résultats : absence de corrélation chez cette la population TAVI	50%

Master 2

Année	*Nom de l'étudiant*	*Titre du mémoire et publications associées*	*Pourcentage encadrement*
2017	Clément Bècle	Compliance de l'Aorte, étude de la distensibilité aortique Communication en congrès : 41 Publication : 34	20%
2019	Charles Jabour	« Machin learning » mise au point de la méthodologie pour l'étude COREYE	50%

Thèse d'Université

Année	*Nom de l'étudiant*	*Titre de la thèse et publications associées*	*Pourcentage encadrement*
2019 - En cours	Nina Ghigo Université Lyon 1 / ED 162 MEGA	« Imagerie ultrasonore rapide 2D et 3D du mouvement pariétal et du flux vectoriel pour l'étude de l'aorte abdominale » Publication ***45*** Communication en congrès : 22, 38	20%
2019 - En cours	Charles Jabour INSA Lyon / ED 162 MEGA	« Estimation de la résistance coronarienne par analyse du réseau vasculaire du fond de l'œil » Etude COREYE en cours	50%

Encadrement d'étudiants en thèse de médecine

En tant que directeur de thèse 100%

2015	Mathieu Montoy Titre de la thèse : « La charge calcique de l'aorte, un puissant prédicteur de mortalité après remplacement valvulaire aortique percutané» Présentation en congrès national et international : **5,6** Publication de l'article : **9**
2015	Philippe Emsellem Titre de la thèse : « Infarctus du myocarde, impact du Stenting différé sur la taille de l'endoprothèse» Présentation en congrès national : communication affichée 6 Publication de l'article : **18**
2016	Florence Good Titre de la thèse: «Early discharge strategy after ≤ 48 hours in patients with ST segment elevation myocardial infarction: Safety assessment at one-year follow-up» Présentation en congrès national et international : **13, 29**
2017	Hélène Fay Titre de la thèse : « L'impédance valvulo-artérielle, outil intégratif de la charge imposée au ventricule gauche dans le rétrécissement aortique serré. Evolution et implication pronostique après TAVI»
2019	Benjamin Duband Titre de la thèse : « Calcifications de l'anneau mitral chez les patients porteurs d'un rétrécissement aortique traités par remplacement valvulaire aortique percutané : prévalence facteurs prédictifs et impact pronostic» Présentation en congrès national et international : **19, 40** Publication de l'article : *Soumission de l'article en cours*
2020	Mahfoud Mebazza Titre de la thèse : « a pression pulsée basse est un puissant prédicteur de mortalité précoce chez les patients présentant un SCA ST+»
2021	Matthieu Giraud Titre de la thèse : Coronary Artery Disease in Infective Endocarditis, « CADIE study»

En tant que membre du Jury

2019	Flora Kochly Titre de la thèse : Evaluation de la prise en charge et du pronostic des patients de plus de 80 ans admis aux soins intensifs cardiologiques pour un syndrome coronarien aigu

Encadrement d'étudiants en DES, DU, DIU

Mémoire de DES de cardiologie

2015	Mathieu Montoy Titre du mémoire: tachycardia à QRS large sur anevrysme du ventricule gauche Publication de l'article : **43**
2016	Leonard Descaillot Titre du mémoire: « utilisation du ballon de contre pulsion intra aortique dans le choc cardiogénique» Présentation en congrès national : **33**
2016	Tamar Spingarn Titre du mémoire: « Aortic calcifications burden: a major drawback for left ventricular recovery after TAVI» Présentation en congrès national : **27**
2017	Clément Bècle Titre du mémoire : « Mise au point d'une technique de mesure semi-automatique des calcifications de l'anneau mitral» Ce travail a été la base de la thèse de Benjamin Duband

Mémoire de DIU d'USIC
12 encadrements : Leonard Descaillot, Mathieu Montoy, Clément Bècle, Carole Chambonnet, Chloé Lesiuk, Camille Strube, Geoffroy Ditac, Tarek Guelmaoui, Matthieu Giraud, Elena Deman, Romain Barthelemy, Ludovic Maxo

Mémoire de DU de cardiologie Interventionnelle :
3 encadrements Philippe Emsellem, Carole Chambonnet et Marc Bonnet (Prix du meilleur mémoire)

Brevets

2 brevets déposés sur la vitesse de l'onde de pouls coronaire

- n° EP16305641.9 déposée le 02/06/2016, Pierre LANTELME, Brahim HARBAOUI, Andrei CIVIDJIAN, UCBL, HCL, PULSALYS. SYSTEME DE DETERMINATION D'UNE VITESSE D'ONDE DE POULS CORONAIRE. Brevet délivré en UE réf. EP3251591.
- n° EP18205481.7 déposée le 09/11/2018, Pierre LANTELME, Andrei CIVIDJIAN, Brahim HARBAOUI, UCB, HCL, PULSALYS. SYSTEME DE DETERMINATION D'UNE VITESSE D'ONDE DE POULS ARTERIELLE. https://patents.google.com/patent/US20200178816A1/en

3/ Résumé synthétique de l'activité de recherche

Mon activité de recherche s'articule autour de la « rigidité vasculaire en cardiologie interventionnelle et en soins intensifs cardiologiques », elle est en lien direct avec mon activité clinique. La rigidité vasculaire se définie comme la résistance à la déformation : elle est inversement proportionnelle à la compliance qui correspond à une variation de volume sur une variation de pression.

J'ai étudié le concept de rigidité vasculaire dans le domaine de la cardiologie interventionnelle en développant principalement 2 axes : Valvulaire et Coronaire. Le fil conducteur de ma recherche est de mieux comprendre la physiopathologie afin d'améliorer la qualité des soins. Exerçant une spécialité avec des actes invasifs, ces axes de recherche permettent d'enrichir la réflexion sur la pertinence des soins, plus précisément la pertinence des actes.

A. Axe valvulaire

Cet axe s'intéresse à l'étude de l'impact de la rigidité artérielle estimée par le volume scanographique de calcifications de l'aorte chez les patients présentant un rétrécissement aortique serré et traités par prothèse valvulaire aortique TAVI (Transcatheter Aortique Valve Implantation). L'hypothèse était qu'une fois l'obstacle valvulaire levé, le cœur devait faire face à un nouvel obstacle vasculaire, l'aorte rigide calcifiée. L'étude « proof of concept » a été publiée en 2015 et montrait une augmentation des évènements cardiovasculaires chez les patients avec aorte thoracique ascendante calcifiée(1). Ceci a été confirmé par un travail complémentaire qui étudiait le volume de calcifications sur la totalité de l'aorte avec un suivi plus long des patients traités par TAVI(2). Depuis, ces données ont été confirmées au cours d'un travail collaboratif avec une équipe américaine(3) mais également par une équipe indépendante(4).

23

Nos travaux monocentriques ont été complétés par l'étude multicentrique C4CAPRI développant un score de risque de mortalité incluant les calcifications de l'aorte mesurées semi automatiquement, le CAPRI Score(5). En plus de prédire la mortalité, le CAPRI Score permet de prédire les hospitalisation pour insuffisance cardiaque(6). Aussi, l'impact des calcifications de l'aorte et des calcification de la valve aortique est différent chez les patients présentant un rétrécissement aortique serré à haut et à bas gradient valvulaire aortique(7).

L'idée de ces travaux est de voir s'il est possible de mieux cibler les patients qui bénéficient du TAVI et d'éviter de réaliser des interventions futiles. Ces dernières consomment des ressources médico-économiques en plus de poser des questions éthiques en terme de service rendu au patient.

B. Axe coronaire

Cet axe s'est d'abord intéressé aux liens entre rigidité vasculaire et événements cardiaques. Ces travaux épidémiologiques (bases de données de patients hypertendus et de patients ayant présentés un syndrome coronaire aigu), ont étudié l'impact de la rigidité vasculaire, estimée par la pression pulsée, sur les événements cardiovasculaires(8,9). Une association entre la rigidité vasculaire (aortique) et la survenue d'infarctus du myocarde (rupture de plaque d'athérome coronaire) a été mise en évidence. Afin de mieux comprendre la genèse de l'infarctus du myocarde (la rupture de plaque d'athérome), nous avons pu développer et breveter une méthode de mesure de la rigidité coronaire : la vitesse de l'onde de pouls coronaire (VOPc) (10). Les patients présentant un infarctus du myocarde avaient des artères coronaires plus compliantes que ceux ayant une coronaropathie stable. Ceci pourrait avoir une implication clinique majeure en termes de compréhension et de prévention des maladies coronaires. Ce travail(10) a été récompensé par le 1er Prix jeune chercheur de la Société Française de Cardiologie en 2017. En recherche fondamentale chez l'animal, en collaboration avec l'école Vetagro-Sup, nous avons

24

testé cette VOPc dans plusieurs conditions hémodynamiques(11). Afin de poursuivre le développement de ce nouveau paramètre physiologique coronaire, nous avons monté une start-up « i-COR technologies » dont l'objectif est de développer une interface mesurant la VOPc. Nous avons obtenu 290 K Euros de financements pour le développement de cette start-up. Par ailleurs, j'ai participé à une réflexion sur les paramètres physiologiques coronaires permettant de juger du caractère ischémiant ou non d'une sténose coronaire(12). Dans cette lignée, l'étude COREYE (Can we predict COronary Resistance by EYE examination) financée à hauteur de 250 K Euros par la Fédération Française de Cardiologie, a pu être lancée. Ce travail évalue la corrélation entre les paramètres physiologiques coronaires et oculaires en fonction de données cliniques telles que les facteurs de risques cardiovasculaires, l'hypothèse étant de pouvoir prédire une atteinte de la microcirculation coronaire de façon non invasive en étudiant l'œil comme détaillé à la fin de ce manuscrit.

C. Perspectives

Concernant l'axe valvulaire nous avons pour projet de construire un score de risque basé sur scanner pré-TAVI utilisant l'intelligence artificielle. Ce score de risque inclura le volume de calcification de l'aorte et d'autres paramètres cardiaques et extracardiaques tels que les calcifications valvulaires aortique et de l'anneau mitrale, la masse musculaire…. Il pourra facilement être implémenté sur d'autres centres de cardiologie interventionnelle et fera l'objet d'une étude de large ampleur.

Concernant l'axe coronaire, via la start-up I-COR technologies, nous souhaitons mettre au point un guide coronaire capable de mesurer la VOPc. En parallèle, je poursuis l'étude COREYE dont les premières analyses devraient être disponibles en 2022.

25

4/ Travaux sur la rigidité vasculaire et la pathologie coronaire

A) Travaux épidémiologiques, rigidité vasculaire, infarctus du myocarde

a) Rigidité vasculaire et mortalité cardiaque chez les patients hypertendus

Association of various blood pressure variables and vascular phenotypes with coronary, stroke and renal deaths: potential implications for prevention

Harbaoui B, *Courand PY, Milon H, Fauvel JP, Khettab F, Mechtouff L, Cassar E,Girerd N, Lantelme P*

Atherosclerosis. *2015 Sep 8; 243(1): 161-168*

Hypothèse : La rigidité aortique est un facteur de risque cardio-vasculaire bien validé dans différentes populations. L'hypothèse est que cet impact pronostique pourrait être différent selon le territoire vasculaire pour une simple raison de proximité ; en particulier, la rigidité aortique pourrait être plus étroitement associée aux évènements coronaires qu'aux autres.

Objectif : déterminer la valeur pronostique de marqueurs de rigidité aortique sur la survenue d'évènements coronaires et cérébro-vasculaires et rénaux.

Population, Méthodes : étude menée sur une cohorte de 1034 patients hypertendus recrutés dans les années 60. Les marqueurs de rigidité vasculaire appréciés ont été la pression pulsée et l'athérosclérose de l'aorte abdominale estimée lors d'une artériographie pratiquée largement à cette époque pour le dépistage d'une sténose des artères rénales (appréciation semi-quantitative).

26

Les outcomes considérés étaient les suivants ;

- coronaires : décès par infarctus du myocarde ou décès par maladie coronaire
- cérébro-vasculaires : décès par accident vasculaire cérébraux ou décès par maladie cérébro-vasculaire
- rénaux : décès en lien avec une insuffisance rénale

Résultats : après 30 ans de suivi, une association indépendante est retrouvée entre pression pulsée ou athérosclérose aortique et mortalité par infarctus du myocarde ou mortalité par maladie coronaire. Cette association est spécifique car non retrouvée pour décès par accidents vasculaire cérébral, maladie cérébro-vasculaire, ou maladie rénale. Pour ces dernières, c'est surtout le niveau de pression artérielle moyen qui est prédicteur.

Conclusion, discussion : Les évènements coronaires, cérébraux et rénaux ont des mécanismes physiopathologiques différents. Les premiers sont très liés à la rigidité vasculaire. Les résultats et conclusions de ce travail ont été résumés dans une figure récapitulative (Figure 1).

27

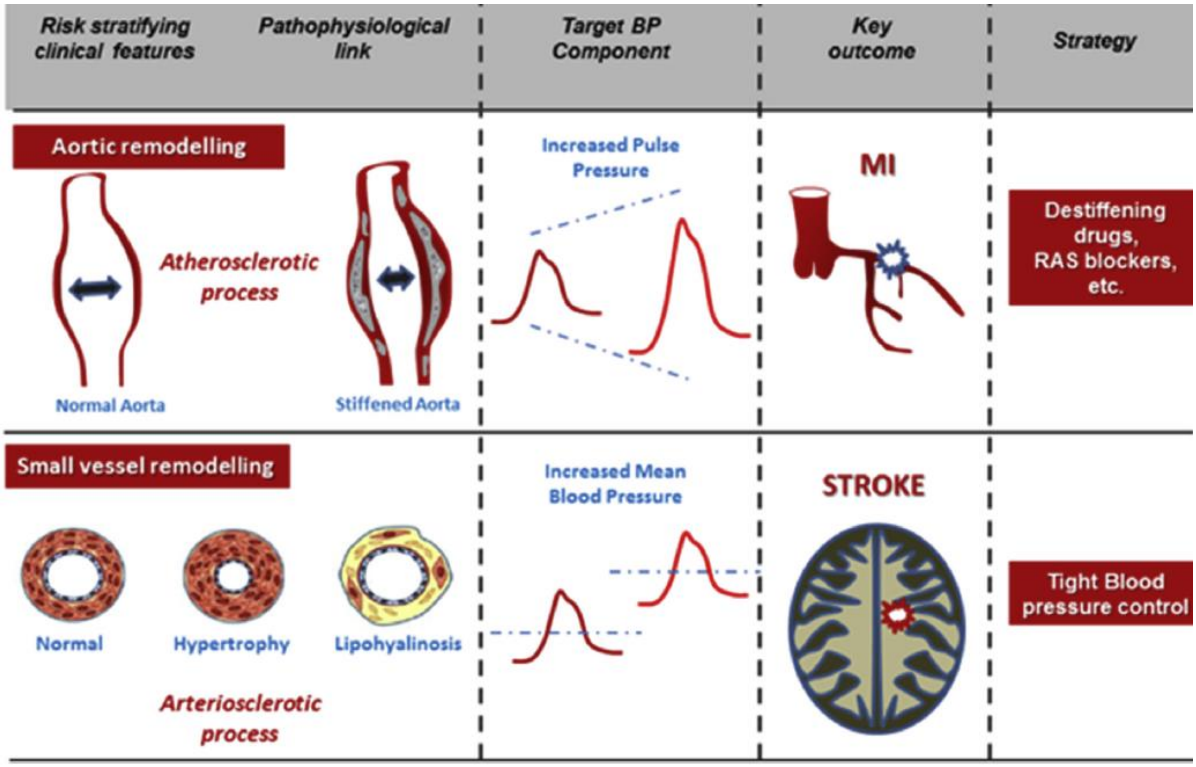


Figure 1 : Résumé des liens entre rigidité vasculaire ou niveau de pression artérielle et accidents coronaire ou cérébro-vasculaires aigus.

La rigidité vasculaire entraine une élévation de la pression pulsée et est liée à la survenue d'infarctus du myocarde. L'élévation de la pression artérielle moyenne est liée à la survenue cérébro-vasculaires.

Une des hypothèses pouvant expliquer le lien entre rigidité vasculaire et mortalité coronaire pourrait résider dans l'interaction (mismatch) entre rigidité globale et rigidité locale *ie* coronaire, ou bien dans des zones de différences de rigidité au niveau même du vaisseau coronaire (13). Malheureusement il n'existe pas de moyen d'évaluer la rigidité coronaire en pratique clinique. Les limites de cette étude résident essentiellement dans l'absence de marqueur direct de rigidité type VOP carotido-fémorale mais il s'agit d'étude historique, et la VOP n'était pas disponible à cette époque.

28

Perspectives : La pression pulsée et la rigidité aortique pourraient représenter des cibles thérapeutiques spécifiques pour diminuer la survenue d'évènements cardiaques. La caractérisation de la rigidité locale, notamment coronaire pourrait permettre d'améliorer la compréhension du processus physiopathologique (14). En effet, des études élastographiques et histopathologiques ont souligné que les complications de plaque survenait préférentiellement au niveau des zones de « compliance mismatch » (15,16).

29

Atherosclerosis 243 (2015) 161–168

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Association of various blood pressure variables and vascular phenotypes with coronary, stroke and renal deaths: Potential implications for prevention

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ABSTRACT

The relationship between blood pressure (BP) and cardiovascular diseases has been extensively documented. However, the benefit of anti-hypertensive drugs differs according to the type of cardiovascular event. Aortic stiffness is tightly intertwined with BP and aorta cross-talk with small arteries. We endeavored to elucidate which BP component and type of vessel remodeling was predictive of the following outcomes: fatal myocardial infarction (MI), fatal stroke, renal -, coronary- or cerebrovascular-related deaths. Large vessel remodeling was estimated by an aortography-based aortic atherosclerosis score (ATS) while small vessel disease was documented by the presence of a hypertensive retinopathy.

We included 1031 subjects referred for hypertension workup and assessed outcomes 30 years later. After adjustment for major risk factors, ATS and pulse pressure (PP) were predictive of coronary events while mean BP (MBP) and retinopathy were not. On the contrary, MBP was predictive of cerebrovascular and renal related deaths while ATS and PP were not. Retinopathy was only predictive of cerebrovascular related deaths. Lastly, the aortic atherosclerosis phenotype and increased PP identified patients prone to develop fatal MI whereas the retinopathy phenotype and increased MBP identified patients at higher risk of fatal stroke.

These results illustrate the particular feature of the resistive coronary circulation comparatively to the brain and kidneys' low-resistance circulation. Our results advocate for a rational preventive strategy based on the identification of distinct clinical phenotypes. Accordingly, decreasing MBP levels could help preventing stroke in retinopathy phenotypes whereas targeting PP is possibly more efficient in preventing MI in atherosclerotic phenotypes.

1. Introduction

The relationship between blood pressure (BP) and cardiovascular disease, namely cardiac ischemic events, heart failure and stroke, has been extensively documented [1] culminating in anti-hypertensive treatment being the cornerstone of prevention. Each additional 20 mmHg systolic BP (SBP) and 10 mmHg diastolic DBP (DBP) doubles the risk of cardiovascular events [2]. Large meta-analyses have proven the benefit of BP lowering on various outcomes [3]. Hypertension is also one of the leading causes of renal failure with BP lowering shown to be efficient at preventing renal function decline [4]. There are differences however in the extent of such preventive benefits, the latter being typically less pronounced for coronary prevention than for stroke prevention [5,6]. In

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0021-9150/

addition, certain drugs may be more efficient than others on specific outcome e.g., calcium channel blockers on stroke [3] or renin angiotensin blockers on renal deaths [4,7], suggesting that different pathophysiological mechanisms may intervene in the genesis of these diseases.

Tightly intertwined with BP, aortic stiffness is a key player in this process by conveying pulsatility to small arteries with a permanent cross talk between large and small vessels [8] while being a major determinant of central pressure waveform. Aortic stiffness is also an accepted risk marker for cardiovascular events [9–13].

Yet, the anatomical features of target organs and consequently, the characteristics of the diseases, are notably different: 1) myocardial infarction (MI) is an homogenous disease driven by plaque rupture at the level of large epicardic arteries which are in close proximity to the aorta; 2) Stroke is a polymorphic disease although, in its hypertension-specific expression, is related to small vessel disease, i.e. vessels located far from the aorta; 3) The process of renal disease is, to some extent, akin to that of brain disease while intra-renal circulation is much closer to that of the aorta than intra-cerebral circulation.

The objective of the present study was to determine the respective contributions of BP level, aortic remodeling and small vessel diseases on coronary events compared to cerebrovascular and renal-related events, considered separately. To our knowledge, this has never been performed within the same cohort. The study took advantage of an historical cohort of hypertensive patients with an aortic atherosclerosis score based on aortography [14], and a retinopathy score based on optic fundus, with documented cause-specific mortality 30 years later.

2. Methods

A complete methods description is available in online only materials.

This study cohort [14] included 1031 patients who had a workup of their hypertension at Louis Pradel Hospital (1969–1976). Their outcomes were controlled after thirty-years of follow-up. Oral consent was obtained for every patient according to French regulations prevailing in the seventies and the study received approval of the Commission Nationale Informatique et Libertés (CNIL).

A specifically-designed form was filled out for every patient and included morphometric characteristics, cardiovascular risk factors, history of cardiovascular disease and current medication and symptoms. Peripheral BP was measured with a manual sphygmomanometer after a 10-min rest period in supine position. Systolic BP (SBP) and Diastolic BP (DBP) were each determined as the average of six measurements. As the present study aimed at identifying the pressure and the vascular contributions to the diseases, mean peripheral BP (MBP) = [SBP + 2DBP]/3 and peripheral pulse pressure (PP) = [SBP − DBP] were deemed to identify respectively the steady-state component of pressure – a rather "pure" indicator of pressure level *per se* - and the pulsatile pressure component known to be closely related to stiffness. An overnight fasting blood sample was drawn for hemogram and plasma chemistry analysis. Renal function was assessed by the Modification in Diet in Renal Disease (MDRD) formula. An optic fundus was available for all of the patients.

Aortography was performed by puncture of the femoral artery. The descending thoracic and abdominal aorta was explored. Signs of aortic atherosclerosis included calcifications, atherosclerotic plaque, stenosis or aneurysms were examined. These were initially categorized according to the severity of atherosclerosis using a 3-modality score variable (ATS): 0 when atherosclerosis was undetectable (ATS 0), 1 for mild atherosclerosis (ATS 1), 2 for moderate or severe atherosclerosis (ATS 2).

An ophtalmoscopic fundus examination was performed to assess hypertensive retinopathy using the four-grade classification of Keith, Wagener, and Barker [15].

Patients were not individually followed by our team. Outcome were assessed and classified by consulting the Institut National d'Etudes Economiques (INSEE) mortality records and the death certificates provided by INSERM SC8, following the International Classification of Diseases, Ninth Revision (ICD-9).

2.1. Statistical analysis

Continuous variables with close-to-normal distributions are expressed as means ± standard deviations. Continuous variables with skewed distributions are expressed as medians (interquartile ranges). Categorical variables are expressed as percentages. Thus, the non-parametric Kruskal Wallis test was used to compare continuous variables between ATS or retinopathy subgroups and χ^2 testing was used for between-group comparisons of dichotomous variables.

Unadjusted hazard ratios were assessed with Cox regression model for PP, MBP, ATS, and retinopathy. Adjusted hazard ratios for MBP and ATS (model 1), PP and ATS (model 2), MBP and retinopathy (model 3), PP and retinopathy (model 4) were calculated in multivariable forced Cox regression models (χ^2 statistic adjusted for age, sex, diabetes, smoking status, previous cardiovascular disease, body mass index (BMI), antihypertensive treatment and estimated glomerular filtration rate). The same models were used for fatal MI, fatal stroke and renal-related mortalities in the first analysis and then for coronary and cerebrovascular related deaths thereafter. Kaplan–Mayer curves were used to assess the predictive value of 2 vascular phenotypes i.e. (atherosclerotic or retinopathy phenotypes), in order to identify potential relevant clinical features that may help risk stratification.

The analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, USA). A P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics according to ATS or retinopathy scores

Patient demographics are summarized in Table 1. Nearly half of patients received at least one antihypertensive treatment at baseline: thiazide diuretics (37%), centrally acting drugs (32%), anti-aldosterone (15%) and beta-blockers (2%). The risk profile of patients rose with increasing ATS score. In addition, the more the calcifications, the higher the PP and MBP levels. Similarly, the risk profile markedly increased with the presence of retinopathy (Table S1).

3.2. Relationship of outcomes with pressure, ATS and retinopathy scores

During the 30-year follow-up period, 90 fatal MI were documented, 80 fatal strokes, 77 renal related deaths, 129 coronary related deaths, and 100 cerebrovascular deaths. All pressures and vascular variables of interest were associated with each outcome (Tables S2 and S3). Most other classical risk factors were also found associated with outcomes (data not shown).

Multivariable analyses are shown in Table 2 and S4. ATS was strongly associated with fatal MI and with coronary related deaths whereas it was not associated with fatal stroke or cerebrovascular related deaths. A marginal association was found with renal related deaths. PP showed the very same associations as ATS with coronary outcomes but not with cerebrovascular ones. This effect was

Table 1
Baseline characteristics according to the three grades of aortic atherosclerosis.

Aortic atherosclerosis grade					
Characteristics	All grades	ATS 0	ATS 1	ATS 2	P value
Number of subjects	1031	715	191	125	
Demographic characteristics					
Age (years)	44 ± 11	41 ± 10	49 ± 8	52 ± 9	<0.001
Women/Men (%)	38.2/61.8	40.4/59.6	42.4/57.6	19.2/80.8	<0.001
Smokers (%)	52.5	47.3	52.4	82.3	<0.001
BMI (kg/m^2)	25.0 (22.5–28.1)	25.2 (22.2–28.2)	25.2 (23.4–28.3)	24.5 (22.6–27.1)	0.082
Cardiac parameters					
Heart rate (bpm)	80 ± 13	80 ± 13	80 ± 13	78 ± 13	0.496
SBP (mmHg)	182 (165–210)	180 (162–202)	190 (170–220)	200 (175–222)	<0.001
DBP (mmHg)	111 ± 19	110 ± 20	114 ± 19	112 ± 17	0.020
MBP (mmHg)	136 ± 22	134 ± 21	139 ± 22	141 ± 20	<0.001
PP (mmHg)	75 (60–90)	71 (60–85)	78 (63–95)	88 (65–110)	<0.001
Medical history					
Diabetes (%)	15.3	12.7	22.0	20.0	0.002
History of HF (%)	12.7	9.4	15.7	27.2	<0.001
CAD (%)	6.4	3.9	11.0	13.6	<0.001
PAD (%)	3.3	0.6	2.6	20.0	<0.001
Stroke (%)	11.2	8.4	16.8	18.4	<0.001
Treatment of HT (%)	49.4	44.8	56.5	64.8	<0.001
Biochemical variables					
eGFR (mL/min/1.73 m^2)	81 (64–97)	84 (68–102)	76 (62–92)	71 (48–88)	<0.001
Albuminuria (%)	15.1	11.7	17.8	30.4	<0.001
Total cholesterol (g/L)	2.2 (2.0–2.5)	2.2 (1.9–2.4)	2.3 (2.0–2.6)	2.4 (2.1–2.6)	<0.001

Unless otherwise stated, data are means ± SDs or medians (interquartile ranges). BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PP: pulse pressure; HF: heart failure; eGFR: estimated glomerular filtration rate; bpm: beats per minutes; CAD: coronary artery disease; PAD: peripheral artery disease; HT: hypertension; ATS 0: absence of aortic atherosclerosis; ATS 1: mild aortic atherosclerosis, ATS 2: moderate or severe aortic atherosclerosis.

additive to that of ATS. MBP was only associated with fatal stroke (Table 2) and cerebrovascular related deaths, as was retinopathy (Table S4).

3.3. Baseline characteristics of atherosclerotic and/or retinopathy phenotypes

In this portion of the analysis, different vascular phenotypes were examined, namely severe atherosclerosis (ATS score = 2), severe retinopathy (HRIII-IV) as well as both or none of the latter (Table S5).

There was limited overlap between atherosclerotic and retinopathy phenotypes, with only 31 patients exhibiting both. The four phenotypes were significantly different with regard to age, gender, smoking, body mass index, cardiac parameters, medical history, renal function and total cholesterol level.

3.4. Associations of atherosclerotic or retinopathy phenotypes with outcomes

The impact of atherosclerotic or retinopathy phenotype on coronary, cerebrovascular and renal related mortalities was tested by Kaplan Mayer curves (Figs. 1 and 2). The survival probabilities of patients with atherosclerotic phenotype were worse than those with retinopathy phenotype with regard to fatal MI and coronary related deaths. On the contrary, patients with retinopathy

Table 2
Multivariate cox regression analyses.

	Fatal myocardial infarction		Fatal stroke		Renal related death	
	HR [95% CI]	P value	HR [95% CI]	P value	HR [95% CI]	P value
Multivariate model 1						
MBP (+10 mmHg)	1.05 [0.95–1.16]	0.356	1.21 [1.09–1.35]	<0.001	1.16 [1.04–1.29]	0.010
ATS 1 vs. ATS 0	1.56 [0.92–2.64]	0.100	1.30 [0.78–2.19]	0.314	1.16 [0.65–2.09]	0.615
ATS 2 vs. ATS 0	2.26 [1.21–4.23]	0.011	0.85 [0.39–1.86]	0.684	1.86 [0.95–3.66]	0.072
Multivariate model 2						
PP (+10 mmHg)	1.10 [1.00–1.19]	0.040	1.07 [0.98–1.17]	0.149	1.07 [0.98–1.17]	0.110
ATS 1 vs. ATS 0	1.57 [0.93–2.65]	0.092	1.45 [0.87–2.42]	0.155	1.29 [0.72–2.33]	0.389
ATS 2 vs. ATS 0	2.14 [1.14–4.04]	0.018	0.79 [0.36–1.75]	0.565	1.78 [0.90–3.53]	0.097
Multivariate model 3						
MBP (+10 mmHg)	1.05 [0.94–1.18]	0.390	1.17 [1.04–1.31]	0.008	1.13 [1.01–1.28]	0.048
Retinopathy I/II vs. 0	1.42 [0.80–2.51]	0.226	1.65 [0.81–3.37]	0.171	1.02 [0.50–2.10]	0.948
Retinopathy III/IV vs. 0	1.05 [0.49–2.24]	0.905	2.29 [1.00–5.50]	0.050	1.22 [0.53–2.83]	0.636
Multivariate model 4						
PP (+10 mmHg)	1.12 [1.02–1.23]	0.017	1.02 [0.93–1.13]	0.634	1.06 [0.97–1.16]	0.223
Retinopathy I/II vs. 0	1.47 [0.84–2.55]	0.177	1.99 [0.99–4.00]	0.054	1.19 [0.59–2.40]	0.621
Retinopathy III/IV vs. 0	0.98 [0.48–2.01]	0.952	3.35 [1.52–7.38]	0.003	1.59 [0.74–3.44]	0.223

HR, hazard ratio; MBP, mean blood pressure; ATS, atherosclerosis score; PP, pulse pressure.
All models adjusted for age, gender, previous cardiovascular diseases, glomerular filtration rate, body mass index, diabetes, smoking status and antihypertensive treatment. In addition to these variables, other specific variables were included: MBP and ATS for model 1, PP and ATS for model 2, MBP and retinopathy for model 3, PP and retinopathy for model 4.

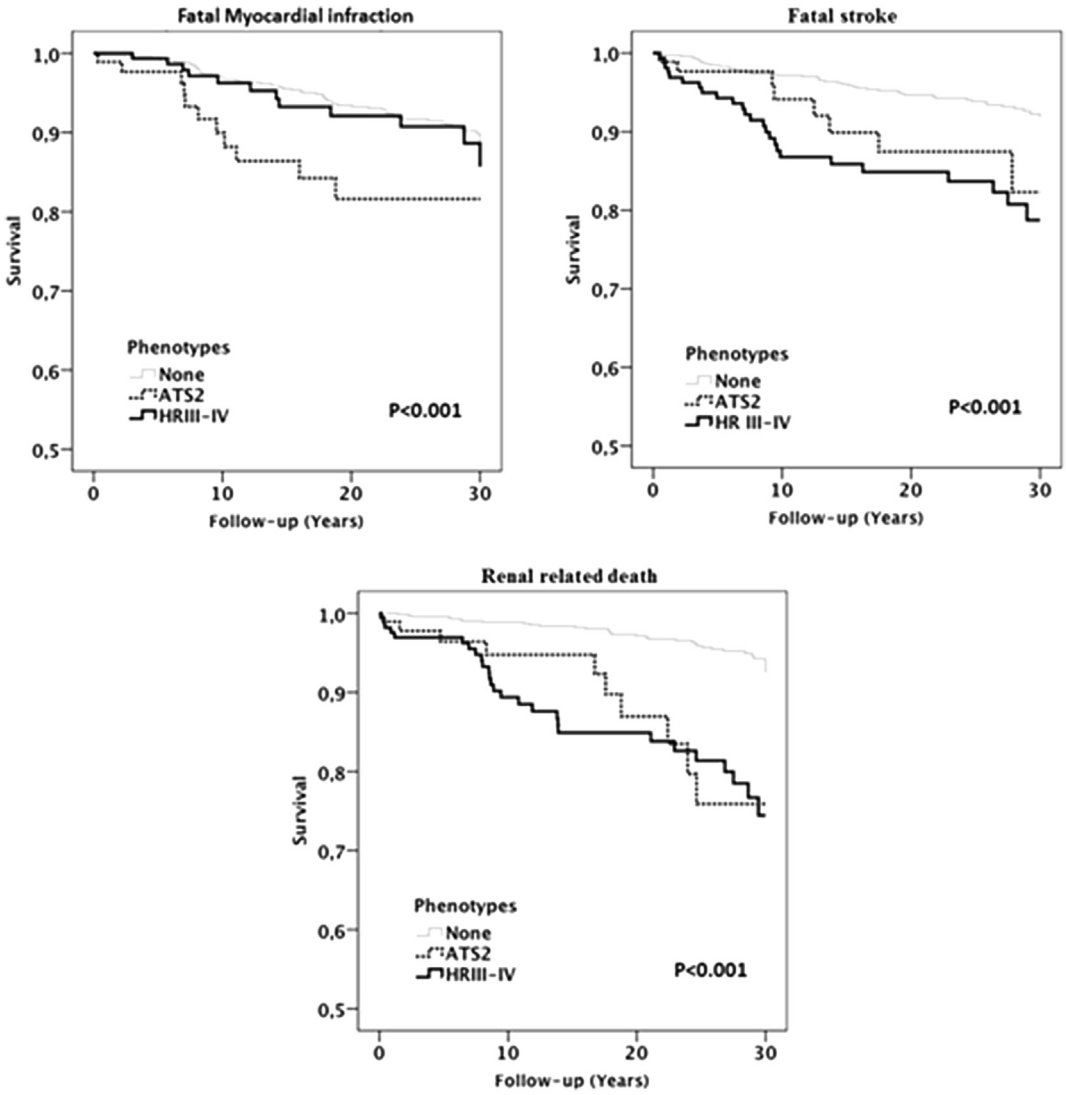

Fig. 1. Kaplan–Meier survival curves according to atherosclerotic or retinopathy phenotype on coronary- and cerebrovascular-related mortalities. ATS 2, moderate or severe atherosclerosis; HRIII-IV, hypertensive retinopathy grade III–IV.

phenotype had has higher mortality by fatal stroke or cerebrovascular related deaths than those with atherosclerotic phenotype. The situation was less straightforward for renal related deaths, with both phenotypes being associated with the latter.

4. Discussion

The present study thoroughly investigated the relationship between the various components of both vascular damage and BP on specific cardiovascular endpoints. Although hypertension is a risk factor for MI, aortic remodeling appeared to be more directly associated with MI than BP levels within hypertensive patients. This represents a major difference with the 2 other vascular endpoints, i.e. those related to brain and kidney, which were mainly associated with BP levels and to small vessel disease (for the brain). This could explain previous reports in which BP lowering did not achieve the same preventive efficacy for coronary events as that observed for cerebral or renal events [5]. These findings also provide two interesting stratifying clinical features that may help in implementing optimal preventive strategies.

MI and stroke are associated with important disabilities and represent an enormous health burden worldwide, which makes prevention an absolute priority for all health care systems. Improving the understanding of the pathophysiology of these diseases beyond the simple BP effect is critical in implementing new preventive strategies as well as optimizing the use of those currently available. Evidences from the literature suggest that coronary events, albeit clearly triggered by hypertension, do not share the same relationship with BP as other cardiovascular events such as stroke [5]. Taking into account vessel dynamics is probably critical in understanding this relationship coupled to the fact that small and large vessels, despite their permanent cross-talk [8], likely play a different role in coronary, cerebrovascular and renal damages. Nevertheless, the BP/vascular interaction on the risk of these different cardiovascular endpoints has not been clearly addressed within the same study and these outcomes are moreover typically merged within a single “cardiovascular morbi-mortality endpoint”.

4.1. Determinants of coronary mortality

Coronary epicardic vessels are in close proximity to the aorta

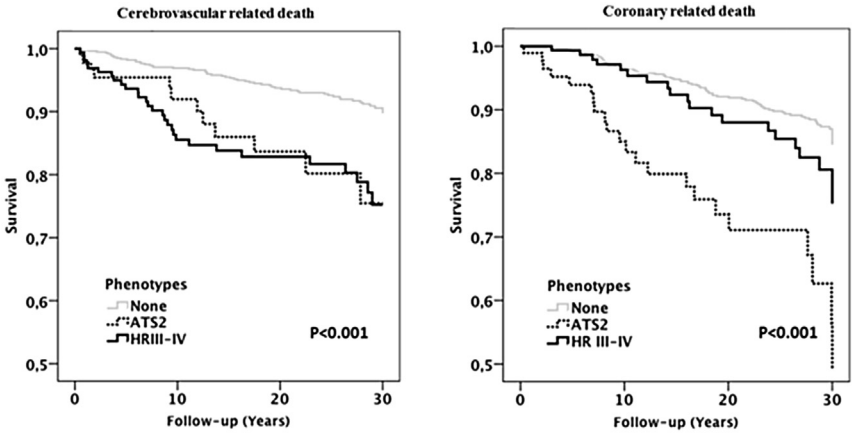

Fig. 2. Kaplan–Meier survival curves for cerebrovascular death and coronary related death. ATS 2, moderate or severe atherosclerosis, HRIII-IV, hypertensive retinopathy grade III–IV.

and are thus directly affected by aortic pulsatility. In addition, they have an important role in buffering the reversed systolic flow from small intramuscular (intramyocardial) vessels [16]. Our data show that both ATS/PP are tightly linked to the risk of MI and more generally to the risk of death by coronary diseases. ATS may of course reflect the atherosclerotic burden at the level of the coronary tree thus explaining its link with MI. However, ATS may also reflect a specific role of aortic stiffening on coronary events. Indeed, previous studies have shown an association between aortic calcifications and even aortic atherosclerosis with increased stiffness [17,18] and it is likely that the ATS score observed herein is associated with stiffening in accordance with its association with PP. Interestingly, Aboyans et al. reported a poorer prognosis when aortic atherosclerosis was proximal (i.e. at the aortic level) than distal, thus suggesting a specific pathological mechanism that may indeed be due to its consequences on stiffening [19]. This latter hypothesis is congruent with the present results since in addition to ATS, PP (which is an accepted surrogate of stiffness) was also a predictor of the risk of MI. This is also in accordance with a recent meta-analysis confirming that PWV was a strong predictor of coronary heart disease [13]. MI is a somewhat homogenous disease related to plaque rupture at the level of large epicardic vessels whereas aortic stiffness is associated with coronary artery disease severity [20,21]. In addition, local coronary compliance assessed by IVUS may favor plaque rupture [22]. It is conceivable that this local compliance is closely entwined with aortic stiffness and thus represents the link between aortic stiffness and MI. Aortic stiffening may indeed lead to an increased pulsatility transmission to the proximal aspect of the coronary artery especially if coronary stiffness is increased thus moving the mismatch more distally at the level of the plaque and increasing cyclic stretch, thereby favoring plaque rupture [23]. In addition to being a marker of stiffness, increased central PP pressure also has a deleterious effect in terms of coronary perfusion by decreasing central DBP [24]. On the contrary, small vessel disease, i.e. retinopathy, was found not to be predictive of coronary related deaths. Current data regarding the predictive value of retinopathy on coronary events are rather scarce and somewhat inconclusive [25,26]. Finally, MBP level was not predictive of MI which explains that solely lowering BP did not achieve the expected preventive benefit on this outcome [5].

4.2. Determinants of cerebrovascular mortality

The picture with regard to stroke is exactly the opposite with the duo MBP/small vessel disease driving the outcome. Stroke is an heterogeneous condition which encompasses hemorrhagic and ischemic stroke mainly related to cardiac emboli, carotid plaque rupture, or small vessel disease [27]. Hypertension is a global risk factor of stroke and is specifically implicated in stroke related to small vessel disease, i.e. lacunar infarction and intracerebral hemorrhage. Indeed, cerebral small vessels are particularly exposed to sustained BP elevations which can be easily transmitted from the aorta to the low resistant cerebral vascular bed [28]. Pressure damages are mainly represented by loss of smooth muscle cells from the tunica media, deposition of fibro-hyaline material, narrowing of the lumen and thickening of the vessel wall [27]. Affected small arteries are then prone to rupture and thrombosis. Stroke related to small vessel disease are probably overrepresented in our cohort of severe hypertensive patients.

In our cohort, retinopathy is a predictive variable of fatal stroke. The association between retinopathy and stroke has been already described, particularly with small vessel disease related stroke [29,30]. Indeed, retinal circulation shares anatomical, physiological and embryological features with the cerebral circulation and suffers the same systemic damages related to hypertension [31,27].

Aortic atherosclerosis was not found here as a predictor of fatal stroke. Some studies have found an association between aortic stiffness and stroke, particularly lacunar infarction [32,33] but the evidence in favor of a predictive role of PWV on stroke is much less abundant than that for MI [34] with the situation often rendered complex by the fact that both endpoints are analyzed jointly in order to increase statistical power, hence precluding a precise analysis [35]. Henskens et al. [36] pointed out that an increased PWV was associated with cerebral small-vessel disease in hypertensive patients. Yet, PWV is not free from bias as a marker of stiffness since it is highly heart rate and pressure dependent [37,38]; thus it may be difficult to dissociate what is due to pressure to what is due to stiffness *per se*; it may be indeed a particular strength of our atherosclerosis parameter to provide an index of aortic remodeling which is pressure-independent. Henceforth, it is conceivable that aortic remodeling could predict plaque rupture in vessels close to the aorta (coronary and carotid arteries). On the contrary, in small vessels distal to the aorta, pulsatility is probably dampened by the numerous arterial branchings at which point the mean BP level becomes the prevailing factor.

4.3. Determinants of renal related-mortality

Renal failure also appeared mainly due to high BP in the present study. This outcome should be considered with caution however

since it likely encompassed several different situations including some patients under dialysis who died from a cardiac event. Nonetheless, while renal related deaths might not have been recorded properly in some instances, it is very unlikely that patients in whom death certificates mentioned "renal death" were not experiencing either end stage renal disease or acute renal failure. As a consequence, although this outcome might only capture part of the renal events, it represents a very stringent renal failure variable that, from our viewpoint, could be of great value and novelty. The predictive value of MBP regarding renal death observed herein was in accordance with available literature [4]. Atherosclerosis appears to play a moderate role while retinopathy was not predictive at all. This is entirely consistent with the fact that the renal circulation shares certain key features with the cerebral circulation; in particular it is also a torrential circulation, functioning at low resistance and thus particularly exposed to varying pressure levels. Our results are also consistent with the fact that arterial stiffness may also exert some role on renal disease progression as recently reviewed by Safar et al. [39]. This involvement may be conceptualized by the fact that renal vasculature is closer to the aorta as opposed to cerebral circulation and thus is more dependent on its stiffness than the latter.

Overall the results herein show that cerebrovascular and renal related deaths are mainly driven by mean BP while coronary mortality is mainly driven by aortic remodeling. Such findings may reconcile epidemiology and disease prevention. Being a major BP disease, stroke is efficiently prevented by anti-hypertensive treatment as shown years ago by Collins and Peto [5]. This is also the case for renal disease since all anti-hypertensive treatments share the same preventive efficacy on renal outcome [40]. This is of course no longer the case in overt nephropathy, particularly when associated with proteinuria. By contrast, MI is less efficiently prevented by lowering BP alone while treatments that have a vascular effect are usually more efficient [41].

5. Limitations

Although mortality was assessed in the present study, events adjudication relied on death certificates. This was probably accurate for fatal MI and fatal stroke but may have been less accurate for coronary and cerebrovascular related deaths. Nevertheless, the associations remained the same, in particularly regarding the "harmful duos" implicated. Another important aspect regarding the heterogeneity of the disease was the absence of type of stroke (i.e. ischemic vs. hemorrhagic). However, it should be noted that such homogeneity was also not addressed in many studies investigating the epidemiology of stroke and its relationship with aortic stiffness. Renal related deaths might also have been confounded by certain cardiac deaths that were not adequately coded.

No information was available regarding treatment during the follow-up period whereas it may have affected the outcome and its relationship with the vascular variables.

Finally, direct aortic stiffness was not assessed which precludes a firm conclusion. However, aortic calcifications and stiffness are intertwined, with PP reinforcing the consistency of the hypothesis.

This study has major strengths particularly the long duration of follow-up which allows gathering sufficient events to have the statistical power to address each event separately.

6. Clinical perspectives

In our study, we identified two clinical phenotypes that could be determined with a simple standardized hypertension workup including a fundoscopy and an evaluation of aortic remodeling

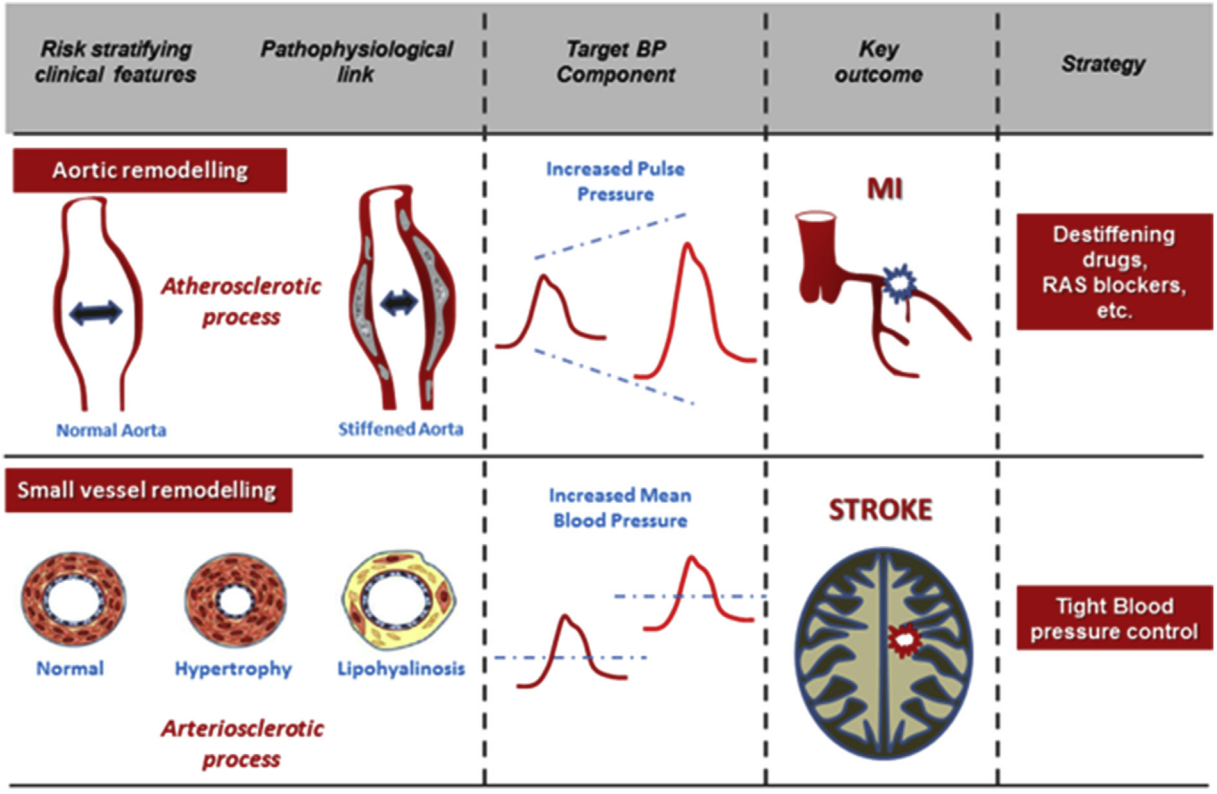

Fig. 3. Interaction of atherosclerotic and retinopathy phenotypes with outcomes and treatment strategy.

(whether it is anatomical or functional should be tested with modern approaches). Fig. 3 summarizes how each BP component interacts with atherosclerotic and retinopathy (small vessel disease) phenotypes in triggering different outcomes. This simplified conceptual framework paves the way for a more rational preventive strategy aimed at decreasing mean BP levels for stroke (and probably renal failure) in patients with a "retinopathy phenotype" and to promote new destiffening drugs for MI in patients with an "atherosclerosis phenotype".

This is consistent with previously-suggested differential BP targets. With respect to rather "pure" BP disease such as brain and kidney injuries, an aggressive BP intervention with low BP target is widely recommended and has documented efficacy [4]. For MI prevention, a standard "target" is warranted while a lower target may be hazardous.

Finally, with regard to choice of drugs, the use of calcium channel blockers or thiazide may be the first choice in the retinopathy phenotype because of their superiority on stroke prevention. On the contrary, in less severe hypertensive but atherosclerotic patients, MI has to be efficiently prevented. While awaiting the availability of destiffening drugs [42], RAS blockers currently represent the first line drug [7]. This of course should be tested in large prospective trial.

This framework, if proven useful in other studies - mostly post-hoc analysis of clinical trials - may open a new avenue for personalized cardiovascular prevention in the field of hypertension.

7. Conclusions

Although tightly related to hypertension, MI, stroke and renal related deaths obey different pathophysiological mechanisms implying, in turn, various vascular remodeling, BP or both. This is likely explained by the specificity of each organ in terms of vascular features and circulatory physiology. It prompts us to seek vascular strategies to maximize coronary prevention in patients with an "atherosclerosis phenotype" whereas a strategy focused on MBP control might be more appropriate in patients with a "retinopathy phenotype". This simple clinical framework could open a prospective avenue for personalized cardiovascular prevention in the field of hypertension.

Authors disclosure

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.09.011.

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b) Rigidité vasculaire, mortalité et récidive d'infarctus du myocarde post syndrome coronaire aigu

Prognostic value of pulse pressure after an acute coronary syndrome

Harbaoui B, Nanchen D, Lantelme P, Gencer B, Heg D, Klingenderg R, Raber L, Carballo D, Matter CM, Windecker S, Mach F, Rodondi N, Eeckhout E, Monney P, Antiochos P, Fournier S, Luscher T, Muller O. **Atherosclerosis**, doi.org/10.1016/j.atherosclerosis.2018.07.013.

Hypothèse : Nous avons montré que la rigidité aortique estimée par la mesure de la pression pulsée était étroitement associée aux évènements coronaires sur une population de patients hypertendus. Nous émettons l'hypothèse qu'elle pourrait également prédire les évènements cardiovasculaires notamment les récidives d'infarctus du myocarde chez des patients hospitalisés pour syndrome coronaire aigu.

Objectif : Déterminer l'impact pronostique de la pression pulsée sur la mortalité totale, la récidive d'infarctus du myocarde et la survenue d'accident vasculaire cérébraux durant la première année suivant un syndrome coronaire aigu.

Population, Méthodes : Etude menée sur une cohorte prospective de patients hospitalisés pour syndrome coronaire aigu dans 4 hôpitaux universitaires suisses.

Les patients sans pression disponible, avec choc cardiogénique ou insuffisance cardiaque avancée étaient exclus. Une analyse de régression logistique de Cox a été réalisée afin de déterminer l'association entre la pression pulsée et les évènements. Les modèles multivariés étaient ajustés sur des variables hémodynamiques, des facteurs confondant cardiovasculaires et extracardiovasculaires.

Les outcomes considérés étaient les suivants ;

- Composite de mortalité totale, récidive d'infarctus du myocarde et accident vasculaire cérébraux puis chacun des événements pris séparément.

Résultats : 5070 patients ont été inclus, l'analyse multivariée confirme l'impact pronostique de la pression pulsée, pour le critère composite, pour la mortalité, la récidive d'infarctus du myocarde mais par pour les accidents vasculaires cérébraux. La figure 2 illustre la relation entre pression pulsée et évènements.

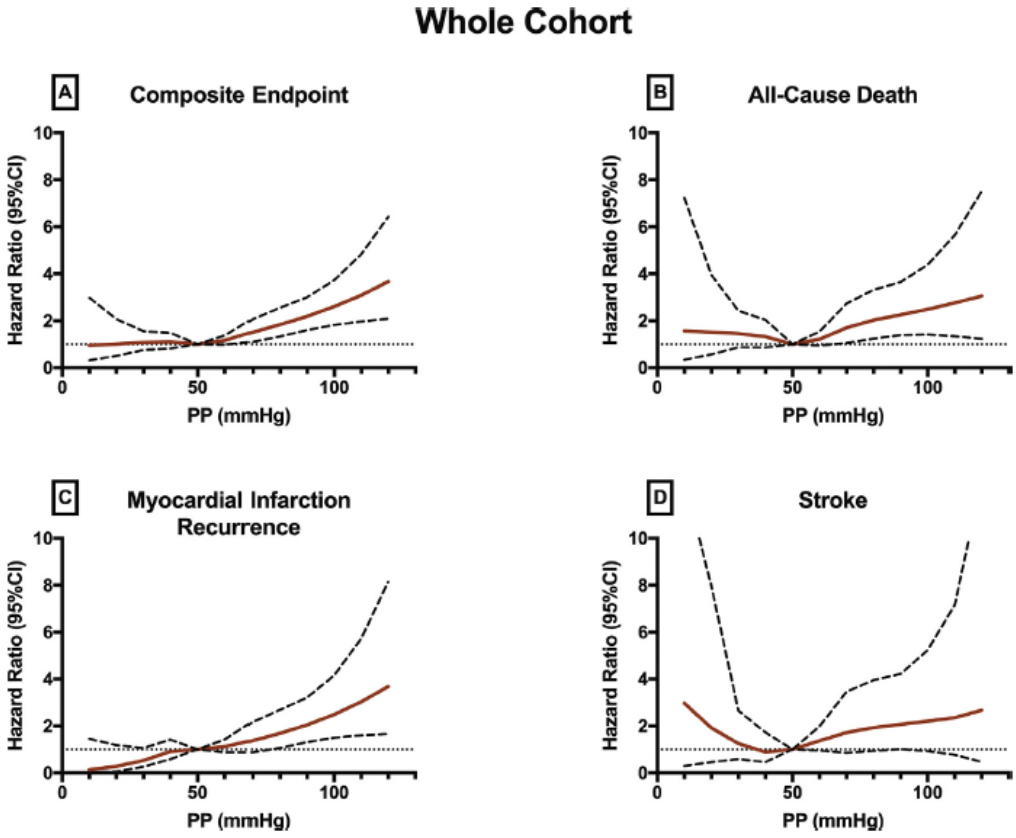

Fig 2. Continuous relationships between PP and outcomes.

Figure 2 : Relation entre pression pulsée et événements

Conclusion, discussion : La pression pulsée mesurée à l'admission chez les patients qui présentent un syndrome coronaire aigu est associée de façon indépendante à la mortalité et à la survenue d'infarctus du myocarde à 1 an. La pression pulsée pourrait être une cible

thérapeutique pour la prévention secondaire après un syndrome coronaire aigu. Elle pourrait également nous aider à mieux comprendre la genèse de l'infarctus du myocarde.

Le lien entre rigidité vasculaire et mortalité coronaire pourrait résider dans l'interaction (mismatch) entre rigidité globale et rigidité locale *ie* coronaire, ou bien dans des zones de différences de rigidité au niveau même du vaisseau coronaire (13). Malheureusement il n'existe pas de moyen d'évaluer la rigidité coronaire en pratique clinique. Les limites de cette étude résident essentiellement dans l'absence de marqueur direct de rigidité type VOP carotido-fémorale.

Perspectives : La pression pulsée et la rigidité aortique pourraient représenter des cibles thérapeutiques spécifiques pour diminuer la survenue d'évènements cardiaques. La caractérisation de la rigidité locale, notamment coronaire pourrait permettre d'améliorer la compréhension du processus physiopathologique (14). En effet, des études élastographiques et histopathologiques ont souligné que les complications de plaque survenaient préférentiellement au niveau des zones de « compliance mismatch » (15,16).

Ces travaux épidémiologiques ont a conduit au développement d'une technique de mesure de la rigidité coronaire.

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Prognostic value of pulse pressure after an acute coronary syndrome

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ABSTRACT

Background and aims: Pulse pressure (PP) is a surrogate of aortic stiffness (AS) easily obtainable. The link between AS and cardio-vascular disease is documented, however, data regarding acute coronary syndrome (ACS) patients are scarce and contradictory. We aimed to assess the prognostic value of PP measured at admission, with regard to major adverse outcomes (all-cause mortality, recurrence of MI, and stroke), during the first year following an acute coronary syndrome (ACS).

Methods: The SPUM–ACS project is a prospective cohort study of patients with ACS conducted in 4 Swiss University hospitals. Patients with no PP at admission or with severe clinical heart failure or cardiogenic shock were excluded. Cox regression analyses were performed to determine associations between PP and outcomes (all-cause mortality, recurrence of myocardial infarction (MI), and stroke). Three multivariate Cox regression models were adjusted for hemodynamic, cardiovascular, and non-cardiovascular confounders, added successively.

Results: Of 5635 eligible patients, 5070 met the inclusion criteria. Mean patient age was 63 years (range: 54–72), 79.6% were male, and mean blood pressure and PP were 93.9 ± 15.6 and 54 ± 17 mmHg, respectively. Multivariate analyses confirmed the prognostic significance of PP for each 10-mmHg increase for the composite endpoint, hazard ratio (HR) 1.126 [1.051–1.206], $p = 0.001$; all-cause mortality, HR1.129 [1.013–1.260], $p = 0.029$; and recurrence of MI, HR1.206 [1.102–1.320], $p < 0.001$; but not for stroke, HR1.014[0.853–1.205].

Conclusions: PP measured at admission is a strong, independent prognostic marker predicting mortality and recurrence of MI after ACS. PP should be considered for the management of secondary prevention.

1. Introduction

High pulse pressure (PP) is a powerful, independent predictor of outcome in various populations of patients. However, there is a gap in knowledge regarding PP and patients with an acute coronary syndrome (ACS). PP data on patients with an acute coronary syndrome (ACS) are scarce, contradictory and outdated. Blood pressure (BP) is a rather complex variable, which can be dissociated into a steady state component (mean BP) and a pulsatile one (pulse pressure). PP is defined as the difference between systolic and diastolic BP. Mean BP and PP have different physiological meanings. PP is considered a surrogate for aortic stiffness (AS), i.e. the higher the PP, the stiffer the aorta. However, PP also reflects cardiac

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performance and stroke volume. This dual significance may be particularly relevant in the context of ACS as it could explain discrepancies in the current literature and provide a unique clinical tool to help stratify risk after diagnosis of ACS. In particular, high PP may play a role in triggering plaque complications at the coronary and cerebral levels [1]. On the other hand, a low PP may help identify patients at risk due to severe left ventricular dysfunction. Currently, clinicians caring for patients with ACS hardly perform PP measurements because the prognostic information conveyed at the time of ACS is unclear. Thus, the present study aimed to assess, in a prospective large real world ACS registry, whether PP measured at admission would predict a one-year composite endpoint encompassing all-cause mortality, recurrence of myocardial infarction (MI), and stroke.

2. Materials and methods

2.1. Study population

The SPUM–ACS study (Special Program University Medicine–Acute Coronary Syndromes) is a prospective cohort study of consecutive ACS patients hospitalized in Switzerland. The study was designed to identify new determinants and consequences of coronary heart disease. Details concerning the SPUM–ACS study have been reported previously [2]. Briefly, all patients hospitalized with ACS in four Swiss university hospitals were encouraged to participate, with no exclusion criteria except severe physical disability, inability to give consent owing to dementia, and life expectancy of <1 year for non-cardiac reasons. Inclusion criteria were age ≥18 years, ST-segment elevation myocardial infarction (STEMI), non-ST-segment–elevation myocardial infarction, or unstable angina. A large proportion of patients received adequate discharge drug treatment [2]. In the present study, patients with no PP at admission or with severe clinical heart failure or cardiogenic shock were excluded.

2.2. Pulse pressure

PP was defined as systolic BP (SBP) minus diastolic BP (DBP). SBP and DBP were measured using a brachial sphygmomanometer at first assessment in an emergency room. Mean BP was defined as [SBP + 2DBP]/3. A quality-control check of the number of BP readings ending in zero showed that 23.43% of SBP and 23.41% of DBP readings did so (20% expected) [3], which compares favorably to other studies in the setting of hypertension and to a recent study on PP [4].

2.3. Clinical outcomes

Occurrences of clinical events during the first year after an index event were obtained by questioning participants by telephone 30 days after discharge and at a face-to-face clinical consultation one year after ACS. The composite endpoint was defined as all-cause mortality (cardiac, vascular, or non-cardiovascular death), recurrence of MI (using the universal definition of MI [5]), and stroke. To account for potential pathophysiological differences in event types, PP prognostic value was measured on each outcome separately (secondary outcomes). A panel of three certified cardiologists serving as independent experts, blinded to BP values, adjudicated on all the endpoints used in this analysis.

2.4. Covariates

Hypertension was defined as SBP ≥140 mmHg, DBP ≥90, or use of BP lowering drugs. Smoking status was defined as current, former, or never. Diabetes mellitus was either self-reported or diagnosed from the use of antihyperglycemic medication or a hemoglobin A1c level ≥6.5% at admission. Dyslipidemia was defined as a total cholesterol level >5 mmol/l or use of any lipid-lowering drug.

2.5. Statistical analysis

Continuous variables are presented as means and standard deviation; categorical variables as counts and percentages. PP was considered as either a continuous or categorical variable. Intervals of 10 mmHg were used to define categories of PP: < 35 mmHg, 36–45 mmHg, 46–55 mmHg, 56–65 mmHg, 66–75 mmHg, and >75 mmHg. Patients' characteristics in each PP category were compared using p for trend.

Cubic splines and multivariable Cox proportional hazard models were built to assess associations between PP and outcomes. HRs and their 95% CIs were plotted, with 50 mmHg PP as a reference, to graphically represent relationships between PP and outcomes. Plotted HRs were based on the univariate Cox proportional hazard model with a restricted cubic spline transformation of PP using knots at 30, 42, 52, 63, and 87 mmHg. For Cox analysis, three incremental models were constructed, adding potential confounders known to influence PP and prognosis after a diagnosis of ACS. Additionally, Model 1 was adjusted for hemodynamic variables, *i.e.* mean BP, heart rate, and left ventricular ejection fraction (LVEF). Model 2 included Model 1 plus cardiovascular variables, *i.e.* diabetes, hypertension, age, sex, dyslipidemia, smoking, history of coronary artery disease, vascular disease (peripheral vascular disease or stroke), type of MI, Killip class, type of revascularization, and medication using statins. Model 3 included potential non-cardiovascular confounders, *i.e.* renal function and history of malignancy.

Based on previous works [4], the statistical interaction terms between PP and sex, age, LVEF, renal function, and type of ACS were tested for each outcome. Interactions with a p-value < 0.05 were retested in each appropriate subgroup. Exploratory analysis only found one significant interaction: between PP and LVEF, for all-cause mortality, $p = 0.03$.

Further unadjusted and fully adjusted cox regression analyses were performed considering PP as a categorical variable.

Additional analysis was performed to evaluate whether the inclusion of PP on top of a fully adjusted model helps reclassify participants into categories of predicted outcomes risk. Using the cut-off risk categories of <5%, 5–10%, and ≥10%, we assessed the categorical net reclassification improvement (NRI) as well as the integrated discrimination improvement (IDI), which integrates the NRI over all possible cutoffs of predicted risk [6,7].

2.6. Further sensitivity analyses were performed

- SBP and DBP were tested in turn, to replace mean BP in the multivariate models.
- In a subset of 3854 patients with an available GRACE score, this was added to Cox models to replace appropriate variables.
- Additional adjustment was performed on peak creatine kinase MB (CKMB) in a subset of 2324 patients in whom the dosage was available.

Finally, Kaplan–Meier representations of each outcome were built considering the lowest and highest PP groups according to LVEF phenotypes, *i.e.* ≤ 40% or not.

All hypothesis tests were two-sided, and the significance level was set at 5%. Statistical analyses were performed using SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, New

York) and STATA statistical software (Version 14, STATA Corp, College Station, TX, USA). Figures were generated using Graphpad Prism v.6.0d (Graphpad Software).

2.7. Ethics statement

The study was approved by each university hospital's medical ethics committee (Lausanne, Geneva, Bern, and Zurich). All participants gave written informed consent.

3. Results

3.1. Study participants' characteristics

Of 5635 patients hospitalized with ACS, 418 were excluded because they had been classified as Killip class 4 (133) or their Killip class was missing (285), and 147 were excluded as their PP at admission was missing. Final analysis therefore involved 5070 patients. Supplementary Table 1 summarizes patients characteristics according to PP groups. Mean age was 63 years (range: 54–72), 79.6% were men, and 52.7% presented with a STEMI. Mean PP was 54.2 ± 17.5 mmHg, and Supplementary Table 2 summarizes the associated variables.

3.2. Association of PP and outcomes: univariate analysis

One year after discharge, 337 patients (6.6%) had experienced the composite endpoint, 155 (3.1%) had died, 151 (3%) had a recurrent MI, and 68 (1.3%) had had a stroke. Fig. 1 shows rates of events according to the PP group. Rates of events for the composite endpoint and all-cause mortality were highest in both the lowest and highest PP groups. This J-shaped trend was not observed for recurrent MI as the rate of events increased linearly across PP subgroups. There was no clear trend for stroke. Supplementary Figs. 1 and 2 show rates of events according to PP groups stratified by LVEF. The curvilinear trend was still observed for the composite endpoint and all-cause mortality in cases where LVEF ≤40% but not in cases where LVEF >40%. All other secondary endpoints displayed the same trends, whatever the LVEF.

Fig. 2 and Supplementary Fig. 3 show associations between PP and outcomes assessed using cubic splines (see methods section). A non-linear J-shaped trend was observed for the composite endpoint and mortality. By contrast, the relationship was rather linear for recurrent MI. The risks of experiencing each endpoint increased markedly for PP above 70 mmHg. When considering only patients with LVEF >40%, the excess hazard associated with low PP regarding the composite endpoint and all-cause mortality vanished (Supplementary Fig. 3).

3.3. Association of PP and outcomes: multivariate analysis

Table 1 summarizes the multivariate Cox analyses for associations between PP and outcomes. All the multivariate models showed an increased HR of experiencing the composite outcome as PP increased. In particular, for each 10 mmHg increase in PP in the fully adjusted model, the composite endpoint HR was 1.126 (95% CI [1.051–1.206], $p = 0.001$). This was also the case for all-cause mortality with a HR 1.129 (95% CI [1.013–1.260], $p = 0.029$), and

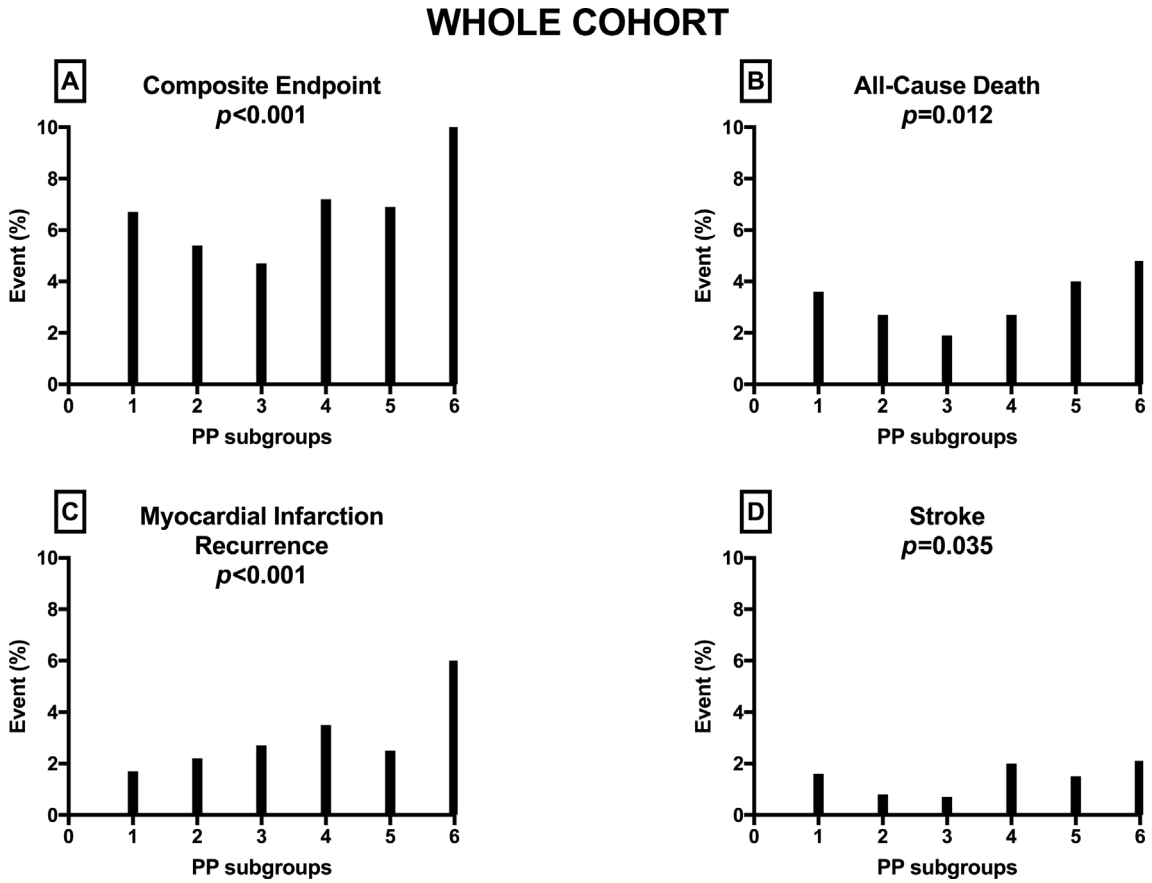

Fig. 1. Relationship between outcomes and PP groups.
The PP subgroups shown are: (1) <35 mmHg; (2); 36–45 mmHg; (3) 46–55 mmHg; (4) 56–65 mmHg; (5) 66–75 mmHg; and (6) >75 mmHg.

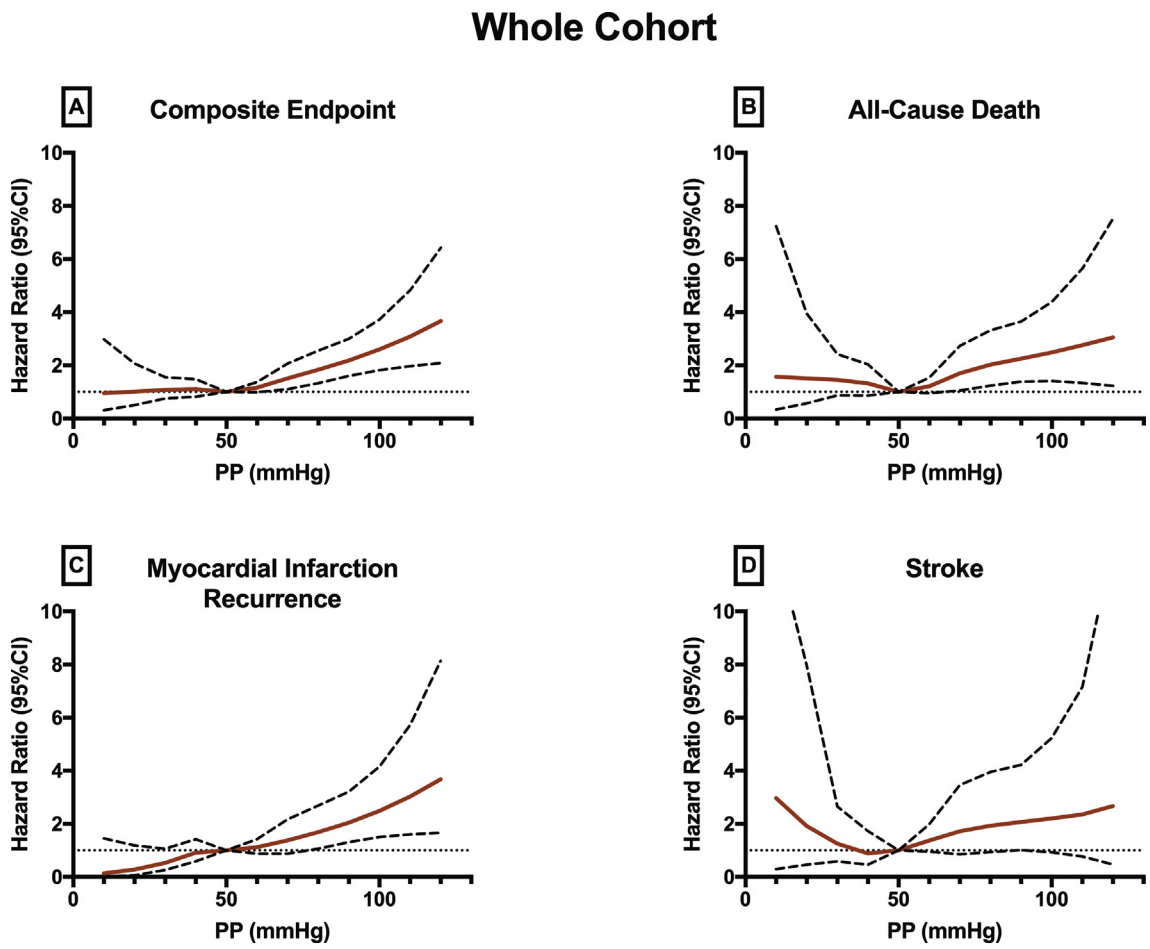

Fig. 2. Continuous relationships between PP and outcomes.

Table 1
Unadjusted and adjusted Cox models.

	Composite MIR, stroke, mortality		MIR		Stroke		All-cause mortality	
	HR [95% CI]	*p*	HR [95% CI]	*p*	HR [95% CI]	*p*	HR [95% CI]	*p*
PP +10 mmHg[a]	1.146 [1.084–1.212]	< 0.001	1.207 [1.114–1.308]	< 0.001	1.001 [1.012–1.285]	0.048	1.101 [1.012–1.198]	0.025
PP +10 mmHg[b]	1.241 [1.165–1.321]	< 0.001	1.213 [1.113–1.322]	< 0.001	1.173 [1.032–1.332]	0.015	1.267 [1.156–1.388]	< 0.001
PP +10 mmHg[c]	1.126 [1.053–1.205]	0.001	1.206 [1.103–1.320]	< 0.001	1.017 [0.857–1.206]	0.850	1.121 [1.008–1.247]	0.036
PP +10 mmHg[d]	1.126 [1.051–1.206]	0.001	1.206 [1.102–1.320]	< 0.001	1.014 [0.853–1.205]	0.877	1.129 [1.013–1.260]	0.029

MI: recurrence of myocardial infarction; HR, hazard ratio; CI, confidence interval; PP, pulse pressure.
[a] Unadjusted.
[b] Model 1, adjusted on hemodynamic parameters: heart rate, mean blood pressure, left ventricle ejection fraction.
[c] Model 2, adjusted on Model 1 plus CARDIOVASCULAR variables: cardiovascular risk factors *i.e.* age, sex, diabetes, hypertension, smoking, dyslipidemia, coronary artery disease, vascular disease (history of peripheral vascular disease or stroke), type of acute coronary syndrome, Killip class, modality of revascularization, statin medication.
[d] Model 3, adjusted on Model 2 plus non-CARDIOVASCULAR comorbidity: renal function (estimated glomerular filtration rate) and history of malignancy.

for the recurrent MI with one of 1.206 (95% CI [1.102–1.320], $p < 0.001$). After adjustment, PP was no longer predictive of stroke (HR 1.014, 95% CI [0.853–1.205], $p = 0.877$).

When only considering patients with LVEF >40%, PP remained a strong predictor of the composite endpoint, all-cause mortality, and recurrence of MI in multivariate analysis (Supplementary Table 3). Again, it did not predict stroke.

3.4. Association of PP considered as a categorical variable and outcomes

Results remained the same when considering PP as a categorical variable in both cox regression main analysis (Supplementary Table 4) and LVEF stratified analysis (Supplementary Table 5). Patients belonging to group 3 (46–55 mmHg) were at lower risk compared to others for all-cause mortality. Regarding recurrence of MI, patients belonging to group 6 (>75 mmHg) were at higher risk compared to all others groups.

3.5. Improvement in risk stratification by PP

Supplementary Table 6 summarizes both NRI and IDI values according to outcomes. Regarding the composite endpoint, an improvement was noticed with the IDI but not with the NRI. The

improvement of reclassification for recurrence of MI was of borderline significance for NRI, NRI = 7.1%, $p = 0.065$ and significant for IDI, IDI = 0.44, $p = 0.005$. For the other outcomes, the NRI an IDI were not significant.

3.6. Sensitivity analysis

Replacing mean BP by DBP or SBP did not change the results, with PP remaining a strong predictor of the composite endpoint, all-cause mortality, and recurrent MI in multivariate models with a composite endpoint HR of 1.126 (95% CI [1.051–1.206], $p = 0.001$) for all-cause mortality with a HR of 1.129 (95% CI [1.013–1.260], $p = 0.029$) and for recurrent MI with one of 1.206 (95% CI [1.102–1.320], $p < 0.001$). Other blood pressure variables predicted none of these outcomes in fully adjusted model.

When using the Grace Score (instead of age, heart rate, mean BP, Killip, and eGFR only) in the Cox models, PP (+10 mmHg) remained a strong independent predictor of the composite outcome, with an HR of 1.201 (95% CI [1.118–1.291], $p < 0.001$). This was also the case for all-cause mortality with one of 1.307 (95% CI [1.170–1.469], $p < 0.001$) and for recurrent MI with one of 1.187 (95% CI [1.078–.308], $p = 0.001$). Again, PP was no longer predictive of stroke.

When further adding peak CKMB to the fully adjusted model, results remained similar: HR 1.164 95% CI [1.058–1.281], $p = 0.002$ for composite endpoint; HR 1.193 95% CI [1.039–1.370], $p = 0.01$ for recurrence of MI; HR 0.940 95% CI [0.715–1.235], $p = 0.6$ for stroke; HR 1.238 95% CI [1.084–1.414], $p = 0.002$ for all cause death.

3.7. Associations between PP and LVEF phenotypes and outcomes

The impact of low and high PP on low and high LVEF were illustrated for all endpoints using Kaplan–Meier curves. In patients with LVEF >40%, the high-PP phenotype was associated with a decreased event-free survival for all outcomes when compared to the low-PP phenotype, except for stroke. In patients with LVEF ≤40%, the high-PP phenotype was only associated with a decreased incidence of recurrent MI compared to the low-PP phenotype (Fig. 3).

4. Discussion

The present study is the first one to evaluate the prognostic value of PP at admission in a large contemporary ACS population receiving modern guideline-based management. Our study fulfills the research gap from previous studies published so far regarding the prognosis value of PP in the setting of ACS, and reinforces the results obtained in the reach registry regarding stable high-risk patients [4]. Here we for the first time show that this easily obtainable variable measured in the emergency room is a powerful predictor of all-cause mortality and recurrent MI. Of note, for every 10 mmHg increase in PP, there was a 13% increase in all-cause mortality and more than a 20% increase in recurrent MI. We also highlighted for the first time the critical role of LVEF in interpretation of PP in the setting of ACS.

Landmark studies on the general population [8], in hypertensives [9] and, more recently, in high-risk patients [4] have established aortic stiffness as a powerful, independent predictor of outcomes. Data in patients following ACS are scarce and contradictory [10–12]. Thus, the present study allows a gain in knowledge. Indeed, increased PP was unambiguously associated with mortality and cardiac morbid events, namely recurrent MI. Furthermore, the improvement in risk stratification analysis illustrates the strong and unique link that exists between PP and recurrence of MI. Previous studies in this patient population were potentially biased due to subgroups selection, outdated ACS management, and confounding factors [10–13]. In contrast, the present SPUM cohort is representative of current ACS guideline-based management, including revascularization and medical treatment. Furthermore, the extensive adjustments made using 3 multivariate models yielded very consistent results. Indeed, the prognostic value of PP remained valid across the entire LVEF spectrum, which is at variance with a SAVE Trial sub-study which concerned only patients with altered LVEF who did not receive modern evidence-based ACS management [10]. Thus, the present results, based on a particularly well-characterized large ACS population managed according to the most recent guidelines [2]with sufficient statistical power for an extensive adjustment of confounders, are likely to reflect todays ACS patients.

PP is more than a simple pressure variable; rather, it is primarily a variable that integrates several aspects of cardiovascular function, but mostly reflects aortic stiffness. Importantly, aortic stiffness and diastolic BP determine coronary perfusion pressure [14]; as such aortic stiffness is a strong determinant of fatal MI in patients with severe hypertension [15]. PP moreover integrates atherosclerotic burden, which is largely intertwined with aortic stiffness which is a reflection of vascular aging [16]. Whereas atherosclerosis may have an impact on the physical properties of arterial wall, aortic stiffness likely contributes to the occurrence and progression of atherosclerosis [16]. It is of note that increased PP was associated with the primary outcome and a recurrent MI within a relatively short period of time of around one year. This would suggest that aortic stiffness facilitates plaque rupture rather than atherosclerotic plaque progression. Indeed, increased cyclic stretch (which is associated with vascular stiffness) imposed on coronary plaques in the presence of high PP has been associated with plaque rupture [15,17].

The effect of high PP on mortality has been extensively documented in different patient populations and may be related to target organ damage and atherosclerotic burden [4,15,18]. Notably, we also observed a paradoxical excess risk of all-cause mortality with low PP, a finding which seemed rather specific and was markedly different from that observed for recurrent MI. These results also differ from those of observed in other studies, except for high-risk patients. Indeed, Steg et al. also reported a J-shaped relationship, although they were unable to explain their findings [4]. We would suggest that the J-shaped relationship is likely explained by the confounding effect of left ventricular performance on the relationship of PP and aortic stiffness. Indeed, PP not only depends on aortic stiffness, but also on ventricular stroke volume [19].In fact, in patients with a low LVEF, PP is no longer a marker of aortic stiffness [20,21]. In randomly selected ACS patients, as in the SPUM cohort, the prevalence of LV dysfunction is around 20%. This substantial contingent likely explained the J-shaped relationship to the primary endpoint and to mortality as it disappeared after the exclusion of patients with LVEF ≤40%. A statistical interaction with LVEF seemed very specific for mortality and did not persist with other outcomes. Here we for the first time report such relationship in a large real world cohort of patients with ACS and long-term follow up based on a comprehensive assessment of potential confounders. In line with our findings, Ma et al. found in a population of STEMI patients mainly treated by thrombolysis, that low PP was associated with an increased risk of short-term mortality, however LVEF wasn't available [11]. Other studies have also associated low PP with increased mortality [12,21], but these associations were probably largely driven by patients with cardiogenic shock or severely decompensated heart failure. To avoid these confounders, we excluded Killip class 4 patients with severe pump failure. Finally, low PP may reflect reverse causality and thus be a marker of frailer, sicker and older patients, thus identifying a subset with a

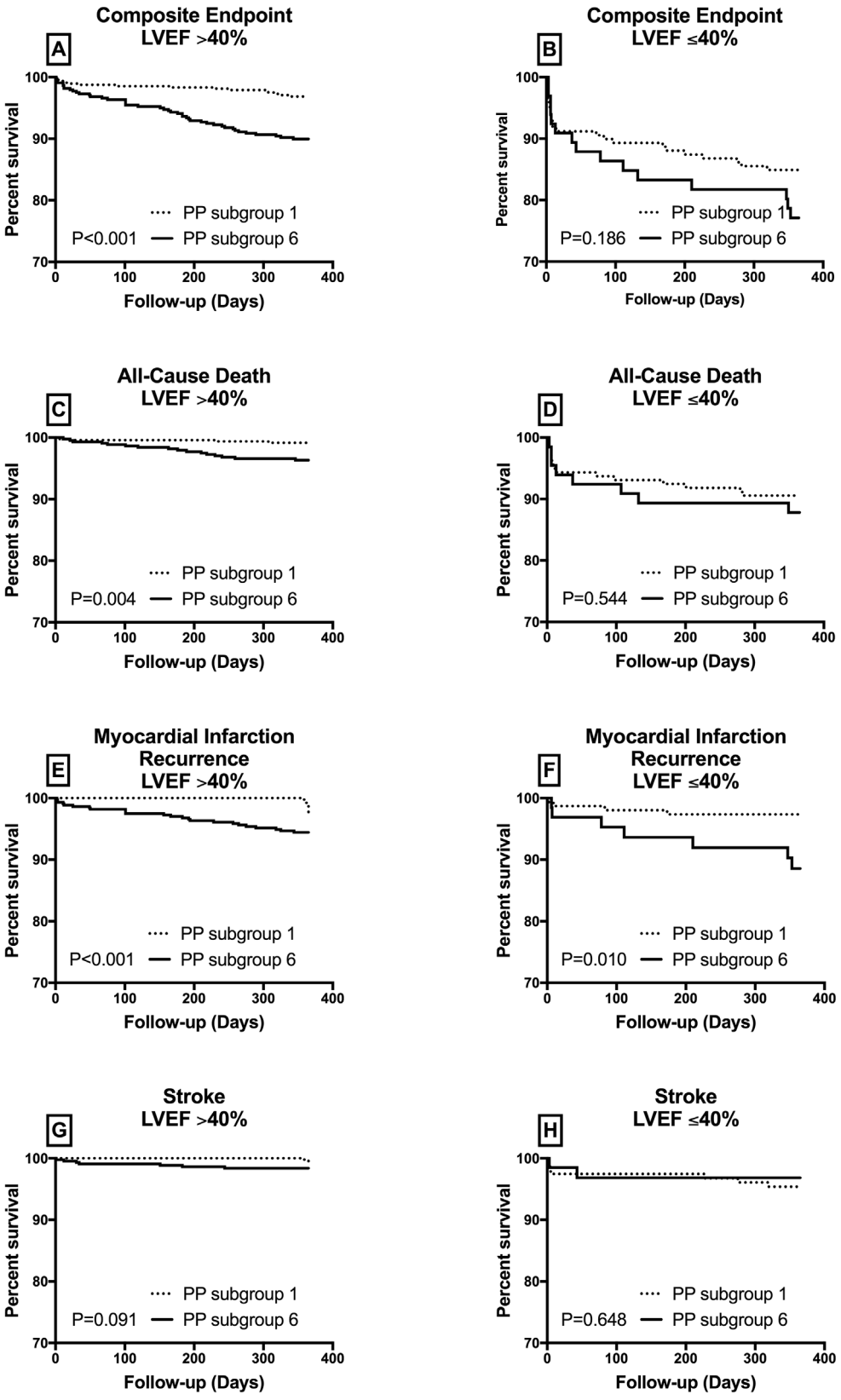

Fig. 3. Kaplan–Meier curves according to four phenotypes *i.e.* lowest (subgroup 1) and highest PP (subgroup 6) groups, without and with LVEF $\leq$ 40%, respectively.
In patients with LVEF >40%, higher PP was associated with an increased risk of all outcomes, whereas low PP was rather protective for stroke, although without reaching statistical significance. On the contrary, in patients with LVEF $\leq$40%, lower PP was not more protective, except for a recurrence of MI, for which a higher PP was associated with an increased risk, regardless of the LVEF.

poor prognosis, as previously suggested [22]. However, in the present study, a history of malignancy was not independently associated with PP.

Apart from this confounding effect of LVEF on the prognosis associated with low PP, mortality and recurrent MI share the same association with high PP. Surprisingly, stroke was no longer associated with PP in multivariate analysis. Possibly this may be related to the fact that stroke is an event with heterogeneous causes [23], while recurrent MI is mainly due to plaque rupture [15]. In particular, stroke appears to be more closely related to the steady state component of BP, *i.e.* mean BP, rather than to PP [15]. Yet, the number of stroke was low, precluding a definite conclusion in multivariable analysis.

Should PP be the blood pressure goal after an ACS diagnosis? After an ACS, event rates remain high, despite advances in medication and invasive strategies [24]. Yet, prevention has become an absolute priority for all healthcare systems [24]. Currently, it is mainly SBP and DBP that are addressed by guidelines [25] and included in prognostic risk scores. No specific recommendations concerning PP have been proposed except for the need to cautiously lower SBP in patients with a wide PP as this may cause very low DBP and impair myocardial perfusion that occurs mainly in diastole. However, the present study suggests that PP might have greater prognostic significance in ACS patients than all the other BP variables. Indeed, a high PP was associated with an increased risk of a recurrent MI and mortality after ACS, independently of the commonly used GRACE score. On the other hand, a low PP appeared rather protective unless LV function was notably compromised. Mean BP level was not predictive of MI, which explains why lowering BP alone has not achieved the expected preventive benefits on this outcome [26], strengthening our interest in considering PP.

Using PP seems to be perfectly in line with the paradigm of personalized medicine and would promote the development of strategies to reduce aortic stiffness, as some dietary and lifestyle interventions seem to do [27]. However, before proposing PP as a target for therapy, further randomized studies are needed to determine whether PP is a risk factor or a risk marker. Many studies suggest that certain medication, such as ACE inhibitors may affect aortic stiffness at least in part independent of their blood pressure lowering effects [28]. High-dose statin and prolonged dual antiplatelet therapy should also be tested as regards to the effects on aortic stiffness in these high-risk patients. However, very low PP in ACS must also be highlighted in this context as it may identify patients with altered LVEF and poor prognosis.

4.1. Limitations

PP is a surrogate for aortic stiffness and it would have been of great interest to get a direct assessment of aortic stiffness using pulse-wave velocity, for example. However, in practice PP is a more universally and easily available variable than pulse-wave velocity. Moreover, PP is also dependent on stroke volume and may provide specific information in patients with impaired LVEF, independently of aortic stiffness. Of note, due to pulse wave amplification, peripheral measurement of PP does not perfectly match central PP. However, pulse wave amplification is less pronounced when PP is measured at the brachial rather than at the femoral level and in older than in younger patients. Moreover, a meta-analysis showed that central PP had no improved predictive value over peripheral PP [18]. Coronary anatomy is lacking while it would have been interesting to adjust on this parameter. However, by adding in the model the modality of revascularization, we have probably partially, circumvent this limitation. Some patients with aortic valvular disease (which could affect PP) may have been included in the study, however this number may be very limited and should not affect the results.

4.2. Conclusions

The present study demonstrated that PP measured at admission is a robust and independent prognostic marker after diagnosis of ACS. Improving understanding about the pathophysiology of diseases by going beyond the effects of “simple” BP could be critical to the development of new preventive strategies and to optimize the use of existing ones. Measuring PP may help in the evaluation of the individual risk and therapeutic decision-making.

Conflicts of interest

R.K received lecture fees from Eli Lilly, Servier, and Bayer. T.F.L reports receiving research grants to the institution from Abbot, Biosensors, Biotronik, Boston Scientific, Daichi Sankyo, Eli Lilly and Medtronic, and consultant payments from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, Merck, and Pfizer, MSD, Roche, and Servier. C.M.M. reports receiving grants from MSD, AstraZeneca, and Roche, and having patents from Mabimmune, CH. S.W. reports receiving research contracts to the institution from Abbott, Biotronik, Boston Scientific, Biosensors, Cordis, Medtronic, St Jude Medical, and speaker fees from Abbott, Biotronik, Boston Scientific, Biosensors, Medtronic, Eli Lilly, and AstraZeneca. F.M. has received research grants to the institution from Amgen, AstraZeneca, Boston Scientific, Biotronik, Medtronic, MSD, Eli Lilly, Sanofi, Pfizer, and St. Jude Medical including speaker of consultant fees. MR has received institutional research grants from Abbott Vascular, Medtronic, Boston Scientific, Terumo, Biotronik as well as speaker fees from Astra Zeneca and Cordis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.07.013.

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B) Rigidité coronaire, physiologie coronaire

a) Mesure de la compliance des artères coronaires

Development of Coronary Pulse Wave Velocity: New Pathophysiological Insight Into Coronary Artery Disease

Harbaoui B, Courand PY, Cividjian A, Lantelme P

J Am Heart Assoc. 2017;6:e004981

Hypothèse : Il pourrait exister un lien entre rigidité coronaire et complication de plaque d'athérome. Un moyen de mesure de la rigidité coronaire est nécessaire mais non disponible en routine clinique. Quelques études ont décrit la compliance ou la distensibilité coronaire en IVUS (17-20). Cette approche est intéressante mais limitée en raison de la résolution de l'IVUS, des mouvements du cœur, du caractère très focal de la compliance mesurée et de l'absence de mesure précise de la pression artérielle locale instantanée.

Objectif : Développer une technique de mesure de la vitesse de l'onde de pouls coronaire.

Population, Méthodes : Nous avons étudié des patients coronariens stables et instables chez qui une mesure du gradient de pression trans-sténotique par guide de pression a été réalisée. Comme explicité précédemment, la vitesse de l'onde de pouls est égale au temps que met l'onde de pouls pour parcourir un segment d'artère tel qu'expliqué sur la figure 3.

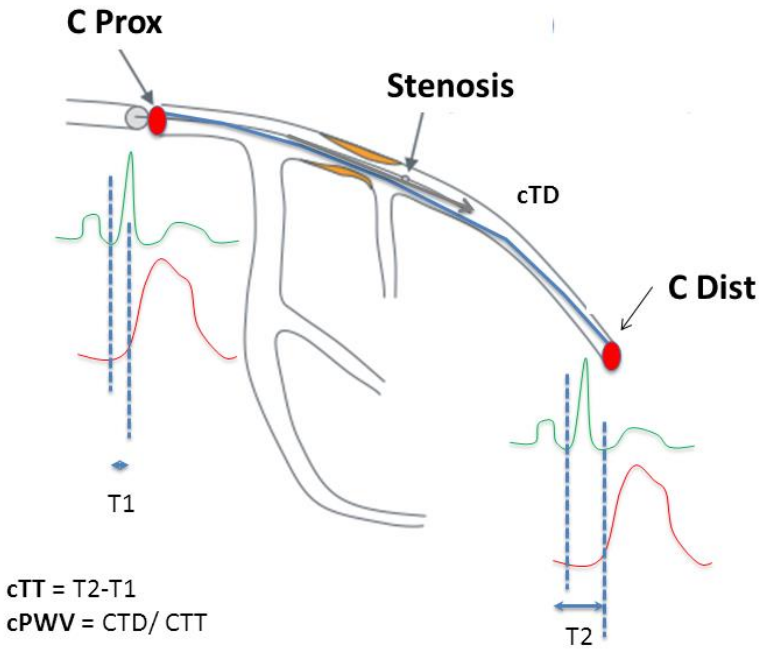

Figure 3: *Illustration du principe de mesure de la VOP coronaire dans l'artère interventriculaire antérieure.*

Les délais ECG-pied de l'onde de pression (T1 and T2) sont enregistrés successivement au niveau distale (cDist) et proximale (cProx). Le temps de transit (cTT) et la distance (cTD) permettent le calcul de la VOP coronaire (cPWV).

Il existe différentes façons de déterminer la VOP, la méthode « foot to foot » étant la plus connue car utilisée pour la VOP carotido-fémorale. Dans le cas d'une artère coronaire, cette méthode « foot to foot » semble difficile à réaliser car la longueur de l'artère coronaire est courte (<13 cm pour une artère interventriculaire en général) et par conséquent le délai ou temps de transit de l'onde de pouls l'est également (figure 4).

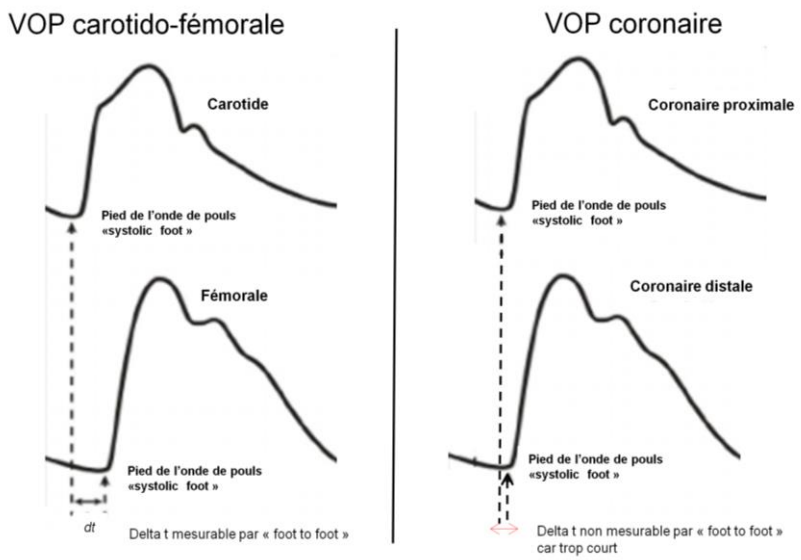

Figure 4 : Principe de la méthode « foot to foot »

Le pied de l'onde de pression est repéré à chaque site de mesure, carotide et fémorale pour le VOP carotido-fémorale et coronaire proximale et distale pour la VOP coronaire. Le temps de transit de l'onde de pouls (dt) est mesurable pour la VOP carotido-fémorale mais pas pour la VOP coronaire car ce délai est trop court et la détermination précise du pied de l'onde de pression est difficile.

Les principales difficultés résidaient dans la possibilité de mesurer des deltas de temps très faibles de l'ordre de quelques millisecondes et de pouvoir évaluer précisément la longueur du segment d'artère coronaire évalué. Nous nous sommes basés sur le traitement des signaux de pression artérielle intra-coronaire bruts, en récupérant le signal via un guide de pression classique. Nous avons rééchantillonné à 2000Hz afin d'avoir une résolution temporelle suffisante (0.05 msec). Nous avons donc essayé via d'autres méthodes, en passant par la dérivée première puis seconde de l'onde de pouls. L'analyse du signal de l'onde de pouls était rendu difficile par la présence d'une forme anormale du pied de l'onde au niveau distal de l'artère coronaire. Nous avons interprété cette déformation comme un artefact lié à la contraction myocardique pouvant créer une onde réfléchie.

Résultats : Mise au point d'un algorithme basé sur la reconnaissance de forme de l'onde dicrote permettant la mesure de la VOP sur 71 artères coronaires chez 49 patients. Les VOP coronaires mesurées étaient en moyenne de 10.3±6.1 m/s. Les patients présentant un syndrome coronaire aigu avaient des VOP coronaires plus basses témoignant d'artères coronaires plus souples que les patients présentant une coronaropathie stable 7.6±3 vs 11.5±6.4 m/s; p=0.02. L'implantation d'un stent dans l'artère coronaire entrainait une augmentation de la VOP coronaire.

Conclusion, discussion : La mesure de la rigidité des artères coronaire est possible par détermination de la VOP coronaire. Celle-ci nécessite un guide pression et un algorithme dédié. La VOP coronaire a été initialement décrite chez l'animal (21,22). Chez l'homme, elle n'a jamais été décrite dans une étude clinique, seulement dans des études méthodologiques de faible effectif (23-25). Dans notre étude, les patients présentant un syndrome coronaire aigu avaient des artères coronaires moins rigides ; ces caractéristiques sont semblables à celles des plaques à risques décrites plus haut dans cette thèse. Aussi, les propriétés mécaniques du vaisseau coronaires pourraient moduler la capacité d'une sténose épicardique à entrainer une ischémie. Pour une sténose donnée, la valeur de FFR pourrait varier en fonction de la rigidité vasculaire ce qui pourrait impacter la décision thérapeutique chez les patients en zone grise de FFR (26). Nous avons présenté un travail préliminaire montrant une corrélation entre VOP coronaire et FFR à l'ESC 2017 Barcelone.

Perspectives : Cette étude pilote ouvre de nombreuses perspectives de recherche qui seront développées dans le chapitre perspectives. L'algorithme de mesure de cette VOP coronaire a été breveté avec le soutien des Hospices Civils de Lyon et de l'Université Claude Bernard Lyon I.

ORIGINAL RESEARCH

Development of Coronary Pulse Wave Velocity: New Pathophysiological Insight Into Coronary Artery Disease

Brahim Harbaoui, MD, MS; Pierre-Yves Courand, MD, PhD; Andrei Cividjian, PhD; Pierre Lantelme, MD, PhD

***Background*—**Although aortic stiffness assessed by pulse wave velocity (PWV) is a strong predictor of coronary artery disease, the significance of local coronary stiffness has never been tackled. The first objective of this study was to describe a method of measuring coronary PWV (CoPWV) invasively and to describe its determinants. The second objective was to assess both CoPWV and aortic PWV in patients presenting with acute coronary syndromes or stable coronary artery disease.

***Methods and Results*—**In 53 patients, CoPWV was measured from the delay in pressure wave and distance traveled as a pressure wire was withdrawn from the distal to the proximal coronary segment. Similarly, aortic PWV was measured invasively when the wire was pulled across the ascending aorta; carotid–femoral PWV was also measured noninvasively using the SphygmoCor system (AtCor Medical). Mean CoPWV was 10.3±6.1 m/s. Determinants of increased CoPWV were fractional flow reserve, diastolic blood pressure, and previous stent implantation in the recorded artery. CoPWV was lower in patients with acute coronary syndromes versus stable coronary artery disease (7.6±3 versus 11.5±6.4 m/s; P=0.02), and this persisted after adjustment for confounders. In contrast, aortic stiffness, assessed by aortic and carotid–femoral PWV, did not differ significantly.

***Conclusions*—**CoPWV seems associated with acute coronary events more closely than aortic PWV. High coronary compliance, whether per se or because it leads to a distal shift in compliance mismatch, may expose vulnerable plaques to high cyclic stretch. CoPWV is a new tool to assess local compliance at the coronary level; it paves the way for a new field of research. **(*J Am Heart Assoc*. 2017;6:e004981. DOI: 10.1161/JAHA.116.004981.)**

Key Words: acute coronary syndromes • aortic stiffness • compliance • coronary artery • fractional flow reserve • plaque rupture • pulse wave velocity • stiffness

Vascular stiffness plays an important role in the pathophysiology of cardiovascular events.[1,2] Aortic pulse wave velocity (AoPWV), a marker of large artery stiffness, is a strong predictor of coronary artery disease (CAD),[3] probably because aorta conveys pulsatility to coronary vessels. The close proximity of the aorta and small arteries fuels permanent cross-talk between them.[4] Nevertheless, because of their different biomechanistic properties, a stiffness gradient is usually observed between the aorta and the peripheral arteries, leading to areas of compliance mismatch. These areas induce wave reflection, which is critical to reduce downstream pulsatility.[5] Consequently, local coronary compliance should differ from aortic compliance and may be more relevant for predicting plaque rupture.[6] However, the impact of local coronary stiffness on acute coronary events has never been studied. This is most likely because appropriate tools for assessing coronary stiffness are currently lacking.

Some attempts have been made to assess local coronary compliance surrounding a plaque using intravascular ultrasound,[7] but a global appraisal of vessel biomechanics may be more appropriate. Arterial compliance is widely assessed by measuring the speed of the pressure wave across a particular segment. This approach, known as pulse wave velocity (PWV) measurement, has been used primarily for large vessels and is currently considered the gold standard to determine aortic stiffness.[8] Some previous attempts have been made to assess coronary PWV (CoPWV) in animal studies[9] and methods papers.[10,11] However, the approaches used raise important methodological issues that preclude use in routine practice.[12] The objectives of the present study were to propose a method of CoPWV measurement that could be implemented easily during a standard coronary angiogram, allowing for

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description of determinants, and to compare coronary and aortic compliance with respect to the patient's clinical status (ie, with acute coronary syndrome [ACS] or stable CAD).

Methods

Patients and Study Design

Patients with an ACS or stable CAD undergoing a standard coronary angiogram at the Croix-Rousse Hospital (Lyon, France) with an indication for fractional flow reserve (FFR) measurement were included in the study. The indication for FFR was based on the visual estimate of the stenosis percentage of diameter reduction (≥50%). ACS was defined by usual clinical, ECG, and troponin criteria. Stable CAD indicated stable angina or silent ischemia presenting a stenosis ≥50% on at least 1 coronary artery. Exclusion criteria were age <18 years, valvular heart disease, or the presence of decompensated heart failure. Risk factors, history of CAD or peripheral artery disease, left ventricular ejection fraction, and ongoing pharmacologic medication were obtained from the patients' medical files. Renal function was calculated according to the Modification of Diet in Renal Disease formula. Conventional blood pressure (BP) and carotid–femoral PWV were measured just before the coronary angiogram. Three BP measurements, obtained at 1-minute intervals in a reclining position after 5 minutes of rest, were averaged. Carotid–femoral PWV was measured next with a Sphygmocor device (AtCor Medical); a 0.8 scaling factor was applied to the carotid–femoral distance, as described previously.[13]

CoPWV was assessed with the ECG signal and the local pressure wire signal using a computerized algorithm in all coronary arteries undergoing FFR measurement. CoPWV was reassessed during the same procedure in a subset of patients after intracoronary injection of adenosine to evaluate CoPWV reproducibility—this short-acting drug is not expected to have any sustained effect on wave speed in humans[12]—and in a second subset of patients treated with percutaneous coronary intervention, to assess the effect of stenting as a way to validate our measurement.

Aortic PWV (AoPWV) was measured invasively using the same methodology. The study protocol received ethics committee approval (Comité de Protection des Personnes Sud-Est IV). All participants gave written informed consent to participate.

Invasive Pressure and ECG Recordings

A 0.014-mm pressure guidewire (PressureWire Aeris; St. Jude Medical) was introduced via a 5F or 6F guiding catheter. ECG (Philips) and invasive BP waveforms were acquired using RECAN software (Alpha2) via an analog/digital acquisition board (KUSB-3100; Keithley-Tektronix) at 500 Hz. CoPWV was assessed with asynchronous recordings of the ECG-BP delay at 2 different sites of the coronary segment to determine the propagation time of the pressure wave (Figure 1). Synchronized BP and ECG signals were recorded for 1-minute periods at the coronary proximal and distal levels.

The distance between the 2 positions (coronary travel distance), was assumed to be equal to the elongation of the external part of the catheter after pull-back (distal to proximal). The latter was measured with a millimeter-precision ruler (Figure 1).

Pressure, ECG Analysis, and Invasive PWV Assessment

Data analysis was performed offline using an automated customized procedure with RECAN software. To improve time resolution, the signals were resampled at 2000 Hz after interpolation using cubic splines. R wave was detected for each cardiac cycle from the ECG signal using a template-matching method after memorizing an averaged R-wave shape. The onset time of the BP rise was calculated for each cardiac cycle by adapting the intersecting tangents method,[14] as described later. When the catheter was in the proximal position, onset time was calculated as the intersection of the tangent to the BP wave at the time corresponding to the peak of the BP derivative with the horizontal line passing through

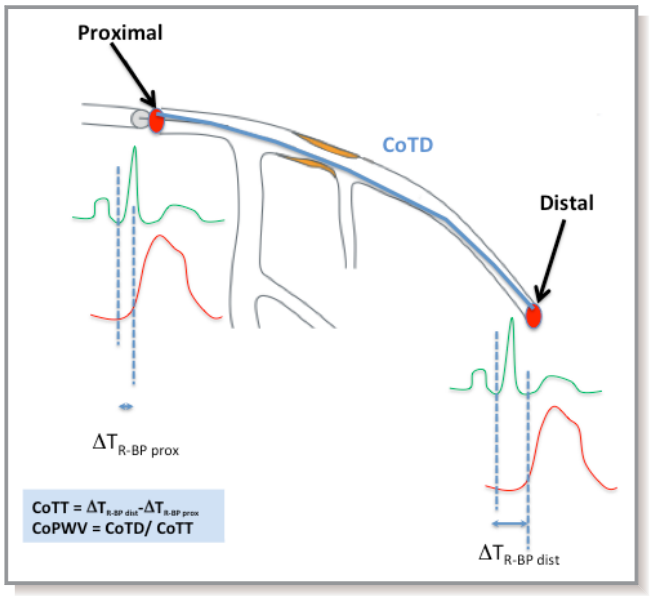

Figure 1. Illustration of the principle of coronary pulse wave velocity (CoPWV) measurement in the left descending artery. ECG–blood pressure delays ($T_{R\text{-}BP}$) are recorded successively at the distal ($T_{R\text{-}BP\ dist}$) and proximal ($T_{R\text{-}BP\ prox}$) sites. Coronary travel time (CoTT) and coronary travel distance (CoTD) allow the calculation of CoPWV.

the preceding diastolic BP (DBP) (Figure 2). When the catheter was in the distal position, the detection of onset time of the BP rise was more difficult because of a frequent premature pressure increase that impeded accurate application of the intersecting-tangents method (Figure 2). For both proximal and distal positions, a recomposed signal was created that was equal to 0 everywhere except for the period of ±10 ms centered on the onset time of BP rise, when this recomposed signal was equal to the averaged R-wave shape used to detect the R wave for each cardiac cycle (Figure 3A). A cross-correlation between the ECG and this recomposed signal was performed to calculate the delay between the R

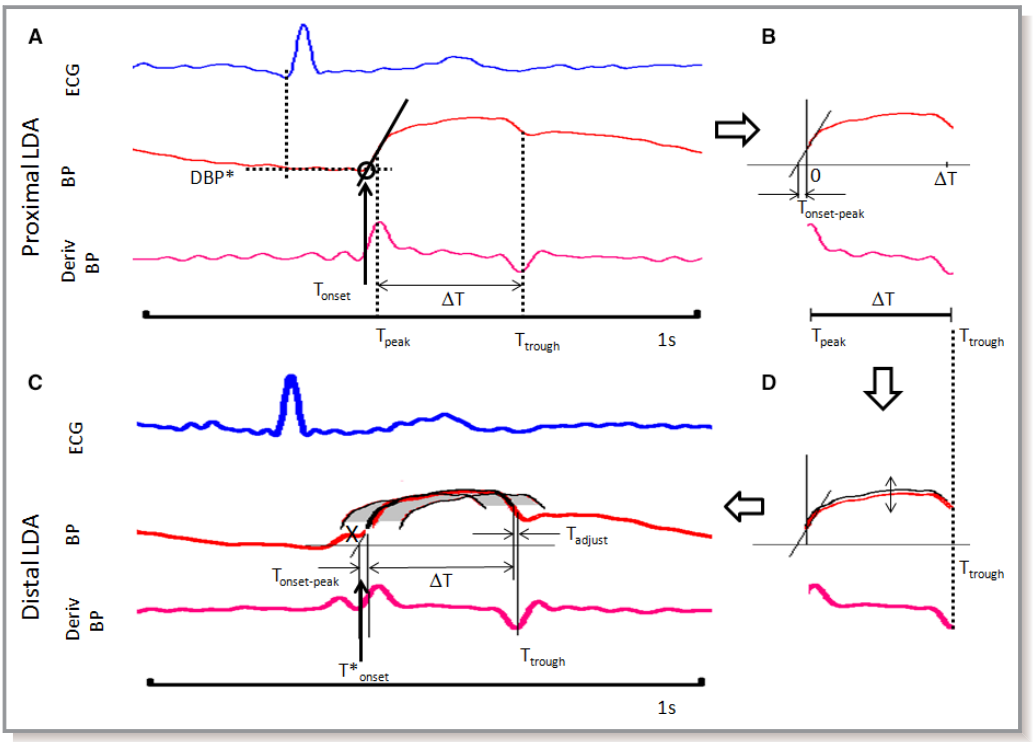

Figure 2. Detection of onset time of the blood pressure (BP) rise in the proximal and the distal positions of a coronary artery. A, For each cardiac cycle, the peak corresponding to the pressure rise and the trough corresponding to the dicrotic notch were detected in the first derivative of the BP at the times T_{peak} and T_{trough}, respectively. When the catheter was in the proximal position, the onset time (T_{onset}) of the BP rise was calculated for each cardiac cycle as the intersection of the tangent to the BP wave at T_{peak}, with the horizontal line passing through the preceding diastolic BP (DBP). To avoid the effect of microcirculation on the DBP, an extrapolated value (DBP*) was used, being equal to the value of the BP at the moment just before the onset of the R wave. B, A normalized BP wave was calculated for each cardiac cycle between T_{peak} and T_{trough} by subtracting from each BP sample the value of the preceding extrapolated DBP*. The average of all normalized BP waveforms in the proximal position resulted in an averaged normalized waveform of duration: $\Delta T = T_{trough} - T_{peak}$(time interval : $[0; \Delta T]$). The intersection of the tangent to the averaged normalized BP wave at time t=0 with the axis of abscissa was considered the averaged delay $T_{onset\text{-}peak}$ between T_{onset} of the BP and the peak of the pressure derivative. C, The averaged normalized waveform computed in the proximal position was superimposed on the normalized BP waveform of each cardiac cycle in the distal position by rescaling amplitude and synchronizing the last sample of the averaged waveform with the dicrotic notch time (T_{trough}) of the pressure waveform in the distal position. D, The root mean square error (RMSE) was calculated between the 2 superimposed waveforms. The averaged normalized waveform was shifted sample by sample with an interval of (−10;+10) ms to obtain a minimum value of the RMSE (time shift corresponding to the minimum of the RMSE [T_{adjust}]). Thus, the estimated onset time of the pressure rise for each cardiac cycle in the distal position is as follows: $T^*_{onset} = T_{trough} - \Delta T + T_{adjust} + T_{onset-peak}$. At 5 ms before T^*_{onset}, if the value of the BP ("X" on the BP trace) was lower than the extrapolated DBP*, T_{onset} of the pressure rise was obtained using the intersection of the tangent to the BP at T^*_{onset} with the horizontal line passing through the estimated DBP*. At 5 ms before T^*_{onset}, if the value of the BP was higher than the extrapolated DBP*, we considered that an artifactual premature pressure increase occurred before the pressure rise, and the tangent intersection method was not applicable, as it gave unreliable results: In this case, T_{onset} of the pressure rise was the estimated as T^*_{onset}. LDA indicates left descending artery.

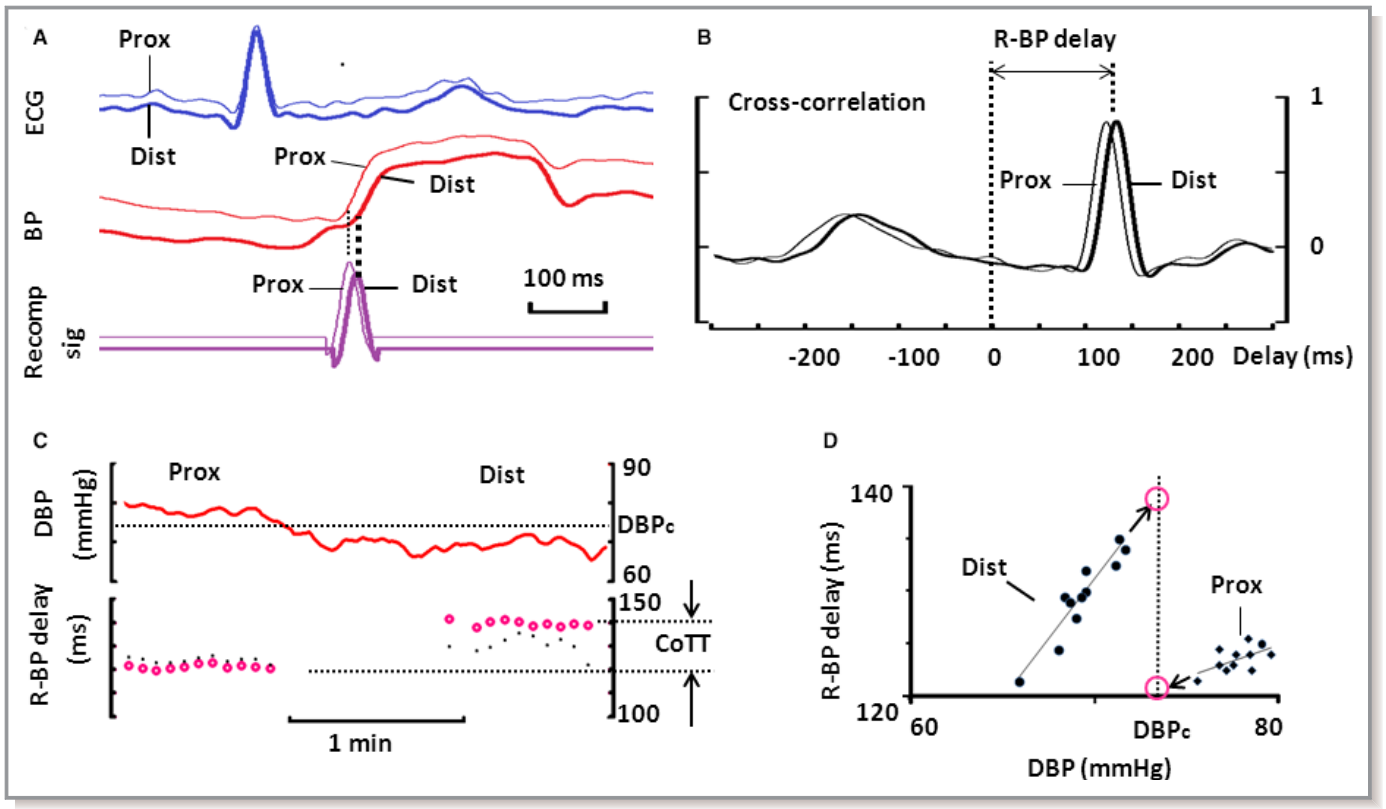

Figure 3. Delay between proximal and distal blood pressure (BP) wave fronts. A, Superimposed ECG, BP, and recomposed ECG signal for proximal and distal left descending artery (LDA), triggered by the R wave. The recomposed ECG signal was equal to the averaged R wave shape at the onset of the BP rise and zero elsewhere. B, Normalized cross-correlation between ECG and recomposed ECG signal in (A) for a ±300 ms shift range. The peak of the cross-correlation function corresponds to the delay between the R wave and the onset of the BP wave (R-BP delay). C, Time series of diastolic BP (DBP) and R-BP delays for adjacent periods containing 5 consecutive cardiac cycles in proximal and distal LDA. Both raw (dots) and extrapolated (open circles) R-BP delay time series are shown. The delay that the pressure wave needs to propagate from the proximal to the distal location (CoTT) is the difference of averaged extrapolated R-BP delays (arrows). D, Extrapolation of R-BP delay time series for a common DBP (DBP_c; mean of proximal and distal DBP), using linear regressions curves between R-BP delay and DBP. CoTT indicates coronary travel time; Dist, distal; Prox, proximal; Recomp, recomposed ECG signal.

wave and the onset of BP rise (R-BP delay). The cross-correlation function was applied for adjacent periods containing 5 consecutive R waves to smooth the influence of respiratory hemodynamic fluctuations. The maximum of this cross-correlation function corresponded to an averaged R-BP delay for the 5 consecutive R waves (Figure 3B). Computing of the cross-correlation function on adjacent groups of 5 consecutive R waves resulted in time series of R-BP delays $\Delta T_{R\text{-}BP}$ (Figure 3C). DBP was also averaged on 5 consecutive cardiac cycles, resulting in averaged DBP time series. A linear relationship was apparent in most patients between $\Delta T_{R\text{-}BP}$ and associated DBP time series for both proximal and distal positions (Figure 3D). Given this linear relationship, the time $\Delta T_{R\text{-}BP}$ series was extrapolated for a common DBP that was the mean of the proximal and distal DBPs (Figure 2). The extrapolated time series (ΔT^*_{R-BP}) was averaged for all 1-minute measurement periods in the proximal position ($Avg\Delta T^*_{R-BP\ prox}$) and in the distal position ($Avg\Delta T^*_{R-BP\ dist}$). The pulse wave front propagated from proximal to distal positions during the coronary travel time (CoTT) calculated as follows:

$$CoTT = Avg\Delta T^*_{R-BP\ dist} - Avg\Delta T^*_{R-BP\ prox}$$

CoPWV was calculated as coronary travel distance/CoTT and was expressed in m/s. For AoPWV measurement, the ECG-pressure delays were measured while the wire was at the level of the valsalva sinus and at the inlet of the brachiocephalic artery. As for CoPWV, the length of the wire externalized from the catheter when withdrawn from the distal to proximal positions represents the travel distance.

Statistical Analysis

Quantitative variables are summarized as mean±SD or numbers and percentages, as appropriate. Owing to a skewed distribution of CoPWV and AoPWV, a logarithmic transformation was performed before the statistical analysis. The

reproducibility of CoPWV was assessed using an intraclass correlation coefficient. Determinants of CoPWV and AoPWV were assessed by multivariable linear regression including univariate determinants in the model with $P<0.05$. Of note, conventional BP measurement was used for all statistical analyses. A paired Student *t* test was used to assess the effect of stenting within the same patients. Patients with an ACS or stable CAD were compared using the chi-square test, Fisher exact test, or the unpaired *t* test, as appropriate. Pearson correlation was used for comparing CoPWV and Aortic PWV. For CoPWV comparison, available measurements (1–3 measurements per patient, depending on the number of

Table 1. Patient Characteristics

Variable	All Patients (n=49)	Patients With Stable CAD (n=33)	Patients With ACS (n=16)	*P* Value*
Demographic characteristics				
Age, y	63.6±10.5	66.3±9.2	57.9±11.5	0.008
Men	39 (79.6)	24 (72.7)	15 (93.8)	0.14
Smoker	32 (65.3)	21 (63.6)	11 (68.8)	0.72
BMI, kg/m^2	27.3±5.4	28.3±6.0	25.2±3.3	0.06
Cardiac variables				
Heart rate, bpm	65.6±9.6	65.9±8.8	65±11.3	0.75
SBP, mm Hg	125.3±17.5	128.7±18.4	118.1±13.1	0.045
DBP, mm Hg	72.6±11.2	73.8±11.1	70.2±11.6	0.31
Medical history				
Diabetes mellitus	19 (38.8)	15 (45.5)	4 (25.0)	0.17
Hypertension	34 (69.4)	24 (72.7)	10 (62.5)	0.52
Dyslipidemia	33 (67.3)	25 (75.8)	8 (50.0)	0.07
CAD	27 (55.1)	21 (63.6)	6 (37.5)	0.09
Peripheral artery disease	7 (14.3)	5 (15.2)	2 (13.3)	0.62
Baseline treatment				
Angiotensin-converting enzyme inhibitor	29 (59.2)	18 (54.5)	11 (68.8)	0.34
Angiotensin II receptor blocker	5 (10.2)	4 (12.1)	1 (6.3)	0.52
Beta blocker	36 (73.5)	24 (72.7)	12 (75.0)	0.58
Calcium channel blocker	10 (20.4)	6 (18.2)	4 (25.0)	0.71
Statin	33 (67.3)	26 (78.8)	7 (43.8)	0.014
Oral antidiabetic drug	15 (30.6)	11 (33.3)	4 (25.0)	0.74
Insulin	9 (18.4)	6 (18.4)	3 (18.8)	0.96
Coronary angiography				
Radial approach	48 (98.0)	32 (97.0)	16 (100.0)	0.46
Number of diseased vessels				0.51
1	20 (40.8)	15 (45.5)	5 (31.3)	
2	18 (36.7)	12 (36.4)	6 (37.5)	
3	11 (22.4)	6 (18.2)	5 (31.3)	
Other variables				
eGFR, mL/min/1.73 m^2	79.4±22.4	78.0±19.8	82.3±27.5	0.54
LVEF, %	55.2±8.1	55.8±8.8	54.0±6.3	0.48

Values are mean±SD or n (%). ACS indicates acute coronary syndrome; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.
*Difference across patients with stable CAD or an ACS using the chi-square test, Fisher exact test, or the unpaired *t* test.

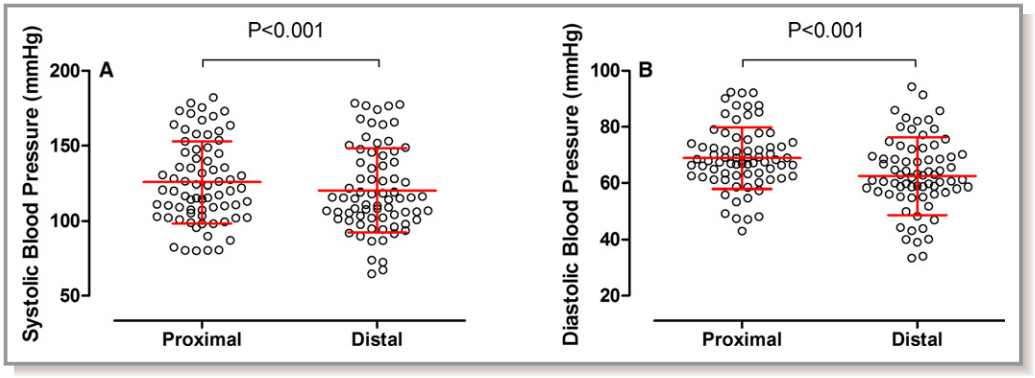

Figure 4. Systolic (A) and diastolic (B) coronary perfusion pressure at the proximal and distal sites.

vessels assessed) were averaged and used as the representative CoPWV for each patient. A sensitivity analysis was performed by comparing the CoPWV of the culprit vessel (ie, 1 vessel per patient) with the representative averaged CoPWV of the stable CAD subgroup. Analysis of covariance was used to provide adjusted means for PWV between patients with ACS and stable CAD. The analyses were performed using SPSS software 20.0.0 (IBM Corp). A value of $P<0.05$ was considered statistically significant.

Results

Patient Characteristics

Of the 53 patients considered, 4 were excluded (3 because of a poor ECG signal and 1 because of pressure artifacts). The population comprised 49 patients, 33 with stable CAD and 16 with an ACS.

The patient baseline characteristics are summarized in Table 1. As expected, a vast majority of patients were hypertensive with no difference in ongoing treatments except in the use of statins. Overall, 71 coronary arteries were analyzed in the 49 patients: 39 left descending artery, 23 right coronary artery, and 9 circumflex artery. Moreover, 24 of the 71 arteries were in patients with an ACS, with 15 of those arteries being culprit vessels (1 ACS patient had a recording only from a nonculprit artery), and 47 were in patients with stable CAD. Invasive coronary pressures are presented in Figure 4; they were significantly lower at the distal than at the proximal recording site ($P<0.001$ for all). No periprocedural complications occurred during CoPWV measurements. AoPWV was measured in 44 patients.

CoPWV and AoPWV Values

On average, CoPWV was 10.3±6.1 m/s, with no significant difference according to territory (10.0±6.6 m/s for left descending artery, 10.1±4.9 m/s for right coronary artery, and 12.4±7.1 m/s for circumflex artery; $P=0.55$). The reproducibility of CoPWV was fair, as assessed by the intraclass correlation coefficient (0.869, 95% CI 0.705–0.945; $P<0.001$). To allow for estimation of measurement precision, coronary travel distance and CoTT were presented separately (Figure 5). Given that the average travel distance was 11.6±2.46 cm, the absolute relative error was <2%. The time resolution for $\Delta T_{R\text{-}BP}$ due to sampling of ECG and BP was

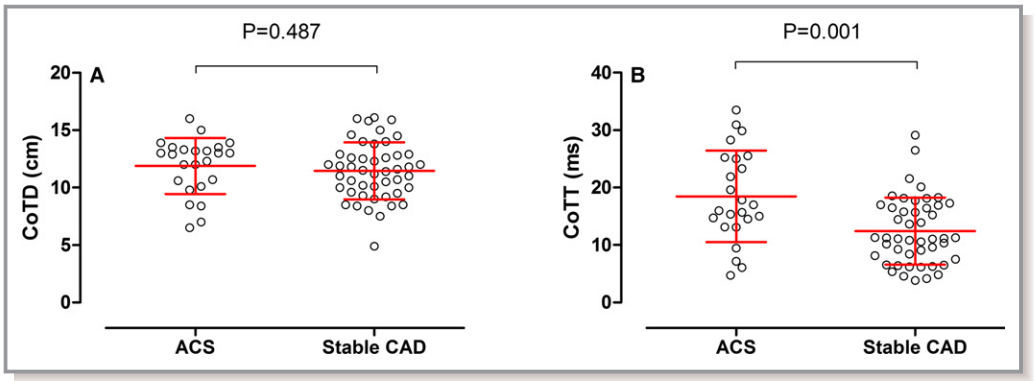

Figure 5. Difference in coronary travel distance (CoTD) (A) and coronary travel time (CoTT) (B) in patients with stable coronary artery disease (CAD) and an acute coronary syndrome (ACS).

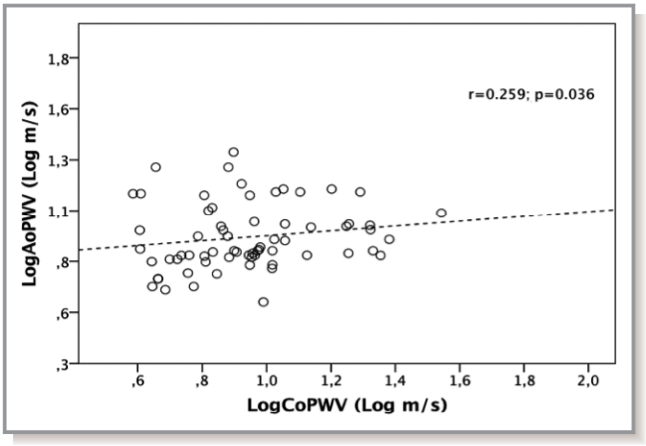

Figure 6. Correlation between coronary and aortic pulse wave velocities. AoPWV indicates aortic pulse wave velocity; CoPWV, coronary pulse wave velocity.

equal to the sampling period (Δt=1/2000 Hz=0.5 ms). Because CoTT is the difference between R-BP delays, its resolution was double the sampling period (ie, 1 ms). This led to an induced relative error for CoPWV <10% for t≥9 ms, which represents the majority of the recordings (average CoTT of 14.45±7.17 ms). The relative error increased to 17% in the few cases of short CoTT at 5 ms. In comparison, mean AoPWV was 8.73±3.74 m/s. A slight correlation was observed between CoPWV and AoPWV (r=0.259, P=0.036) (Figure 6). Carotid–femoral PWV was 9.6±2.8 m/s.

CoPWV and AoPWV Determinants

Table 2 shows the univariate and multivariable determinants of CoPWV and AoPWV. FFR, DBP, and a previous stent in the assessed artery were significant determinants of increased CoPWV. Adding renal function to the same set of variables did not substantially change the results (data not shown). As shown in Figure 7A, a marked increase in CoPWV was observed after stent implantation (during the same procedure) in 33 patients, from 9.7±5 to 17.1±9.01 m/s (P<0.001). For AoPWV, the only significant determinant in univariate and multivariable analysis was age, whereas a trend for a positive association was found with systolic BP in univariate analysis only (Table 2).

ACS Versus Stable CAD

Mean CoPWV was lower in patients with an ACS patients than stable CAD (7.6±3 versus 11.8±6.6 m/s; P=0.012) (Figure 7B). This difference remained after removal of an outlier in the stable CAD group (P=0.016). The difference in CoPWV was mostly due to a difference in CoTT, whereas coronary travel distance was similar between the 2 groups (Figure 5). Considering only the right coronary artery, CoPWV remained lower in ACS than CAD vessels (6.9±2.5 versus 12±5 m/s, respectively; P=0.004). The same trend was observed for the left descending artery (7.5±4.8 versus 10.9±7 m/s for ACS and stable CAD, respectively; P=0.08). The circumflex arteries were not included in this analysis because of their small sample size. When considering only ACS culprit vessels versus stable CAD, the difference was even more marked (6.5±2.2 versus 11.5±6.4 m/s; P=0.001). These differences also remained (P=0.037) after adjustment for the characteristics that differed between patients with stable CAD and ACS (ie, age, systolic BP, statin use) (Table 1). When further adjusting for all cardiovascular risk factors, CoPWV remained different between the 2 groups (P=0.046).

In comparison, a trend of difference was observed between ACS and stable CAD patients concerning AoPWV (7.3±3.2 versus 9.5±3.8 m/s, respectively; P=0.065). After adjustment for differences between ACS and stable CAD patients, the difference was even less marked (P=0.2). This was also true for carotid–femoral PWV (9.8±3.3 versus 9.5±2.5 m/s; P=0.8).

The average severity of coronary stenosis did not differ between patients with ACS and stable CAD (hyperemia FFR values: 0.77±0.08 versus 0.78±0.09, respectively; P=0.842), and a similar proportion of patients had FFR values <0.8 (66.7% versus 68.1%, respectively; P=0.554).

Discussion

We described a method for measuring CoPWV that involves a regular pressure wire and dedicated software. With this approach, we demonstrated—for the first time—a noticeable difference in CoPWV between stable and unstable coronary vessel diseases. No such difference was apparent for AoPWV. CoPWV may prove to be a relevant assessment of instability in coronary vessels.

Determination of CoPWV was based on asynchronous pressure recordings gated on an ECG because synchronous recordings would have required placing 2 pressure wires in the coronary arteries, which is both unethical and not applicable in routine clinical practice. Accurate determination of the wave front was mandatory, requiring rigorous analysis of the signal. The characteristic points are usually chosen near the foot (ie, the nadir) of the pressure waveform,[14] which is believed to be relatively free of arterial wave reflections, so the interference with the calculation of forward wave velocity is minimized. In our study, we used the tangent intersection method, currently regarded as the best technique for proximal wave detection.[14] In the distal part of the artery, this technique was often compromised by a premature pressure rise, probably due to myocardial contraction. In this context, our approach was based on detection of the dicrotic notch

Table 2. Determinants of Increased Coronary and Aortic Pulse Wave Velocity in Univariate and Multivariate Analysis

	CoPWV (m/s), n=49				AoPWV (m/s), n=44			
	Univariate		Multivariable*		Univariate		Multivariable*	
Determinant	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age	0.009	0.94	—	—	0.429	0.004	0.344	0.020
Sex (F=0; M=1)	0.051	0.67	—	—	−0.212	0.17	—	—
Hypertension (N=0; Y=1)	0.047	0.70	—	—	0.297	0.05	0.139	0.34
Diabetes mellitus (N=0; Y=1)	−0.010	0.94	—	—	0.230	0.13	—	—
Smoking (N=0; Y=1)	0.243	0.041	0.196	0.064	−0.223	0.15	—	—
Dyslipidemia (N=0; Y=1)	0.090	0.46	—	—	0.247	0.11	—	—
BMI (+1 kg/m²)	0.260	0.028	0.164	0.142	−0.002	0.99	—	—
History of CAD (N=0; Y=1)	0.145	0.23	—	—	0.183	0.24	—	—
PAD (N=0; Y=1)	−0.031	0.80	—	—	0.169	0.27	—	—
Previous stent (N=0; Y=1)	0.373	0.001	0.247	0.036	—	—	—	—
Number of diseased vessels (+1)	−0.115	0.34	—	—	−0.068	0.66	—	—
Renal function (+1 mL/min)	0.231	0.05	—	—	−0.275	0.07	—	—
ACEI (N=0; Y=1)	0.089	0.46	—	—	−0.056	0.72	—	—
ARB (N=0; Y=1)	−0.047	0.70	—	—	0.238	0.12	—	—
Beta blocker (N=0; Y=1)	0.177	0.14	—	—	0.142	0.36	—	—
CCB (N=0; Y=1)	−0.075	0.54	—	—	0.077	0.62	—	—
Statin (N=0; Y=1)	0.278	0.019	0.026	0.836	0.186	0.23	—	—
Oral antidiabetic drug (N=0; Y=1)	0.126	0.29	—	—	0.345	0.022	0.234	0.11
Insulin (N=0; Y=1)	−0.155	0.20	—	—	−0.018	0.91	—	—
SBP (+1 mm Hg)	0.178	0.14	—	—	0.280	0.07	—	—
DBP (+1 mm Hg)	0.334	0.004	0.280	0.01	−0.009	0.96	—	—
Heart rate (+1 bpm)	−0.067	0.58	—	—	0.087	0.57	—	—
FFR (0=FFR >0.8; 1=FFR ≤0.8)	−0.355	0.002	−0.265	0.012	—	—	—	—
LVEF (+1%)	−0.200	0.10	—	—	−0.151	0.34	—	—

ACEI indicates angiotensin-converting enzyme inhibitor; AoPWV, aortic pulse wave velocity; ARB, angiotensin II receptor blocker; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CCB, calcium channel blocker; CoPWV, coronary pulse wave velocity; DBP, diastolic blood pressure; F, female; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; M, male; N, no; PAD, peripheral artery disease; SBP, systolic blood pressure; Y, yes.
*Adjusted for all variables with $P<0.05$ in univariate analysis.

(trough in the BP-derivative signal). The dicrotic notch is a suitable time reference point for PWV determination, as an alternative to the systolic foot in the carotid artery,[15] but it was not sufficiently precise per se in the context of coronary arteries. Consequently, we used it to trigger a memorized BP waveform in the proximal position; a curve fitting between the proximal and distal BP waveform shapes was applied to improve the detection of the distal waveform. To take into account pressure variation that may occur between the proximal and distal parts of the artery, an adjustment on DBP was made within each coronary artery. Finally, we used high-frequency sampling to increase the precision of the measurement. A few attempts have been made to measure CoPWV, but the methods used (eg, the single-point method) are questionable for the coronary circulation, characterized by short vessels, multiple sources of waves, and changing peripheral resistance during each cardiac cycle.[12,16] Moreover, reproducibility was not assessed in previous CoPWV assessments, and BP variations along the coronary vessel were not taken into account. Conversely, several aspects validate our method in the absence of a gold standard. First, it provides CoPWV values similar to those obtained in dogs[9] and humans.[12] Second, when applied to the aorta, it provides values within the expected range.[17] Third, it can detect the stiffening effect of stenting, demonstrated in other arteries.[18] Fourth, it has good reproducibility. This method has the advantage of evaluating the global mechanical property of an artery, which may be better than previous methods using

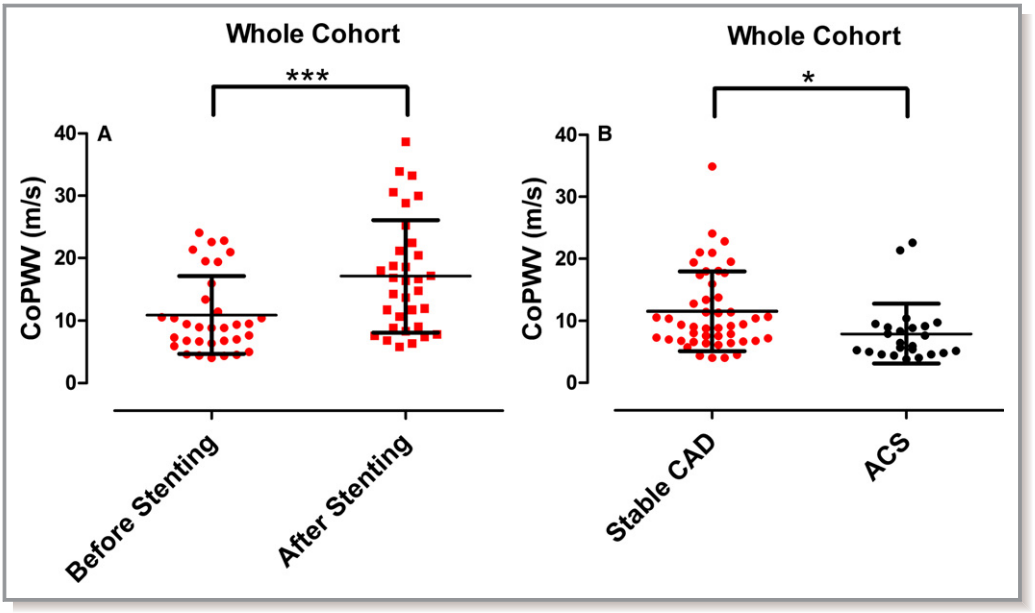

Figure 7. Coronary pulse wave velocity (CoPWV) (A) before and after stenting and (B) in patients with stable coronary artery (CAD) disease or an acute coronary syndrome (ACS). Dots indicate individual recordings, and whiskers represent means and standard deviations. *P=0.012; ***P<0.001.

intravascular ultrasound.[7] Indeed, it seems challenging, given methodological constraints, to precisely determine the variation in diameter between systole and diastole in a coronary artery because of the swing of the heart.

Clinical Relevance of CoPWV

Coronary compliance likely influences several features of myocardial perfusion and plaque complications. It may also represent a potential early marker of endothelial dysfunction and future atherosclerosis.[19] More importantly, it has been suggested as a reliable marker of high-risk plaques.[6] Our results are perfectly in line with this hypothesis, as CoPWV was a marker of vessel vulnerability. To our knowledge, this is the first time that such a difference has been reported; previous attempts to measure CoPWV were performed only in angiographically normal vessels.[12] This difference of CoPWV between ACS and stable CAD vessels was explained mostly by a difference in CoTT. The 6-ms average CoTT difference exceeded the precision of the measurement, which makes the difference of CoPWV between ACS and stable CAD compelling. This finding was also strengthened by the fact that it was verified for the right coronary and left descending arteries considered separately and by the fact that it remained after several adjustments for potential confounders. The degree of stenosis was not different between ACS and stable CAD and did not account for the difference in CoPWV. A major additional finding and strength of our study is that this difference cannot be accounted for by a "vascular aging effect." Indeed, AoPWV and carotid–femoral PWV were not significantly different for patients with unstable and stable disease. In addition, the determinants of AoPWV and CoWPV were not the same, and both were only slightly correlated, in keeping with what has been reported previously for elastic and muscular arteries.[20] Matrix degradation intervenes at the level of a vulnerable plaque, with a shift in the ratio of collagen[21,22] affecting the local elastic properties of coronary arteries, as described by intravascular ultrasound.[7] It is possible that these structural differences between unstable and stable plaques led to detectable differences in global vessel compliance and thus in CoPWV. However, high coronary compliance may also be a determinant of plaque rupture by increasing cyclic stretch. In this respect, an important point to consider is the relation between the aorta and the coronary arteries in terms of compliance because they are in close proximity. It is well established that there is a physiological stiffness gradient between the aorta and peripheral muscular arteries. This impedance mismatch is protective of the microcirculation because it prevents the transmission of forward-traveling pressure (by generating a reflected wave).[5] It fits with what was observed in stable CAD patients because CoPWV was markedly higher than AoPWV. Rolandi et al also reported CoPWV values that were ≈32% higher than those for AoPWV,[12] fueling the hypothesis of a protective mismatch. Conversely, the similar PWV values between the aorta and the coronary artery found in ACS may shift the compliance mismatch more distally in the coronary tree and provoke plaque rupture and ACS in the presence of a

vulnerable plaque.[6] This hypothesis is consistent with the fact that the majority of ACS events concerned the proximal third of the artery,[23] a segment that is probably exposed to high cyclic stretch. Fortier et al recently found that aortic–brachial stiffness mismatch was predictive of mortality in a dialysis population.[24] Our data roughly suggest a similar conclusion, namely, that the aortic–coronary stiffness mismatch may play a role in the occurrence of acute coronary events. Prospective studies, however, are needed to evaluate the prognostic impact of coronary compliance.

Another major effect detected by CoPWV, albeit expected, is that of stenting. This is in line with the increased AoPWV occurring after abdominal aorta stenting reported by our group.[18] Although a metal stent is expected to impair the compliance of an elastic artery, this has never been described in coronary arteries.

Limitations

The patient groups are of moderate size; however, the results were highly statistically significant. Assessments of CoPWV were not available in 4 patients because of artifacts, but improvements in the technique should resolve this point. Hemodynamics and transmural pressure may change between measurements in the catheterization laboratory and between patients; however, patients with heart failure were excluded, and an adjustment for DBP was made to avoid this bias. Measurement of coronary artery length is challenging. It was carefully determined when the wire was pulled outside the guiding catheter, but some errors are still possible. CoPWV values in nondiseased vessels are unknown because it does not seem ethical to perform such measurement in patients. Nevertheless, the fact that both groups (ie, stable and unstable disease) had established cardiovascular disease prevents an important bias in testing the association of CoPWV with vessel vulnerability. With respect to clinical utility, this technique is not appropriate for general population screening because of its invasive nature; however, it could be supplemental to a coronary angiogram to risk-stratify a plaque.

Perspectives

Vascular stiffness has an important prognostic impact. Although aortic stiffness is the parameter generally assessed, local stiffness may be more specific. At the coronary level, we described a safe method to measure CoPWV that can be used in routine practice during a coronary angiography. CoPWV seems to be lower in patients with ACS, but its prognostic consequences must be determined in dedicated prospective trials. This technique paves the way for a new field of research to better understand the pathophysiology of plaque complications and to better risk-stratify patients.

Acknowledgments

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Disclosures

None.

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b) Approche fondamentale : techniques de mesures de la VOPc chez le cochon

Comprehensive assessment of coronary pulse wave velocity in anesthetized pigs.

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Physiol Rep. 2020 May;8(9):e14424.

Contexte : Nous avons montré que la rigidité coronaire pouvait être évaluée par la mesure de la vitesse de l'onde de pouls coronaire (VOPc). La mesure de la VOPc reste complexe en raison de la coexistence des ondes antérogrades et rétrogrades. Ce travail de recherche fondamentale s'est intéressé aux différents algorithmes possible de mesure de la VOPc.

Objectifs : Évaluer la faisabilité, la répétabilité et la capacité des différentes méthodes d'évaluation de la VOPc.

Méthodes : Les manipulations ont été effectuées à l'école Vetagro-Sup sur 10 cochons sous anesthésie générale. Le VOPc a été mesurée en utilisant 2 guides de pression intracoronaire placés au niveau proximal et distal de l'artère interventriculaire aigue. 4 méthodes de mesures ont été étudiées: la méthode de l'intersection tangente appliquée à l'onde antérograde (FW) et à l'onde rétrograde (BK), ainsi que l'onde dicrote (DIC) et la méthode « template matching » (TM) (Figure 5). Les mesures ont été réalisées dans différentes condition hémodynamiques prédéfinies. La pression artérielle était obtenue par des agents vasoactifs et la fréquence cardiaque à l'aide d'un sonde d'entraiment reliée à pace maker externe. Une sténose coronaire a été obtenue par inflation d'un ballon intra-coronaire.

Résultats : Toutes les méthodes étaient significativement différentes entre elles ($p < 0,05$) avec une valeur de VOPc plus élevée par rapport à la méthode FW ($p < 0,05$ et $p < 0,10$). Une

corrélation a été mise en évidence uniquement entre les méthodes BK et FW et entre les méthodes DIC et TM ($p<0,05$). La VOPc augmentait en même temps que de la pression artérielle, cette augmentation étant significative pour les méthodes DIC, TM et en partie pour la méthode FW ($p <0,05$). La fréquence cardiaque n'avait pas d'impact systématique sur la VOPc. La variabilité la plus faible a été trouvée pour les méthodes DIC et TM ($p < 0,05$). Seules les méthodes BK et TM sont applicables en présence d'une sténose coronaire**.**

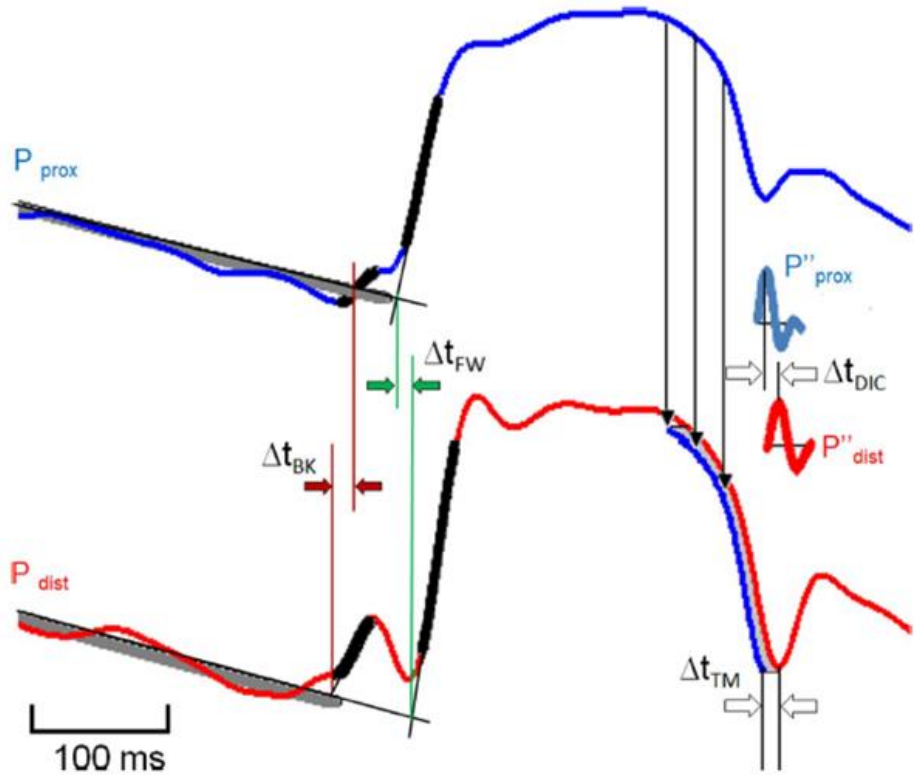

Figure 5 : Illustration des 4 méthodes utilisées pour mesurer la VOPc.

La VOPc est calculée à partir du rapport Δt/d; d étant la distance entre les sites d'enregistrement proximal et distal. Le temps de transit (Δt) de l'onde de pression entre les sites proximal (Pprox) et distal (Pdist) est calculé selon 4 méthodes différentes.
Méthode des tangentes appliquée à l'onde antérograde (FW) ΔtFW, (lignes vertes)
Méthode des tangentes appliquée à l'onde rétrograde(BK) ΔtBK, (flèches marrons)
Méthode basée sur la deuxième dérivée, correspondant à l'onde dicrote ΔtDIC,
Méthode dite de « template matching » (TM) ΔtTM, (lignes bleues).

Conclusion: Bien que la VOPc puisse être mesurée par diverses méthodes, les méthodes BK et TM semblent les plus appropriées pour les études cliniques.

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ORIGINAL RESEARCH

Physiological Reports

Comprehensive assessment of coronary pulse wave velocity in anesthetized pigs

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Abstract

Background: Coronary stiffness represents a new paradigm for interventional cardiology and can be assessed by coronary pulse wave velocity (CoPWV). Assessing CoPWV is complex because of the coexistence of backward and forward waves.

Objectives: Evaluate the feasibility, repeatability, and capacity of methods assessing CoPWV to detect predictable velocity changes.

Methods: CoPWV was measured from distal and proximal pressure guidewires in the left anterior descending artery of 10 pigs under general anesthesia. Four methods were studied: the tangent intersection method applied to the forward (FW) and backward (BK) waves, as well as the dicrotic notch (DIC) and template matching (TM) methods. All were evaluated at baseline, during various arterial pressure and heart rate conditions, during simulated flow limitation (balloon inflation), and after increasing coronary stiffness (stent insertion).

Results: All the methods were significantly different between them ($p \leq .05$) showing a systematic trend toward higher CoPWV when compared to the FW method ($.05 < p < .10$). Results were found to be significantly correlated only between the BK and FW methods and between the DIC and TM methods ($p \leq .05$). CoPWV increased with arterial pressure increase, this increase being significant for the DIC and TM methods and partly for the FW method ($p \leq .05$). Conversely, heart rate had no systematic impact on CoPWV. The lowest variability was found for the DIC and TM methods ($p \leq .05$). Only the BK and TM methods remained applicable during flow limitation; stent increased CoPWV when measured by the BK method only ($p \leq .05$).

Conclusion: Although CoPWV can be measured by various methods, the BK and TM methods seem the most appropriate for clinical studies.

KEYWORDS
coronary physiology, coronary stiffness, pulse wave velocity

1 | INTRODUCTION

Implementation of coronary physiology, that is, fractional flow reserve (FFR) or, more recently, instantaneous wave-free ratio (iFR), has been a major breakthrough in the cath lab (Davies et al., 2017; De Bruyne et al., 2012). In cases of intermediate coronary stenosis, the FFR and iFR indices are used as surrogates for coronary flow reserve (CFR), helping physicians during the decision-making process. Although an FFR > 0.8 identifies a group of patients with a low absolute risk of major adverse cardiac event (MACE) (Barbato et al., 2016), the value of a decision based on this cut-off alone is far from optimal as FFR and CFR, which both aim at identifying ischemia-prone lesions, are in disagreement in almost 30% of cases (Garcia et al., 2019; van de Hoef et al., 2014). Furthermore, these indices are not suitable for predicting acute plaque complication. In this context, new coronary physiology indices are required to improve the diagnosis of stable and unstable coronary artery disease. Coronary stiffness could represent such an index.

The matrix of the plaque and the structures surrounding the lumen of the vessels represent major determinants of mechanical properties of arteries and can explain how a stenosis behaves under increased pressure (such as during exercise stress) or resists to cyclic stretch. This may be important to determine how the stenosis impacts the flow increase. For instance, a "soft" stenosis behaves like a collapsible tube and the lumen diameter increases with flow increase (Conrad, 1969). Coronary stiffness may also impact the assessment of stenosis by pressure indices: FFR is erroneously higher when a fully distensible model of artery is used, that is, when stiffness is lower (Yong et al., 2017). Above all, coronary stiffness may influence the risk of acute coronary events: stiffer (Harbaoui, Courand, Cividjian, & Lantelme, 2017) or calcified (Criqui et al., 2014; Hou et al., 2012) coronary arteries are associated with lower risk of cardiovascular events. It follows that coronary stiffness is an attractive concept in the field of interventional cardiology in addition to pressure and flow indices.

Pulse wave velocity (PWV) in a uniform arterial segment is a surrogate for stiffness (Avolio, 2013; Lieber, 2000) and can be measured at the coronary level (CoPWV) by obtaining two simultaneous pressure measurements at a sufficient distance from one another. However, CoPWV has not yet been developed as a clinical tool, probably because of technical difficulties in signal analysis due to heart being itself a contractile organ. The present study therefore sought to assess, in an animal model, the feasibility of CoPWV measurements using different methods based on pressure wave characterization, but also the robustness of these measurements in well-controlled experimental conditions.

2 | METHODS

2.1 | Methods for measuring CoPWV

Measuring CoPWV is challenging because two pressure waves travel in the coronary tree during myocardial contraction, contrary to what is found in other arteries (Figure 1a): one is generated by the ventricular ejection and is responsible for systolic upstroke (hereafter called "*forward pressure wave*"); the other is generated by the compression of microvasculature during isovolumic cardiac contraction and travels in the opposite direction (hereafter called "*backward pressure wave*") (Davies et al., 2006; Sen, Petraco, Mayet, & Davies, 2014). At the distal side, the two waves are clearly separated and at the proximal side these overlap (Figure 1). The methods used in this study are described in Figure 2 which illustrates characteristic points of the pressure wave during pressure upstroke (compression phase) and pressure fall (decompression phase). The first two methods are obtained during the compression phase; the forward wave (FW) method is the classical foot-to-foot method using the tangent intersection to identify the onset of pressure rise (Chiu, Arand, Shroff, Feldman, & Carroll, 1991) applied to the forward wave; the backward wave (BK) method uses the tangent intersection to identify the onset of pressure rise applied to the backward wave. The two other methods are obtained during the decompression phase of the cardiac cycle; the dicrotic notch (DIC) method uses this characteristic point of the pressure wave (Rolandi et al., 2014), and the template matching (TM) method uses the fall in pressure during the decompression phase (Harbaoui et al., 2017).

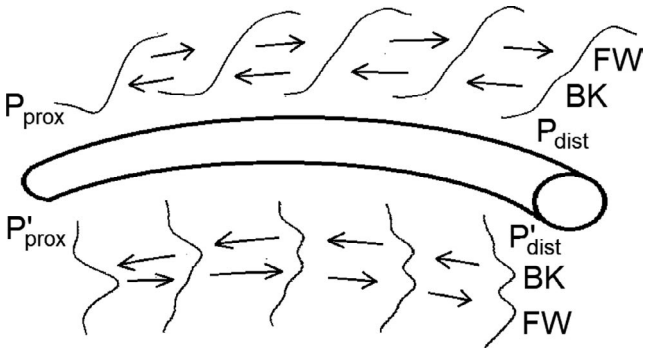

FIGURE 1 Morphology of the intra-coronary pressure at the proximal and distal levels in normal conditions. The propagation of the backward (BK) and forward (FW) pressure waves is shown at several positions across the coronary artery between proximal and distal locations on the pressure waves (upward: P_{prox} and P_{dist}) and on their first derivatives (downward: P'_{prox} and P'_{dist})

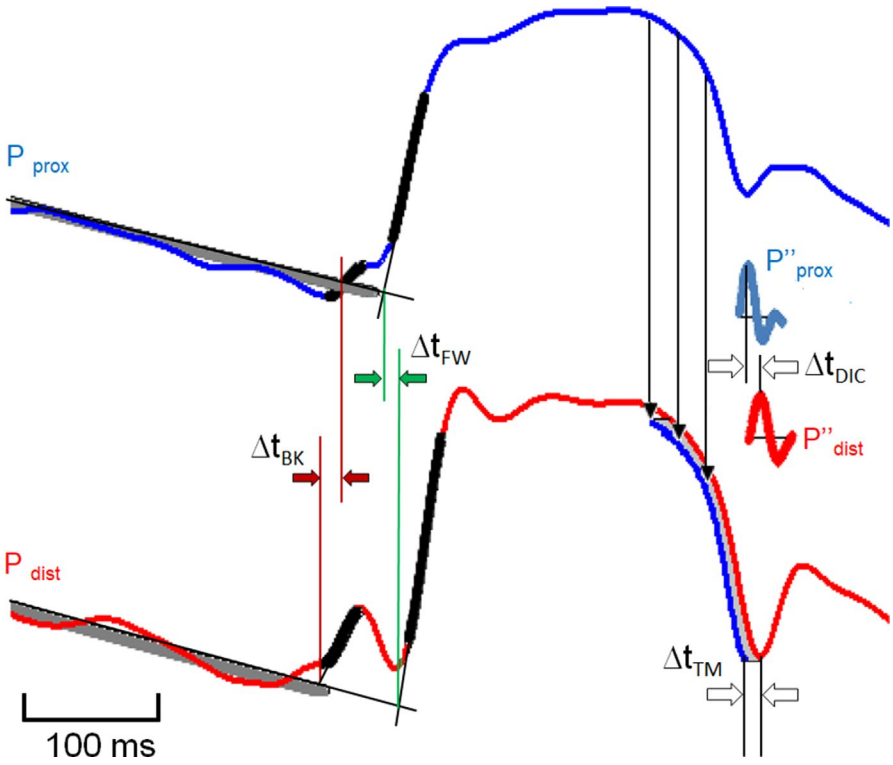

FIGURE 2 Illustration of the four methods used for measuring CoPWV. The transit time (Δt) of the pressure wave between the proximal (P_{prox}) and the distal (P_{dist}) sites can be calculated in four different ways; Δt_{FW}, tangent intersection method applied to the forward pressure (FW) rise (green lines); Δt_{BK}, tangent intersection method applied to the backward (BK) pressure rise (brown arrows); Δt_{DIC}, maximum of the second derivative corresponding to the dicrotic notch (DIC) (black lines); Δt_{TM}, template matching (TM) between two segments after a rescaling (blue lines). In all cases, CoPWV is calculated from the ratio $\Delta t/d$; d is the distance between proximal and distal recording sites

2.2 | Experimental set-up and study design

Experiments were conducted in 10 young (2.5–3.5 months old) female pigs, weighing a median [interquartile range, IQR] of 49 [46.3–50.3] kg, under general anesthesia. The experimental set-up, which is detailed in the Appendix, was approved by the ethics committee of the Ministry in charge of agriculture (n 2017042115139177), and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Heart rate (HR) was controlled by pacing through the jugular vein and intravenous esmolol infusion (Baxter Healthcare; up to 260 mg/h). Mean arterial pressure (MAP) changes were obtained using an intravenous infusion of norepinephrine (Mylan; up to 1.8 mg/h) and isosorbide dinitrate (Sanofi-Aventis; up to 32 mg/h), as needed. Two concomitant intra-coronary pressure signals were obtained using two identical FFR guidewires (Aeris™, Abbott), each connected to a distinct FFR integrated system (Quantien™). CoPWV was measured in the left anterior descending (LAD) coronary artery in the following conditions:

1. *Spontaneous baseline*: The two guidewires were first superimposed in the proximal LAD coronary artery in order to equalize the signals and avoid deviation. Then, while one guidewire ("proximal") was kept in the initial proximal position, the other ("distal") was positioned distally in the LAD coronary artery. Both guidewires were kept in the same position throughout the following steps. The distance between the two external connectors was measured with a millimeter precision ruler and was assumed to be equal to the distance between the proximal and the distal pressure sensors. The mean value and beat-to-beat variability (coefficient of variation, CV) of the CoPWV were calculated in baseline conditions.
2. *Hemodynamic conditions*: three levels of HR (90, 110, and 130 bpm) and aortic MAP (60, 80, and 100 mmHg) were imposed in a non-predefined order, following as closely as possible the current MAP which was more difficult to stabilize in the imposed condition. One condition (110 bpm, 80 mmHg) was repeated at periods separated by more than 20 min for assessment of period-to-period variability (CV) and repeatability (intra-class correlation, ICC).
3. *Induced flow limitation/coronary flow limitation*: at fixed HR and aortic MAP (110 bpm, 80 mmHg), an additional regular wire and an intravascular ultrasound (IVUS) probe (Opticross™, Boston Scientific) were inserted to assess the cross-sectional area of the mid LAD. Then, an angioplasty balloon of appropriate size, inflated at two different pressures, was inserted to resemble as closely as possible a mild (25% luminal surface decrease) and moderate (50% luminal surface decrease) flow limitation. The hemodynamic impact of flow limitation was confirmed by measuring the FFR. Hyperemia was achieved by intracoronary injection of a 150 µg of adenosine as described previously (Toth et al., 2016).

4. *Increased stiffness*: A stent was implanted in the mid LAD between the proximal and distal pressure sensors. The diameter of the stent (Synergy™, Boston Scientific) was chosen according to the mid LAD diameter measured by IVUS.

2.3 | Data acquisition and analysis

Intra-coronary proximal (P_{prox}) and distal (P_{dist}) pressures from the analog output of the two FFR consoles were sampled at 5 kHz using an analog/digital acquisition board (KUSB 3100, Keithley-Tektronix) and software (RECAN, Alpha-2). During acquisition, the acquired waveforms were digitally filtered as described in the Appendix. The acquired signals were pre-processed off-line using RECAN as detailed in the Appendix.

CoPWV was measured off-line using a software library (i-COR, Pulsalys - Université de Lyon/ Hospices Civils de Lyon and i-COR Technologies) linked to RECAN. i-COR library computed, for each cardiac cycle, the pressure-wave transit delay across the artery between the two pressure sensors using the four concomitant methods detailed above. The transit delays were automatically filtered as described in the Appendix and CoPWV was calculated by dividing the filtered delays by the distance between the pressure sensors. The final CoPWV was the mean of all the filtered CoPWV obtained during a 1-min period.

2.4 | Statistical analysis

Data are expressed as median [IQR]. As not all data had normal distribution, non-parametric methods for paired samples were used for comparisons. A Wilcoxon test was used when two comparisons were performed, and a Friedman test followed by the Wilcoxon test were used when more than two comparisons were performed. For the spontaneous baseline step, linear regressions between CoPWV assessed by all possible methods two-by-two were computed. Similarly, Bland-Altman plots were obtained for all methods two-by-two, by plotting differences between CoPWV assessed by two methods against their mean values; the mean and the standard deviation (*SD*) of these differences were used as indices of dispersion. Existance of a proportional bias was tested using linear regression analysis. After verification of the proportionality between *SD* and mean of the CoPWV (significant and positive coefficient of linear regression), variability was assessed for all four methods using the CV of CoPWV within the same 1-min period (called "beat-to-beat": between 90 and 130 values, depending on the HR) or between two different 1-min periods (called "period-to-period": 2 values). A logarithmic transformation of the CV was used prior to statistical analysis. Repeatability between two different 1-min periods was assessed using the ICC. As the onset of the forward wave is the established characteristic point used for the determination of the pressure transit time for the PWV calculation (Chiu et al., 1991), the FW method was considered the reference method for the statistical tests applied to the CoPWV and its variability, excepting the agreements (Bland-Altman) and linear regressions for whom no assumption of reference method was made. A test with $p \leq .05$ was considered significant. The data were analyzed using SPSS software (version 21, IBM Corp).

3 | RESULTS

One pig died at the beginning of the flow limitation step, because of LAD thrombosis resulting in ventricular fibrillation with resuscitation failure. Thus, the first two steps were carried out in all ten pigs, whereas steps 3 and 4 could be carried out in nine pigs only. The results for each experimental condition are presented below.

3.1 | Condition 1: spontaneous baseline

The median [IQR] baseline aortic MAP was 61.5 [55.8–71.8] mmHg and that of HR was 85 [75.2–98.7] bpm. The four methods computing CoPWV yielded significantly different values (Friedman test: $p \leq .05$); there was a systematic trend towards higher CoPWV for all methods when compared to the FW method (Wilcoxon test, as compared to the FW method: $p = .06$ for BK, $p = .07$ for DIC, and $p = .09$ for TM). Beat-to-beat variability was significantly higher for the BK and DIC methods as compared to the FW method, while period-to-period variability was significantly lower for decompression methods (DIC and TM) as compared to the FW method. The highest period-to-period repeatability was observed for the TM method (Table 1).

CoPWV estimated with the BK method was significantly correlated with that obtained with the FW method ($r^2 = .81$, $p < .001$) but not with the others; CoPWV obtained with the DIC method was significanty correlated with that obtained with the TM method ($r^2 = .96$, $p < .001$). The lowest Bland-Altman dispersions were observed for these comparisons. The only proportional bias was observed between the DIC and the TM methods (Table 2; Figure 3).

3.2 | Condition 2: variable hemodynamic conditions

The BK method did not detect the backward wave in the low blood pressure condition (aortic MAP 60 mmHg) and therefore CoPWV was not calculated. There was no systematic significant effect of HR on the CoPWV for each pressure

TABLE 1 CoPWV values obtained by the four methods

	Compression method		Decompression		
	Forward (FW)	Backward (BK)	Dicrotic Notch (DIC)	Template matching (TM)	Friedman
Median [IQR] CoPWV (m/s)					
Baseline	4.6 [4.1–6.1]	5.3 [3.9–7.0]	5.8 [4.6–6.9]	6.3 [3.9–7.4]	$p \leq .05$
Variability: median [IQR] CV of CoPWV (%)					
Beat-to-beat	9.6 [8.5–13.7]	15.2 [13.9–17.8]*	13.4 [11.1–17.8]*	10.3 [8.3–12.9]	$p \leq .05$
Period-to-period	10.1 [4.3–20.3]	12.8 [7.1–35.3]	4.8 [1.6–14.3]*	3.5 [0.7–13.8]*	$p \leq .05$
Period -to-period repeatability: Mean [95%CI] ICC					
Single measures	0.72 [0,14–0,94]	0,74 [0.29–0,93]	0.72 [0,24–0.92]	0.79 [0.39–0.94]	
Average measures	0.84 [0.25–0.97]	0.85 [0.44–0.96]	0.84 [0.39–0.96]	0.88 [0.56–0.97]	

Note: Coronary pulse wave velocity (CoPW) obtained in baseline conditions. Beat-to-beat variability was obtained in spontaneous baseline conditions. Period-to-period variability and repeatability were obtained during two repeated conditions with similar heart rate and mean arterial pressure conditions and expressed as median [IQR]. A logarithmic transformation of the CV was used before the statistical analysis.

Abbreviations: CV, coefficient of variation; ICC, intra-class correlation.

*$p \leq .05$ as compared to FW.

level and each evaluated method; a significant effect was observed with the TM method for aortic MAP = 80 mmHg, and a trend was observed with the BK ($p = .09$) and DIC ($p = .08$) methods for aortic MAP = 80 mmHg. Individual HR values were therefore pooled for each pressure level and each evaluated method. Pooled CoPWV increased for all four methods with increasing aortic MAP, this increase reaching statistical significance for the methods FW, DIC, and TM when aortic MAP increased from 60 to 80 mmHg and for the methods DIC and TM when aortic MAP increased from 80 to 100 mmHg. Of note, the intra-coronary MAP was slightly lower than the aortic MAP (Table 3).

3.3 | Condition 3: flow Limitation

The validity of flow limitation was confirmed by FFR values: the median [IQR] FFR was 0.83 [0.75–0.89] for flow limitation I, and 0.73 [0.63–0.80] for flow limitation II. The FW method did not detect the forward wave at the distal side in the flow limitation condition, due to the higher amplitude of the backward wave during flow limitation (Figure 4), and CoPWV was therefore not calculated. Indeed, during stenosis the tangent to the forward wave was performed on a shorter segment which was in addition tilted by increased amplitude of the backward wave. Using the tangent intersection method induced an error in the determination of the onset of the forward wave. Similarly, the DIC method did no detect the dicrotic notch in the flow limitation condition, precluding the calculation of CoPWV. No significant difference was observed between flow limitation (I or II) and pre-inflation period when CoPWV was assessed by the BK method. When measured by the TM method, the median CoPWV was significantly lower during flow limitation II than pre-inflation (Table 4).

3.4 | Condition 4: increased stiffness

Implanted stents had a length of 28 or 32 mm and a diameter of 2.5 or 2.75 mm to fit the arterial lumen. Stent implantation

TABLE 2 Agreement between methods computing CoPWV during spontaneous baseline

Pair of compared methods	Correlation coefficient r^2	Linear regression p	Bland-Altman dispersion mean (m/s)	Bland-Altman dispersion *SD* (m/s)	Bland-Altman proportional bias (Y/N)
BK - FW	**.81**	**<.001**	0.45	0.71	N
BK - DIC	.33	.08	0.40	1.45	N
BK - TM	.22	.18	0.55	1.85	N
FW - DIC	.31	.1	0.85	1.36	N
FW - TM	.18	.23	1.00	1.82	N
DIC - TM	**.96**	**<.001**	0.15	0.55	Y

Note: Abbreviations: BK, backward wave method; DIC, dicrotic notch method; FW, forward wave method; TM, template matching.

Lines in bold corespond to the combinations with the highest correlation coefficient and the lowest dispersion SD

TABLE 3 Impact of heart rate and mean arterial pressure on CoPWV assessed by the four methods

Methods	HR (bpm)	Median [IQR] CoPWV MAP_a 60 mmHg MAP_c 51.9 mmHg	MAP_a 80 mmHg MAP_c 66.4 mmHg	MAP_a 100 mmHg MAP_c 83.7 mmHg
Forward (FW)	90	4.2 [3.6–5.0]	7.1 [5.0–8.6]	5.3 [3.5–9.5]
	110	4.3 [3.8–5.5]	5.8 [4.0–11.0]	7.3 [5.8–8.1]
	130	4.0 [3.6–4.6]	5.9 [3.5–7.0]	8.3 [5.9–13.0]
	Pooled	**4.1 [3.8–4.9]**	**6.0 [4.2–7.7]***	**7.3 [5.3–9.2]**
Backward (BK)	90	–	4.6 [3.7–7.6]	4.2 [3.8–11.2]
	110	–	4.6 [3.7–7.5]	7.4 [3.4–12.5]
	130	–	7.9 [5.7–9.5]	8.1 [4.5–12.4]
	Pooled	–	**5.1 [4.1–9.0]**	**6.1 [3.9–12.0]**
Dicrotic Notch (DIC)	90	5.3 [4.5–6.3]	6.6 [5.6–8.6]	8.5 [7.5–9.3]
	110	5.2 [4.6–6.4]	7.9 [6.2–8.8]	8.7 [7.1–9.3]
	130	5.7 [4.5–6.3]	7.8 [5.8–8.5]	8.6 [7.9–9.5]
	Pooled	**5.4 [4.6–6.3]**	**7.7 [5.9–8.5]***	**8.6 [7.8–9.3]**
Template Matching (TM)	90	5.4 [4.3–6.4]	8.0 [6.2–8.9]	9.2 [7.2–10.3]
	110	5.2 [4.3–6.8]	8.1 [6.7–9.6]	8.9 [6.8–10.4]
	130	5.9 [4.3–6.7]	7.9 [6.0–9.1]	9.3 [7.2–10.1]
	Pooled	**5.5 [4.4–6.7]**	**7.9 [6.2–9.0]***	**9.0 [7.2–10.2]†**

Note: Data are presented as median [interquartile range]. CoPWV could not be calculated by BK method at 60 mmHg.

Abbreviations: bpm, beats per minute; CoPWV, coronary pulse wave velocity; HR, heart rate; MAP_a, aortic mean arterial pressure; MAP_c, coronary mean arterial pressure. Lines in bold correspond to pooled CoPWV at a given MAP_a.

*$p \leq .05$ versus $MAP_a = 60$ mmHg.

†$p \leq .05$ versus $MAP_a = 80$ mmHg.

did not impede the use of any CoPWV measurement method. When measured by the BK method, the median CoPWV was significantly higher after stenting (Table 4).

4 | DISCUSSION

The present study demonstrates that algorithms used to measure aortic or carotid PWV (FW and DIC methods) may be used for CoPWV measurement in healthy coronary arteries when blood flow is normal, but that these are not adapted to measure CoPWV in vessels presenting a reduction in blood flow. In the case of reduced blood flow, the BK and TM methods should be preferred since they allow the calculation of CoPWV in various hemodynamic conditions, that is, in normal conditions as well as in the presence of a reduced blood flow. It is of note, however, that BK and TM measure wave propagation at different states of the coronary artery (relaxed, i.e., less stiffer, vs. elongated, i.e., stiffer) and that although both provide interpretable results, these are not correlated. Therefore further work is required to determine which of these is the most informative, or if both are necessary for a complete characterization of coronary stiffness.

PWV in a uniform arterial segment is dependent on its stiffness but not on the direction of wave motion. Accordingly, CoPWV could be assessed by the propagation of the forward and backward waves, and both methods gave highly correlated values. The coronary backward wave originates from the contraction of the myocardial apex during isovolumic contraction (van Houwelingen et al., 2012). To the best of our knowledge, a backward wave has never been clearly identified on the intra-coronary pressure itself except by using wave intensity analysis (Davies et al., 2006; Sen et al., 2014). This could be due to the fact that the sampling rate used in previous studies (0.1–1 kHz) is insufficient to clearly observe the backward wave. A previous observation from our group (Harbaoui et al., 2017) was made possible by a 2 kHz sampling, and the higher rate used herein (5 kHz) allowed an even more precise characterization of the backward wave. Conversely, a pressure perturbation due to isovolumic contraction was identified in the aorta (AIC) during

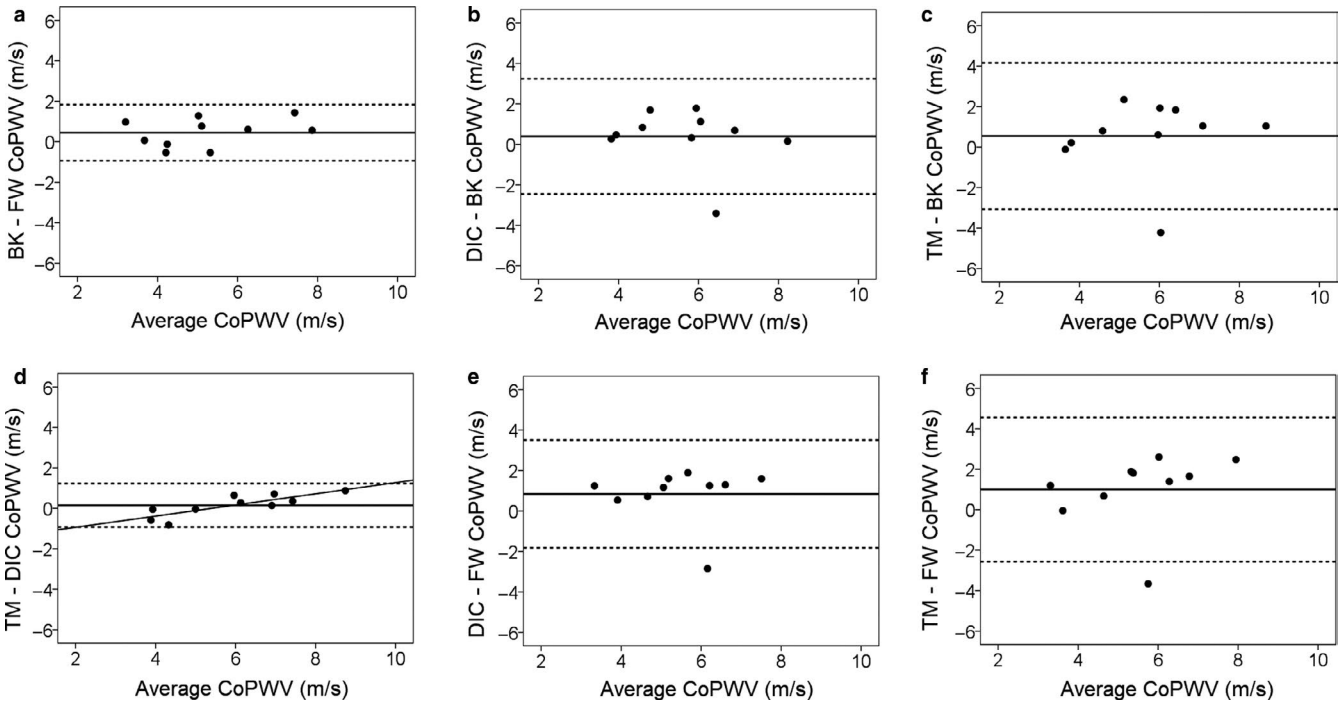

FIGURE 3 Bland–Altman plots comparing all the possible combinations between the four analysis methods in spontaneous baseline conditions: method BK versus FW (a), method DIC versus BK (b), method TM versus BK (C), method TM versus DIC (d), method DIC versus FW (e) and method TM versus FW (F). Horizontal lines indicate mean and 95% confidence interval (±1.96 *SD*). The smallest confidence interval was observed between the method TM and DIC (d) and between the methods BK and FW (a). The only proportional bias was observed for the plot between the method TM ans DIC (D)

TABLE 4 Impact of flow limitation and stenting on CoPWV assessed by the four methods

	Median [IQR] CoPWV (m/s)				
	Pre-inflation	**Flow limitation I**	**Flow limitation II**	**Pre-stenting**	**After stenting**
Forward (FW)	4.9 [4.3–6.0]	–	–	8.9 [4.8–14.3]	3.6 [3.1–10.1]
Backward (BK)	4.1 [3.0–6.2]	4.5 [3.4–5.8]	4.1 [2.4–8.2]	4.9 [2.7–7.4]	5.4 [3.3–9.0]†
Dicrotic notch (DIC)	6.4 [6.2–7.4]	–	–	6.2 [6.1–6.9]	6.0 [5.3–7.0]
Template matching (TM)	6.6 [5.7–7.4]	5.2 [4.5–6.6]	4.9 [4.2–5.4]*	6.0 [5.5–6.7]	5.8 [4.5–6.4]

Note: Data are presented as median [interquartile range]. CoPWV, coronary pulse wave velocity.

*$p \leq .05$ versus Pre-inflation.

†$p \leq .05$ versus Pre-stenting.

isovolumic contraction (van Houwelingen et al., 2012). Whether AIC can also be observed at the proximal coronary level and thus interfere with the detection of the backward wave has never been documented. We consider that this is very unlikely due to the different travelling time of the AIC and backward pressure waves. The limits of backward wave detectability should be extensively validated in humans, especially in case of asynchronous/pathological myocardial contractions that could impact the quality of this waveform.

Regarding coronary stiffness, if it increases, as it is the case after elongation, PWV will increase. This has been reported for the carotid artery, with significantly lower PWV in early systole compared to end systole (Mirault et al., 2015), and observed herein; there was a trend toward higher CoPWV measured in the elongated artery (decompression: DIC and TM) than when this was measured in a relaxed artery (compression phase: FW). Furthermore, these methods were poorly correlated with the compression FW method. Of note, decompression methods had the best performance for

period-to-period variability, which is an important feature for any potential clinical application.

Another condition in which stiffness should vary in relation to artery elongation, is a change in hemodynamic conditions, particularly blood pressure increase; herein, CoPWV increased with increasing MAP and this trend was consistent for all methods tested, which is similar to that reported in the coronary artery in dogs (Arts, Kruger, Gerven, Lambregts, & Reneman, 1979) and in other arteries (Nichols, O'Rourke, & Charalombos, 2011; Vermeersch, Dynamics, & Society, 2010). However, the velocity–pressure relationship in the coronary artery, which is a muscular artery, seems to have a shape (concave power function with exponent < 1) (Arts et al., 1979) different from the shape of the velocity-pressure relationship observed in the aorta which is an elastic artery (convex power function with exponent > 1) (Nichols et al., 2011; Vermeersch et al., 2010). Indeed, for a 10 mmHg aortic MAP increase, CoPWV increased by 0.95 m/s from 60 to 80 mmHg and by 0.64 m/s from 80 to 100 mmHg with FW, by 0.52 m/s from 80 to 100 mmHg with BK, by 1.17 m/s from 60 to 80 mmHg and by 0.44 m/s from 80 to 100 mmHg with DIC, and by 1.17 m/s from 60 to 80 mmHg and by 0.55 m/s from 80 to 100 mmHg with TM method. Regardless of its shape, the fact CoPWV increased with increasing MAP has two implications: first, it strongly supports that CoPWV measurements are indices of stiffness, and secondly, that the variation of MAP required to produce meaningful changes of CoPWV markedly surpass those routinely observed during coronary catheterization. Thus, this pressure effect should not represent an issue for the clinical application of CoPWV. Conversely, the effect of HR was non-significant, which is, again, consistent with previous reports that found that increasing HR was associated with a lower PWV change than increasing blood pressure (Albaladejo et al., 2001; Lantelme, Mestre, Lievre, Gressard, & Milon, 2002). From a clinical perspective, this is important since HR variations are frequent, but will not adversely affect the validity of the CoPWV value.

In the condition of flow limitation induced by balloon inflation, the backward wave became particularly noticeable at the distal coronary side; the resulting overlap between the backward wave and the forward wave prevents using the classical foot-to-foot method applied to the forward wave (*i.e.,* the FW method). The presence of the backward wave has previously been observed in human stenosed coronaries (called "premature pressure increase") (Harbaoui et al., 2017), validating in a reverse manner the observation made in pigs in case of flow limitation: the amplitude of the backward wave decreased after flow restauration by angioplasty in humans (unpublished data). Due to a filtering effect, increasing flow limitation severity also smoothed the dicrotic notch, precluding the use of the DIC method to measure CoPWV in case of flow limitation. Only the BK and TM methods were able to provide data and only the TM method found a lowering of CoPWV with increasing flow limitation. Applying the Bramwell-Hill equations (Nichols et al., 2011) to an annular lumen can explain this lowering: the subtraction of the constant balloon's cross-sectional area from that of the artery's cross-sectional area leads to a lower denominator but unchanged numerator as the area variation is dependent only on the artery diameter which is unchanged by balloon inflation. As the balloon induced a reduction of the lumen's cross-sectional area by a median [IQR] of 31 [25–38]% (flow limitation I) and 38 [36–42]% (flow limitation II), CoPWV should decrease by a median [IQR] of 17 [14–21]% (flow limitation I) and 21 [20–24]% (flow limitation II) according to the Bramwell-Hill equation. Moreover the lowering of the distal intra-coronary pressure due to simulation of flow limitation should have a slight lowering effect according to the velocity–pressure relationship: lowering by a median [IQR] of 2 [0–11]% (flow limitation I) and 9 [6–15]% (flow limitation II). Thus, the overall predicted theoretical effect of a flow limitation should be a decrease by an approximate median [IQR] of 17 [14–34]% (flow limitation I) and 35 [22–41]% (flow limitation II), which is in line with obtained results: 18 [13–25]% (flow limitation I) and 29 [15–31]% (flow limitation II). This is discordant with what is expected to be observed in clinical practice for a true stenosis as the CoPWV should increase according to the Moens–Korteweg relationship (CoPWV is inversely proportional to the square root of the artery's diameter).

Importantly, the presence of two guidewires in the coronary should not have impacted the coronary flow: the sum of the cross-section areas of the 2 guidewires of 0.014'' = 0.35 mm is $2 * \pi * 0.1225/4 = 2 * 0.096 = 0.19$ mm^2 which is much lower than the cross section of the coronary artery measured by IVUS (range 6 – 13.5 mm^2).

Stenting was used to increase the stiffness of the coronary artery, and only the BK method was able to detect a subtle increase of CoPWV, while the TM and other methods were unable to do so. Since the distal guidewire was jailed by the stent, pressure surge may have further reppeled the sensor in contact with the artery wall. This could have affected the upper part of the pressure wave and thus the related methods (TM and DIC methods), but it would have less likely impacted the lower part, explaining that the BK method was the only one providing the expected results. Nevertheless, the TM and DIC methods could have been equally affected during flow limitation by the smoothing of the pressure wave during the decompression fall (Figure 4) inducing a nonphysiological wave tilt. This smoothing was not observed on the backward wave which was, conversely, easier to detect due to its higher amplitude.

4.1 | Limits

The porcine model of coronary circulation is widely accepted as representative of human coronary circulation. Of note, the various methods tested led to CoPWV values around 4–9 m/s,

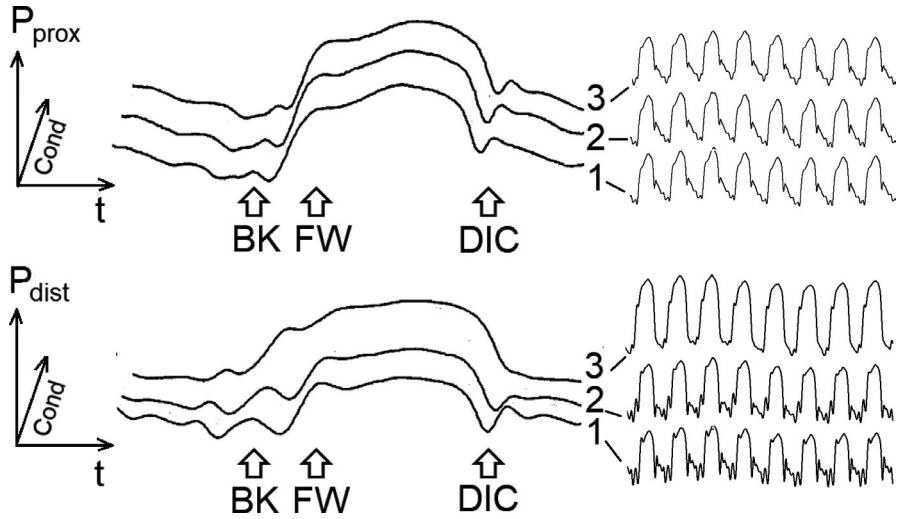

FIGURE 4 Impact of flow limitation on the amplitudes of the backward (BK) wave and of the dicrotic notch (DIC) in the proximal (P_{prox}) and distal pressure (P_{dist}) signals. Conditions 1, 2, and 3 are for baseline, flow limitation I (mild), and flow limitation II (moderate), respectively, at fixed hemodynamic conditions (heart rate = 110 bpm and aortic mean arterial pressure = 80 mmHg). All drawings show typical real traces: detail of a pressure wavefrom during one cardiac cycle at the left side and condensed concecutive pressure waveforms during a respiratory cycle at the right side

which are very close to those reported in dogs, especially for higher pressures (Arts et al., 1979). Indeed, applying a previously reported formula (CoPWV = 1.44 $P^{0.69}$, with P in kPa) obtained using a method similar to the FW method (Arts et al., 1979), the three levels of intra-coronary pressure obtained in our experiments, yielded velocity values of 5.5 m/s, 6.5 m/s, and 7.6 m/s, values very similar to those obtained using the FW method (4.1 m/s, 6.0 m/s, and 7.3 m/s). Regarding the CoPWV obtained in humans, the DIC method yielded higher values (mean ± *SD*: 15.9 ± 1.8 m/s with) than those obtained herein in pigs (median [IQR] :5.8 [4.6–6.9] m/s) (Rolandi et al., 2014), which would be expected as the patients were elderly (68 ± 10) and the investigated arteries were not angiographically normal, both factors leading to an increase in CoPWV,

Implications concerning the use of pharmacologic agents on coronary stifness should be discussed. Norepinephrine has a known beta-adrenergic effect at moderate/high doses, as observed in the present study, as well as a controversial possible vasoconstrictor effect on coronary arteries. Isosorbide dinitrate is a NO-releasing vasodilator which also acts at the coronary level. Isoflurane also has a possible vasodilator coronary effect. It is thus highly possible that the mentioned pharmacological substances have a confounding effect on coronary stiffness, independently of the arterial pressure, but no other options were available to induce pressure variations.

The major limit of this model is, however, the fact that coronary arteries were non-diseased, contrary to the potential clinical application envisioned for CoPWV. Healthy pigs were used in order to study the independent effects of hemodynamic variations, flow limitation, and increased stiffness on CoPWV. These experiments should be reproduced in a porcine model of advanced coronary atherosclerosis. Furthermore, we used a model of coronary flow limitation that is published (Young et al., 2013), but that may not compare to true vessel wall thickening. Another potential limitation is that stenting as an experimental model of coronary stiffening may not lead to a sufficient change of stiffness; stents were rather short and expanded within a normal artery. Furthermore, the distal wire was jailed by the stent, potentially disturbing pressure signal at high pressure. This may explain why only one method was able to reproduce the results obtained in humans in whom stenosis relief and stenting were associated with an increase of CoPWV (Harbaoui et al., 2017).

5 | CONCLUSION

Using a comprehensive analysis of wave propagation, the present study found that CoPWV can be measured by various methods using different characteristic points. Among those tested, two were found to be of potential intersest for further studies in humans.

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CONFLICT OF INTEREST

AC, BH, CC, PYC, and PL are shareholders of I-COR Technologies exploiting two patents concerning the computation of the coPWV. The remaining authors report no relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

AC, BH, and PL conceived and planned the experiments. AC, BH, CC, JMB, CP, PYC, and PL carried out the experiments. AC performed the data analysis. AC and PL performed the statistical analysis. AC, BH, CC, PYC, and PL contributed to the interpretation of the results. AC took the lead in writing the manuscript. AC and PL wrote the manuscript in consultation with BH and PYC. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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APPENDIX 1
METHODS - DETAILED DESCRIPTION

Anesthesia and ventilation

Animals were sedated with an intramuscular administration of a 1:1 mixture of tiletamine and zolazepam (Zoletil™ 100, 100 mg/ml, Virbac, Carros, France), 3.0 mg/kg and morphine 0.1 mg/kg. Induction was carried out with propofol (Propovet, 10 mg/ml, Axience, Pantin, France) 4.0 mg/kg intravenously. After induction of anesthesia, animals were orotracheally intubated and placed under mechanical ventilation with the controlled tidal volume set at 8.0 ml/kg and a respiratory rate of 15 cycles/min. Heart rate was monitored from ECG (screw electrodes inserted in the skin) using a patient monitor (MX700 IntelliVue, Philips, Boeblingen, Germany). Maintenance of anesthesia was ensured by volatile anesthesia with sevoflurane (SevoFlo, Axience, Pantin, France). Intravenous Ringer lactate was administered during the experiment at a basal rate of 10 ml kg^{-1} h^{-1}.

Vascular approach, temporary pacemaker insertion, and coronary angiogram

The skin at the operation site was cleansed with antiseptic solution and the neck covered with sterile drapes to keep the incision area as clean as possible. A right and a left lateral cervicotomy were performed to isolate the jugular vein and the carotid artery on the right side, and the contralateral jugular vein on the left side. A central venous catheter (6 French) was inserted in the left jugular vein for fluid and drug administration. An additional 6 French desilet was inserted into the right jugular vein for the external atrial pacing at the three selected heart rates.

An arterial catheter (7 French, Aeris™, Abbott, Saint-Paul, MN, US) was inserted into the carotid artery allowing to introduce the coronary angiography probe 7 French (JR4 or JL3,5) into the LAD. 10 000 Units of Unfractionated Heparin (Panpharma, Luitré, France) and 250 to 500 mg of Aspirin (Sanofi-Aventis, Gentilly, France) were administrated intravenously. Contrast injection (iobitridol, Guerbet, Roissy, France) was used for testing of the appropriate position. Isosorbide dinitrate (1 mg) (Sanofi-Aventis, Gentilly, France) was administered intra-coronarily before the start of experiments in order to avoid coronary spasm that may occur during a coronary angiogram and to counteract the effects of the other drugs used during experiments. The left coronary artery was chosen because of its similarity to the human coronary artery.

A catheter-based invasive blood pressure measurement tool was inserted until the proximal side of the angiography probe and then connected to the same Philips patient monitor used for the ECG monitoring. To avoid catheter clotting, a heparinized sodium chloride flush was done every minute and before each recording. Two concomitant signals of intra-coronary pressure were obtained using two identical FFR guidewires (Aeris™, Abbott) each connected to a distinct FFR integrated system of same manufacturer's reference (Quantien™, Abbott).

Data filtering during acquisition

During acquisition, the acquired waveforms were digitally filtered: ECG-baseline and power-line and low-pass filter (Finite Impulse Response – FIR filter, Blackman window, 60 Hz, 201 coefficients). P_{prox} and P_{dist}: low-pass filter (FIR filter, Blackman window, 30 Hz, 701 coefficients).

Data pre-processing

The pre-processing of acquired data by the RECAN software (Alpha-2, Lyon, France) are described below. Beat-by-beat HR and systolic and diastolic P_{dist} were automatically calculated and manually edited afterwards in order to exclude extrasystoles or periods with disturbed signals. The graphical user interface of RECAN allowed visual selection of the most stable 1-min analysis periods and of the nadir of P_{dist} after adenosine administration. First derivatives of P_{prox} and P_{dist} were computed for each sample using a three-point central difference algorithm. A positive threshold automatically adjusted on the maximum of P_{prox} and P_{dist} derivatives during a cardiac cycle allowed detection of the onset of the initial pressure rise in P_{prox} and P_{dist} signals. A negative threshold automatically adjusted on the minimum of P_{prox} and P_{dist} derivatives during a cardiac cycle allowed detection of the onset of the pressure fall after the end of the cardiac contraction in P_{prox} and P_{dist} signals.

Computing of the pressure wave transit time

The four methods for the computation of the pressure wave transit time between the two pressure sensors are detailed below. *Forward method (FW)*: The forward wave was considered to be the initial pressure rise detected in P_{prox} and P_{dist} signals (Figure 2) using their derivatives during preprocessing. The tangent intersection method was adapted to the forward wave as follows. A linear regression was performed on a segment of 30 ms centered on the maximum of the pressure derivative corresponding to the forward wave. As long as the regression coefficient was lower than 0.999, the regression was repeated on the segment shifted towards posterior times by a 2 ms increment until the segment reached the maximum

of the pressure or the regression coefficient was higher than 0.999. If the maximum regression coefficient during all the iteration was lower than 0.750, the corresponding cardiac cycle was discarded from further analysis, otherwise, the regression with the maximum regression coefficient was memorized. The natural logarithm of the pressure fall during diastole of the precedent cardiac cycle was calculated. A linear regression was calculated on a segment of the pressure logarithm starting after the dicrotic notch of the precedent cardiac cycle and ending before the onset of the pressure rise of the current cardiac cycle. If the regression coefficient of this linear regression was high enough, the diastolic pressure was given by the extrapolation of this regression at the moment of the pressure minimum before the onset of the forward wave, otherwise, the diastolic pressure was the pressure minimum before the onset of the forward wave. The intersection point between the tangent to the forward pressure rise and the diastolic pressure was considered to be the final value of the foot of the forward wave. The interval of time between the foot of the forward wave of P_{prox} and the foot of the forward wave of P_{dist} was considered to be the transit time of the compression forward wave.

Backward method (BK): The backward wave was detected as follows. The minimum of the P_{prox} and P_{dist} derivatives was detected just before the onset of the initial pressure rise in P_{prox} and P_{dist} signals detected during preprocessing. The maximum of the P_{prox} and P_{dist} derivatives corresponding to the backward pressure rise was detected just before the minimum P_{prox} and P_{dist} derivatives within 70 ms. If this maximum of pressure derivative was not positive or not distinct from the following minimum of the pressure derivative, the final/definite maximum of the pressure derivative corresponding to the backward wave was those detected during preprocessing and corresponding to the onset of the initial pressure rise. The tangent intersection method was adapted to the backward wave for the P_{prox} and P_{dist} signals as follows (Figure 2). A linear regression was performed on a segment of 25 ms centered on the maximum of the pressure derivative corresponding to the backward wave. While the regression coefficient was lower than 0.999, the regression was repeated on the segment shifted towards anterior times by a 2 ms increment until the segment reached the minimum of the pressure or the regression coefficient was higher than 0.999. If the maximum regression coefficient during all the iteration was lower than 0.750, the corresponding cardiac cycle was discarded from further analysis, otherwise, the regression with the maximum regression coefficient was memorized. The natural logarithm of the pressure fall during diastole of the precedent cardiac cycle was calculated. A linear regression was calculated on a segment of the pressure logarithm starting after the dicrotic notch of the precedent cardiac cycle and ending before the onset of the pressure rise of the current cardiac cycle. If the regression coefficient of this linear regression was high enough, the diastolic pressure was given by the extrapolation of this regression at the moment of the pressure minimum before the onset of the backward wave, otherwise, the diastolic pressure was the pressure minimum before the onset of the backward wave. The intersection point between the tangent to the backward pressure rise and the diastolic pressure was considered to be the final value of the foot of the backward wave. The delay between the foot of the backward wave of P_{dist} and the foot of the backward wave of P_{prox} was considered to be the transit time of the compression backward wave.

Dicrotic notch method (DIC): The dicrotic notch was detected as follows. The nadir of the P_{dist} and P_{prox} derivatives was detected immediately after the onset of the pressure fall detected during preprocessing. The second derivative of each pressure signal was calculated on the 60 ms segment between the nadir and the following maximum of the pressure first derivative using a three-point-stencil central difference algorithm applied to the averaged (10-points moving average) first derivative. The maximum of the second derivative on this segment was considered to be the dicrotic notch (Figure 2). The delay between the dicrotic notch of P_{prox} and P_{dist} was considered to be the transit time of the decompression pressure wave. *Template matching (TM)*: The template matching method was applied as follows. The amplitudes of the nadir of P_{prox} and P_{dist} derivatives were calculated. A segment was delimitated on P_{prox} and P_{dist} fall, starting with the point where pressure derivative was 30% of the nadir's amplitude and ending at the point corresponding to the dicrotic notch. The two segments delimitated on P_{prox} and P_{dist}, were rescaled with a coefficient equal to the ratio of the derivative nadir's amplitudes and then shifted sample by sample in order to obtain the best template matching. The shift between the two segments corresponding to the best template matching was considered to be the transit time of the decompression pressure wave (Figure 2).

Filtering of abnormal transit times

Transit times outside the interval [4–40] ms were considered abnormal and were excluded. Then, the mean of all the remaining transit delays was calculated during a 1-min period and only the values in the interval of ±33% of the 1-min mean were kept. Finally, the distance between the sensors was divided by the filtered values of the transit delay, resulting in a time series of instantaneous CoPWV for each cardiac cycle.

c) Relation FFR CFR

Relationship between FFR, CFR and coronary microvascular resistance – Practical implications for FFR-guided percutaneous coronary intervention

Garcia D, **Harbaoui B,** Van de Hoef T, Meuwissen M, Nijjer S, Davies J, Piek JJ, Lantelme P. Relationship between FFR, CFR and coronary microvascular resistance.

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L'objectif de ce travail était de:

1) Déterminer les paramètres physiologiques indépendants qui influencent la valeur de FFR

2) Comprendre les discordances entre la FFR et la CFR

3) Mettre en évidence la nécessité d'évaluation de la FFR et de la CFR dans la prise de décision clinique.

Population/Méthode : Des modèles mathématiques théoriques explicites simples ont été étayés par des données physiologiques coronaires analysées rétrospectivement. La FFR a été exprimée en fonction du coefficient de perte de pression, de la pression aortique et de la résistance microvasculaire coronaire hyperémique (Figure 6). La relation FFR-CFR a également été démontrée mathématiquement et s'est avérée dépendre exclusivement des résistances coronaires microvascular. Les équations ont été validées dans une première série de 199 lésions dont les pressions et vélocité de flux distales avaient été mesurées. Un deuxième ensemble de données de 75 lésions avec des mesures pré- et post-angioplastie de FFR et CFR a également été analysé pour étudier l'impact clinique de notre raisonnement hémodynamique.

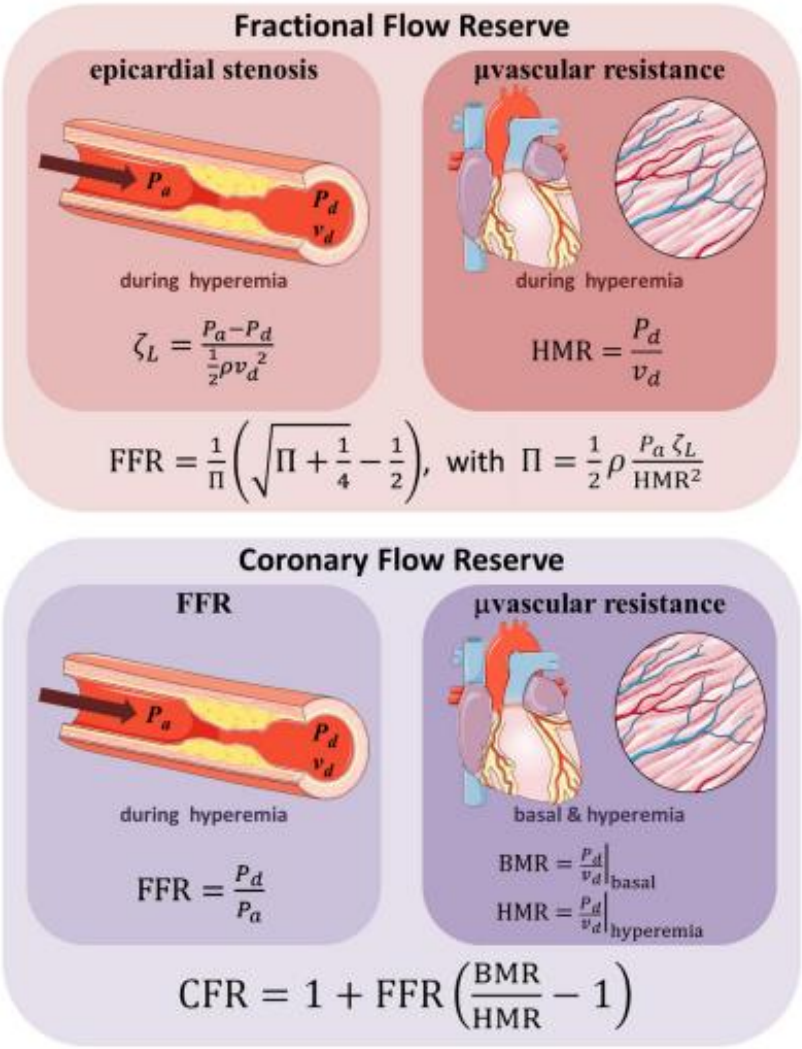

Figure 6 : Formulation théorique de la FFR et la CFR

La FFR peut être exprimée en fonction d'un paramètre sans dimension π, qui relie la pression aortique (Pa), le coefficient de perte de pression (ζ_L) et la résistance microvasculaire hyperémique (HMR). La CFR et la FFR sont interdépendantes par le rapport de résistance microvasculaire basale sur hyperémique.

Résultats La résistance microvasculaire coronarienne hyperémique et le coefficient de perte de pression ont des effets comparables (45% et 49%) sur la FFR. Il y avait une bonne concordance entre la CFR mesurée et la CFR prédite par la FFR et les résistances coronaires. Chez les patients avec CFR < 2 et CFR/FFR > 2, la CFR post-angioplastie était significativement >2 (p

< 0,001), alors qu'elle ne l'était pas (p = 0,94) chez les patients avec CFR < 2 et CFR/FFR < 2 (Figure 7).

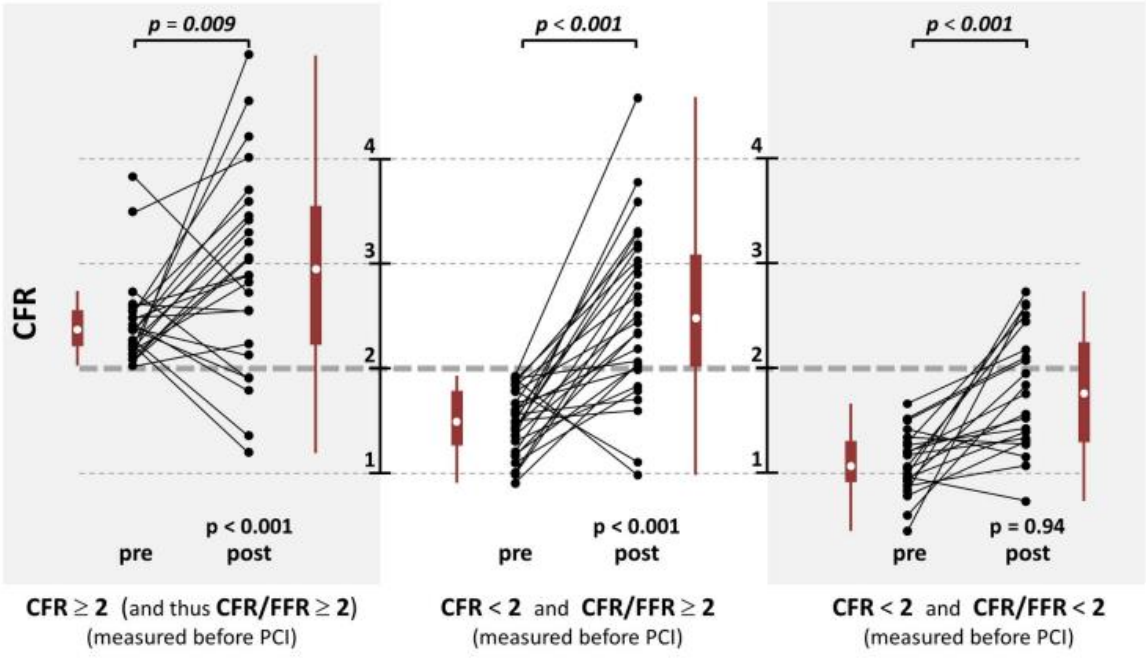

Figure 7 : CFR mesurée avant et après angioplastie coronaire.

Les points blancs dans les boxplots représentent les valeurs médianes.

Conclusion Les valeurs de FFR et de FFR/CFR sont prévisibles en prenant en compte des variables hémodynamiques de base. Les discordances entre FFR et CFR sont expliquées par les résistances vasculaires coronaires. FFR et CFR sont complémentaires; ils pourraient contribuer conjointement à un meilleur guidage de l'angioplastie grâce au rapport CFR/FFR chez les patients atteints de maladie coronaire.

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RESEARCH ARTICLE

Relationship between FFR, CFR and coronary microvascular resistance – Practical implications for FFR-guided percutaneous coronary intervention

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Abstract

Objective

The aim was threefold: 1) expound the independent physiological parameters that drive FFR, 2) elucidate contradictory conclusions between fractional flow reserve (FFR) and coronary flow reserve (CFR), and 3) highlight the need of both FFR and CFR in clinical decision making. Simple explicit theoretical models were supported by coronary data analyzed retrospectively.

Methodology

FFR was expressed as a function of pressure loss coefficient, aortic pressure and hyperemic coronary microvascular resistance. The FFR-CFR relationship was also demonstrated mathematically and was shown to be exclusively dependent upon the coronary microvascular resistances. The equations were validated in a first series of 199 lesions whose pressures and distal velocities were monitored. A second dataset of 75 lesions with pre- and post-PCI measures of FFR and CFR was also analyzed to investigate the clinical impact of our hemodynamic reasoning.

Results

Hyperemic coronary microvascular resistance and pressure loss coefficient had comparable impacts (45% and 49%) on FFR. There was a good concordance ($y = 0.96\ x - 0.02$, $r^2 = 0.97$) between measured CFR and CFR predicted by FFR and coronary resistances. In patients with CFR < 2 and CFR/FFR $\geq$ 2, post-PCI CFR was significantly >2 ($p < 0.001$), whereas it was not ($p = 0.94$) in patients with CFR < 2 and CFR/FFR < 2.

Abbreviations: BMR, basal coronary microvascular resistance; CBF, coronary blood flow; CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic coronary microvascular resistance; P_a, aortic pressure; PCI, percutaneous coronary intervention; P_d, distal pressure; ρ, blood density; v_d, distal blood velocity; ζ_L, pressure loss coefficient.

Conclusion

The FFR behavior and FFR-CFR relationship are predictable from basic hemodynamics. Conflicting conclusions between FFR and CFR are explained from coronary vascular resistances. As confirmed by our results, FFR and CFR are complementary; they could jointly contribute to better PCI guidance through the CFR-to-FFR ratio in patients with coronary artery disease.

Introduction

Fractional flow reserve (FFR) is an invasive measure of the physiological significance of an epicardial coronary stenosis. Since coronary angiography is often insufficient in guiding percutaneous coronary intervention (PCI), FFR has gained wide acceptance for estimating whether a coronary lesion may cause myocardial ischemia [1]. FFR is defined as the ratio of distal (P_d) to proximal (= aortic, P_a) pressure (FFR = P_d/P_a) determined during pharmacologically-induced hyperemia (Fig 1). A lesion with an FFR $\leq$0.80 is generally judged ischemia-prone, whereas it is accepted that a lesion with an FFR $>$0.80 is unlikely to produce myocardial ischemia [2]. The impact of an epicardial stenosis on myocardial perfusion can alternatively be assessed by the Doppler- or thermodilution-derived coronary flow reserve (CFR). CFR denotes the myocardial reserve vasodilator capacity, defined as the ratio of maximal hyperemic coronary blood flow (CBF) to resting CBF [3]. CFR less than 2 is used to distinguish coronary lesions that are likely to trigger myocardial ischemia [4]. Although both FFR and CFR are aimed at identifying ischemia-prone lesions, they are discordant in ~30% of intermediate stenoses [5,6]. This disagreement does not reflect inaccuracy of either tool; but it illustrates that both FFR and CFR are not self-contained diagnostic criteria for a clear-cut decision of whether PCI is required. The FFR does not merely reflect the morphology of the stenosis but rather reveals its functional impact within its physiological surround [1]. Indeed, FFR depends not only upon the severity of the local lesion but also on hyperemic vascular resistance [7,8], and in a lesser but significant extent, on aortic pressure [9,10]. Although the relationship between FFR and CFR has not been unequivocally established, it is known to be mostly modulated by the coronary microvascular resistance [8,11]. For this reason, it has been suggested that intracoronary pressures and flows should be measured simultaneously to distinguish the impact of the focal stenosis from that of downstream coronary resistance for a better therapeutic decision in patients with coronary lesions [8,12,13].

Our first objective was to explicitly determine once and for all the physiological parameters that drive FFR. The second objective was to expound how the coronary microvascular resistances intermingle FFR and CFR. The purpose was to make it clear 1) why a significant stenosis can have an FFR greater than 0.8, and 2) why so-called discordances between FFR and CFR have been reported in recent clinical studies. Based on our theoretical rationale, our third objective was to exemplify the need of both FFR and CFR to better guide percutaneous coronary intervention.

To know how FFR, CFR and coronary physiology are interrelated, we sought to describe the hemodynamic relationships that precisely link these fundamental parameters by using simple mathematical representations. This could help reconsidering the classical 0.8-FFR threshold in situations where an epicardial stenosis exists concomitantly with significant coronary diffuse disease and/or microvasculature disorder. More importantly, an explicit formulation will shed some light on how factors external to the locally stenotic region may quantitatively

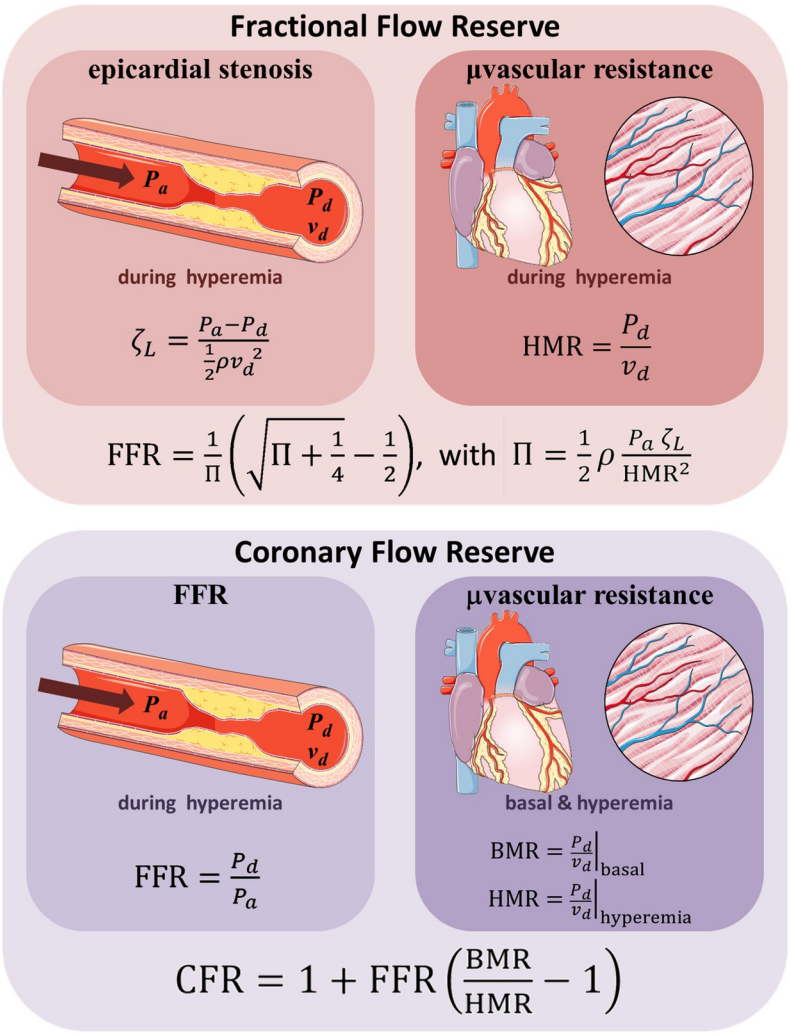

Fig 1. Theoretical expressions of FFR and CFR. FFR can be expressed as a function of a dimensionless parameter Π, which relates aortic pressure (P_a), pressure loss coefficient (ζ_L) and hyperemic microvascular resistance (HMR). CFR and FFR are interrelated through the basal-to-hyperemic microvascular resistance ratio.

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impact FFR and CFR, before and after PCI, allowing one to enhance interpretation of combined pressure-flow measurements and their application in clinical practice. From a clinical viewpoint, the hemodynamic models that we derived also highlight the need to use CFR in conjunction with FFR to predict the potential benefit of PCI for a given stenosis.

Methods

Hemodynamic background

Theoretical expression of FFR. The pressure loss coefficient (ζ_L, also called Euler number) is a fluid-dynamics-based dimensionless parameter that describes the relationship between the pressure drop throughout a flow field and the corresponding kinetic energy. It mainly reflects pressure losses due to wall friction and/or turbulence. In particular, it can quantify the severity of a flow constriction and has been used in the context of epicardial

coronary stenoses [14,15]:

$$\zeta_L = \frac{P_a - P_d}{\frac{1}{2}\rho v_d^2}, \tag{1}$$

where v_d is the distal blood velocity and ρ stands for blood density. In the particular (uncommon) case of a non-elongated axisymmetric stenosis, ζ_L can be related to the stenosis severity (see S1 File) and is not flow-dependent. Flow dependence of ζ_L, however, generally occurs in extended stenoses as a result of wall friction [16], which makes it unfeasible to estimate from geometry only. In practice, computational fluid dynamics is thus required to relate ζ_L to the stenosis geometry [17]. The hyperemic coronary vascular resistance in terms of flow velocity is defined by [8]

$$\mathrm{HMR} = \left.\frac{P_d}{v_d}\right|_{\text{hyperemia}}. \tag{2}$$

HMR corresponds to the microvascular resistance downstream of the focal stenosis. It reflects the resistance due to downstream diffuse disease (if any) in series with the resistance of the coronary microvasculature (Fig 1). By using a dimensional analysis [18] and involving the three linearly independent physical quantities that drive FFR (P_a, ζ_L, and HMR), FFR can be related to this dimensionless parameter:

$$\Pi = \frac{1}{2}\rho\frac{P_a\zeta_L}{\mathrm{HMR}^2}. \tag{3}$$

Developing Π (see S1 File) yields a simple quadratic equation ($\Pi\ \mathrm{FFR}^2 + \mathrm{FFR} - 1) = 0$, whose solution gives a generalized expression of FFR (Fig 1):

$$\mathrm{FFR} = \frac{1}{\Pi}\left(\sqrt{\Pi + \frac{1}{4}} - \frac{1}{2}\right). \tag{4}$$

In this study, we used this expression to investigate how, and to which extent, independent hemodynamic parameters can affect FFR. As a matter of fact, Eq 4 shows that FFR decreases when Π increases *i.e.* when: 1) ζ_L increases, 2) HMR decreases, and/or 3) P_a increases. It follows that FFR decreases in the following situations: 1) when the focal stenosis becomes more severe; 2) when diffuse coronary disease is less significant; 3) when aortic pressure increases. Eq 4 corroborates clinical observations [8,10]. In comparison with previously published models [7,9], it has the advantage to provide an explicit association between FFR and three linearly independent hemodynamic parameters (*i.e.* three degrees of freedom).

Relative effects of P_a, HMR and ζ_L on FFR

We showed through Eq (4) that FFR totally depends upon three independent physiological parameters. These parameters may have different impacts on FFR, depending on their absolute values and ranges. Using the differential of FFR, it can be shown that the amount of FFR variation (ΔFFR) around the 0.8-threshold value is related to P_a, ζ_L and HMR variations (*i.e.* ΔP_a, $\Delta\zeta_L$ and ΔHMR) as follows (see S1 File):

$$\Delta\mathrm{FFR} = \frac{2}{15}\left(2\frac{\Delta\mathrm{HMR}}{\mathrm{HMR}} - \frac{\Delta P_a}{P_a} - \frac{\Delta\zeta_L}{\zeta_L}\right). \tag{5}$$

This equation predicts how an incremental change in any of the three parameters P_a, ζ_L and

HMR affects FFR. As will be confirmed later in the Results, not only the severity of stenosis (ζ_L) but also the coronary microvascular resistance (HMR) have a major impact on FFR.

Theoretical expression of CFR. The coronary flow reserve (CFR) represents the ratio of maximal hyperemic CBF over basal CBF [3]. At first it was thought that there was a one-to-one correspondence between FFR and CFR in coronary pathophysiology. This misconception led to supposedly discordant FFR-vs.-CFR conclusions when quantifying coronary physiology. It is now well accepted that the coronary microvascular resistance comes into play in the CFR-FFR relationship [7]. The latter, however, is still poorly identified. Assuming that aortic pressure is unchanged between baseline and hyperemia, as generally happens with adenosine, it can be shown (in the S1 File) that the coronary flow reserve can be approximated by the following expression:

$$\mathrm{CFR} = 1 + \mathrm{FFR}\left(\frac{\mathrm{BMR}}{\mathrm{HMR}} - 1\right), \tag{6}$$

where BMR and HMR are the basal and hyperemic coronary microvascular resistances, respectively (Fig 1). Eq (6) allows one to offer an unambiguous explanation on previous clinical observations that have reported "discordances" between FFR and CFR. More importantly, it shows that FFR alone or CFR alone cannot be used unequivocally since their relationship is clearly influenced by the coronary microvascular resistances. Eq (6) can be rewritten as follows:

$$\frac{\mathrm{CFR}}{\mathrm{FFR}} = \frac{1}{\mathrm{FFR}} + \frac{\mathrm{BMR}}{\mathrm{HMR}} - 1. \tag{7}$$

Recent clinical studies have shown that elevated coronary microvascular resistances predict poor outcomes in FFR-guided PCI [19,20]. The above expression pointedly shows that the joint information combining FFR and coronary microvascular resistances (right side) is directly related to the CFR-to-FFR ratio (left side). In this retrospective study, we analyzed the clinical impact of the CFR-to-FFR ratio in predicting post-PCI CFR, as explained later.

Invasive CFR and FFR measurements

To validate Eqs (4), (5) and (6), we retrospectively reevaluated 299 coronary stenoses in 228 anonymized patients reported in [8]. Note that we also considered the lesions with FFR<0.60, although they were rejected in [8]. The patients were referred for intracoronary assessment of at least one intermediate coronary lesion. The baseline characteristics of these patients are presented in the Table 1 of reference [8]. Exclusion criteria were listed in [8]. Distal and proximal coronary pressures, as well as distal blood velocities, were measured subsequently during basal and hyperemic conditions. Intracoronary pressures were monitored with a 0.014" guide wire (Volcano, San Diego, USA). Coronary flow velocities were determined using a FloWire Doppler guide wire (Volcano, San Diego, USA). Coronary hyperemia was induced by intracoronary administration of adenosine (20–40 μg). From the recorded pressure and velocity waveforms, FFR was calculated as the ratio of averaged distal to aortic pressure during maximum hyperemia; BMR (HMR) was determined by the ratio of averaged distal coronary pressure to averaged distal velocity during basal (hyperemic) conditions; ζ_L was estimated by the ratio between averaged trans-stenotic pressure difference and distal kinetic energy (see Eq 1) during maximum hyperemia; CFR was calculated as the ratio of hyperemic to basal averaged peak velocities. The procedures were approved by the medical ethical committee of the Academic Medical Center (Amsterdam, The Netherlands) and all patients gave written informed consent.

To validate Eq (6) and investigate the clinical value of combined CFR and FFR, a second dataset of 75 lesions in 67 anonymized patients was reanalyzed retrospectively. This dataset included coronary pressure and velocity measurements before and after PCI [21]. The latter were obtained simultaneously using a dual sensor-equipped guide wire (ComboWire, Volcano, San Diego, USA). Adenosine was administered by intravenous continuous infusion in 43 stenoses (140 μg/kg per minute) and by intracoronary bolus in 32 stenoses (60 μg). The same dose was used before and after intervention. Coronary intervention was performed at the operator's discretion based on usual clinical care, including angiographic and noninvasive findings. Measurements were repeated after angioplasty at the same location as pre-angioplasty. At the end of each recording, the pressure sensor was returned to the catheter tip to avoid any pressure drift. The measurements were repeated when drift was identified. An adequate flow velocity envelope was obtained in all patients permitting the calculation of flow-based indices. The baseline characteristics of these patients are presented in the Table 1 of reference [21]. The procedures were approved by the ethical committees of the Academic Medical Centre (Amsterdam, the Netherlands) and Imperial College (London, UK) and all patients gave written informed consent.

Data analysis

A first series of analyses was carried out using the first dataset (299 lesions). FFR variations around 0.8 (ΔFFR) were estimated from Eq (5) and compared with the measured FFR variations using a Bland-Altman analysis. This analysis was performed around the critical value 0.8, using the subpopulation whose FFR ranged between 0.7 and 0.9 ($N = 168$). The relative variations of P_a, ζ_L and HMR (2nd term of Eq 5) were calculated as $\Delta x/x = (x - \text{median}(x))/x$, with x being P_a, ζ_L or HMR. The actual ΔFFR was determined by (FFR − 0.8). To point up the respective impacts of coronary microvascular resistance and stenosis severity on FFR, FFR was also displayed in a scatter diagram as a function of HMR and $\log(\zeta_L)$, assuming a mean aortic pressure of 95 mmHg. CFR was finally estimated from FFR and basal (BMR) and hyperemic (HMR) coronary microvascular resistances (Eq 6). It was compared with the CFR measured by Doppler guide wire using a linear regression and a Bland-Altman analysis.

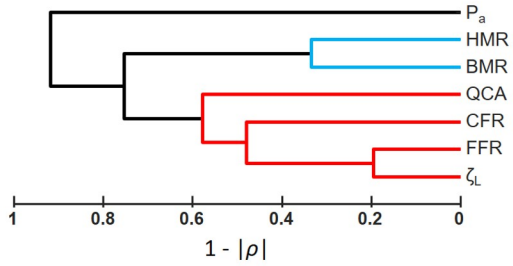
The impact of PCI on CFR was evaluated in the 75 lesions in which pre- and post-intervention pressure and flow measurements were available. Eq (7) reveals that the CFR/FFR ratio might have some prognostic value. The prognostic ability of CFR/FFR in predicting post-PCI CFR>2 was thus evaluated through a receiver operating characteristic (ROC) analysis. The optimal cut-off point was determined by maximizing the Cohen's kappa statistic, which turned out to be almost equal to 2. The 75 lesions were separated in three groups: #1) CFR > 2; #2) CFR ≤ 2 and CFR/FFR ≥ 2; #3) CFR ≤ 2 and CFR/FFR < 2. The cut-off value of 2 was chosen to comply with the ROC analysis. For each group, the pre- and post-PCI CFR were compared using a one-tailed paired t-test to test the alternative hypothesis that CFR mean was greater after than before PCI. Post-PCI CFR were also analyzed using a one-tailed one-sample t-test to test the alternative hypothesis that post-PCI-CFR mean was greater than 2.

Results

Impact of HMR, ζ_L and P_a on FFR

There was a strong Spearman's rank correlation ($\rho = -0.8$) between FFR and ζ_L (see dendrogram in Fig 2). Fig 3 shows that Eq 5 was a good predictor of FFR variation around the critical value 0.8. The median absolute error was 0.008, with a robust standard deviation of 0.025. The pie chart indicates that HMR and ζ_L had comparable impact (45% and 49%) on FFR variation in this subpopulation (whose FFR was around 0.8), whereas aortic pressure had lesser effect

N	P_a (mmHg)	BMR (mmHg.s/cm)	HMR (mmHg.s/cm)	QCA (%)	CFR	$\log_{10}(\zeta_L)$	FFR
199	95 (14)	5.4 (2.9)	2.1 (1.2)	54 (15)	2.2 (1.1)	1.5 (0.77)	0.8 (0.18)



Two main clusters (in color) appear in the dendrogram. The blue cluster is related to the coronary microvasculature resistance. The red cluster reflects the severity of the lesion.

Fig 2. Hemodynamic parameters of the 1st dataset (n = 199). P_a. = aortic pressure; BMR = basal coronary microvascular resistance; HMR = hyperemic coronary microvascular resistance; QCA = diameter reduction (%) by quantitative coronary analysis; ζ_L = pressure loss coefficient; FFR = fractional flow reserve. The table reports median ± robust standard deviations. The dendrogram represents the average-link similarities returned by an agglomerative hierarchical clustering. Modulus of the Spearman's rank correlation coefficient (ρ) was used as a distance metric; it reflects the proximity between two objects by measuring at what point they are similar. Reported values = median (interquartile range).

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(6%). Fig 4 further reveals that FFR was highly dependent on both HMR and ζ_L. These observations are in line with those obtained by Morris *et al.* by computational fluid dynamics [22].

Relationship between FFR and CFR

The linear regression between predicted (see Eq 6) and measured pre-PCI CFR returned $y = 0.96\,x - 0.02$, $r^2 = 0.97$ (Fig 5). The median absolute error was 0.12, with a robust standard deviation of 0.13, which shows that Eq 6 was a good predictor of CFR prior to PCI. The

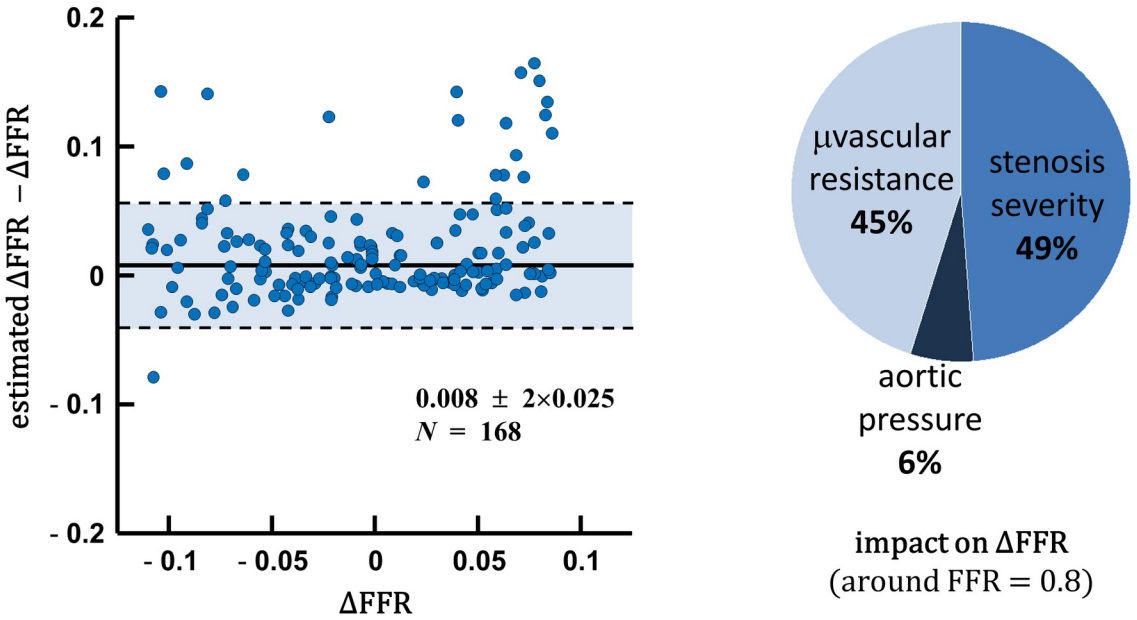

Fig 3. FFR variations around 0.8. Left panel: estimated *vs*. actual FFR variations around the 0.8-threshold value (Eq 5). Right panel: respective impacts of hyperemic microvascular resistance, stenosis severity and aortic pressure on FFR variation.

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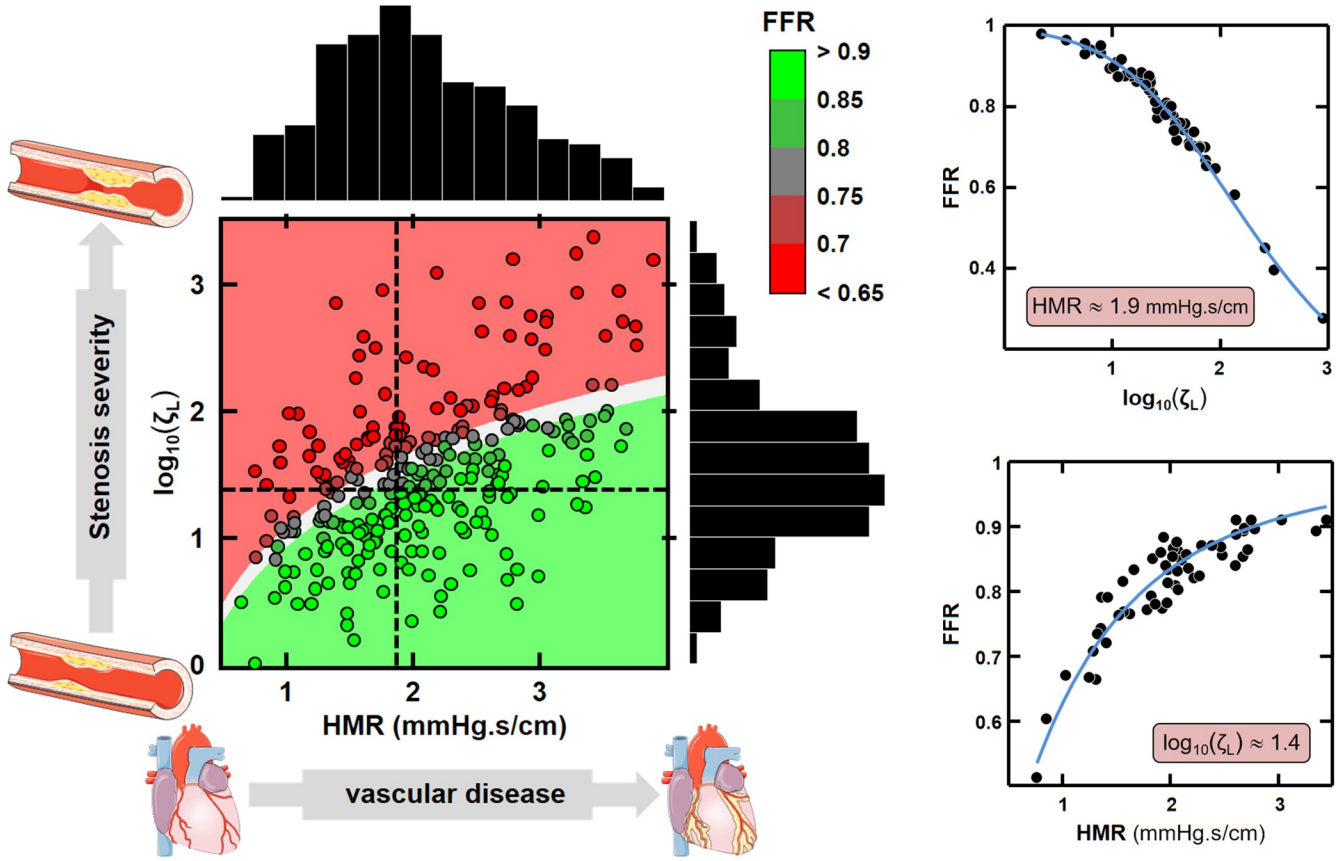

Fig 4. Relationship between HMR, ζ_L and FFR. ***Left panel***: The dot colors represent the FFR measured by the pressure guide wire. The colored background is the theoretical FFR (Eq 4) assuming a proximal pressure of 95 mmHg (red: FFR<0.75; grey: 0.75<FFR<0.8; green: FFR>0.8). The dashed lines identify the modes of ζ_L and HMR distributions. ***Right panel***: Independent effects of ζ_L and HMR on FFR around their respective modes. HMR and $\log_{10}(\zeta_L)$ were fixed at 1.9 ± 0.19 mmHg/cm/s and 1.4 ± 0.14, respectively. The blue curves are theoretical (Eq 4).

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triangle-shaped CFR-FFR relationship is illustrated in Fig 6. This figure confirms that CFR and FFR are mostly related through the basal-to-hyperemic microvascular-resistance ratio.

Pre-PCI CFR/FFR as a prognostic marker?

Weak to modest Spearman's rank correlations ($|\rho| < 0.5$) were observed between pre- and post-PCI FFR, HMR and CFR (see dendrogram in Fig 7). The area under the ROC curve (AUC) was 0.77 (Fig 8), which denoted a fair-to-good discrimination of CFR/FFR in predicting a post-PCI CFR greater than 2. The optimal cut-off determined by the Cohen's kappa statistic was 1.93 ≈ 2. This cut-off yielded a specificity and sensitivity of 87% and 56%, respectively. CFR increased significantly after PCI in the three groups (Fig 9). In groups #1 and #2 (CFR/FFR ≥ 2), post-PCI CFR was significantly greater than 2 ($p < 0.001$), whereas it was not ($p = 0.94$) in group #3 (CFR/FFR < 2).

Discussion

A number of clinical studies have reported that FFR is governed not only by the severity of the epicardial stenosis but also by the downstream coronary vascular resistance. The latter has also been shown to be the main source of discordance between FFR and CFR in roughly 30% of patients with intermediate lesion. In this study, we provided mechanistic evidences to support

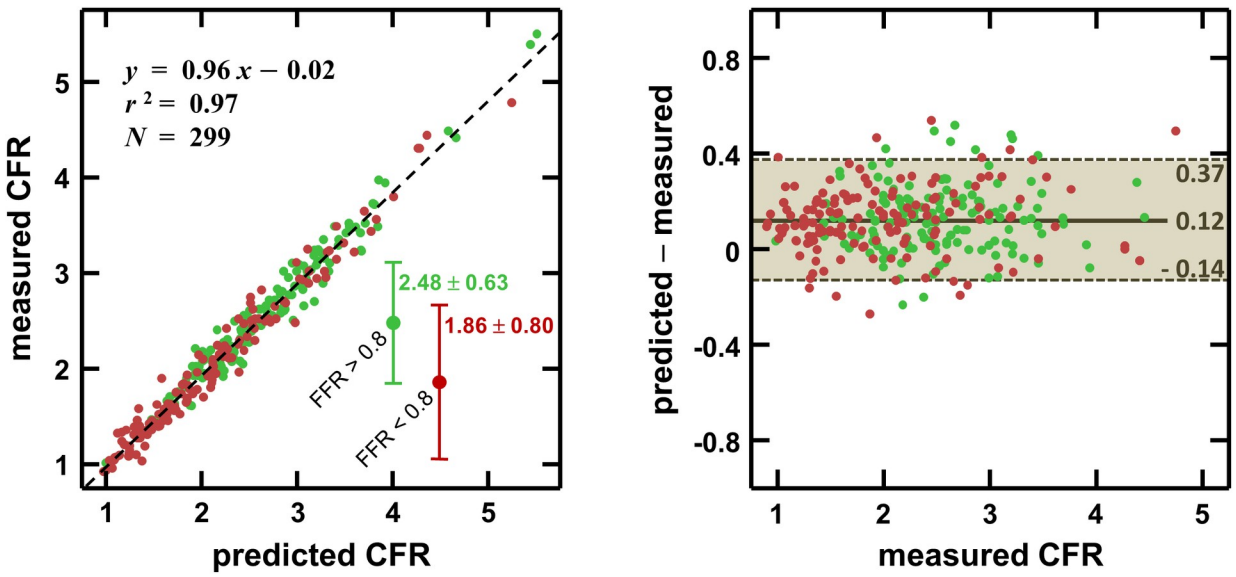

Fig 5. Predicted *vs.* measured CFR. CFR was predicted from Eq (6). The green (red) dots correspond to lesions with FFR greater (less) than 0.8. The inset represents the corresponding median CFR values ± robust standard deviation.

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previous clinical observations. We derived explicit equations to solve the resistance dilemma of FFR. We also demonstrated mathematically the interplay of FFR and CFR. These equations were validated retrospectively using pressure and velocity coronary data. The main findings are that 1) FFR can be completely expressed by three linearly independent hemodynamic variables, and 2) FFR and CFR are directly related through the basal-to-hyperemic microvascular

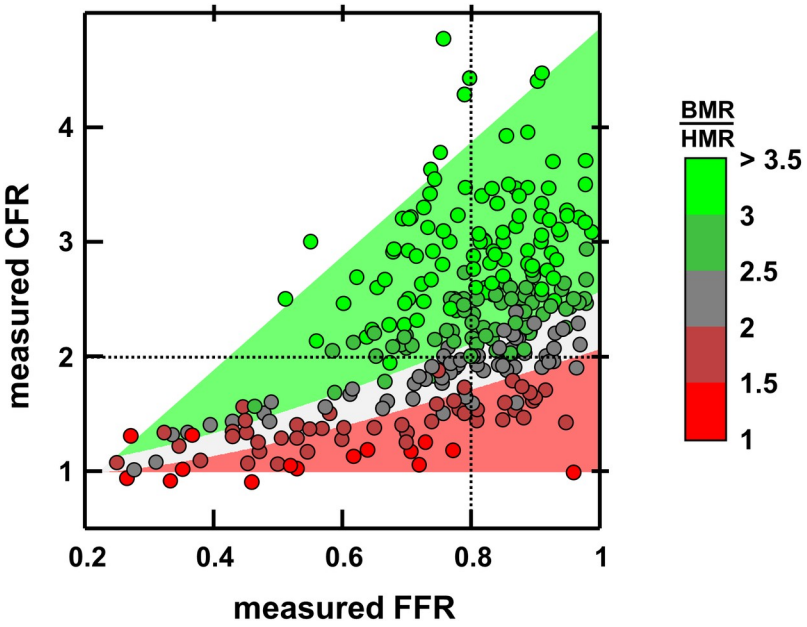

Fig 6. Relationship between FFR, CFR and (BMR/HMR). CFR and FFR are related through the ratio of basal to hyperemic vascular resistances (BMR / HMR); see Eq (6). The dot colors represent the measured BMR-over-HMR ratios. The colored background illustrates the theoretical ratio (red: ratio<2; grey: 2<ratio<2.5; green: ratio>2.5).

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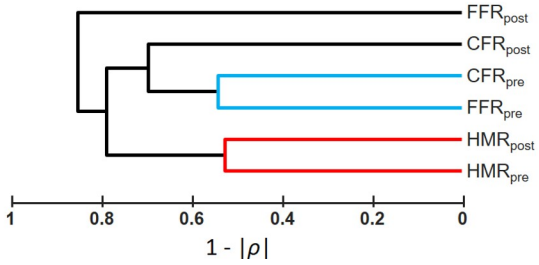
N	FFR_{pre}	FFR_{post}	HMR_{pre} (mmHg.s/cm)	HMR_{post} (mmHg.s/cm)	CFR_{pre}	CFR_{post}
75	0.70 (0.31)	0.90 (0.09)	2.4 (1.5)	1.8 (1.0)	1.6 (1.0)	2.4 (1.2)



Two main clusters (in color) including parameters of relatively weak similarity appear in the dendrogram.

Fig 7. Hemodynamic parameters of the 2st dataset (n = 75). Same acronyms as in Fig 2. Subscripts "pre" and "post" refer to pre- and post-revascularization, respectively. Reported values = median (interquartile range).

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resistance ratio. More importantly, this study also calls attention to conflicting conclusions that may be noticed between CFR and FFR. According to the CFR *vs*. FFR relationship, clinical

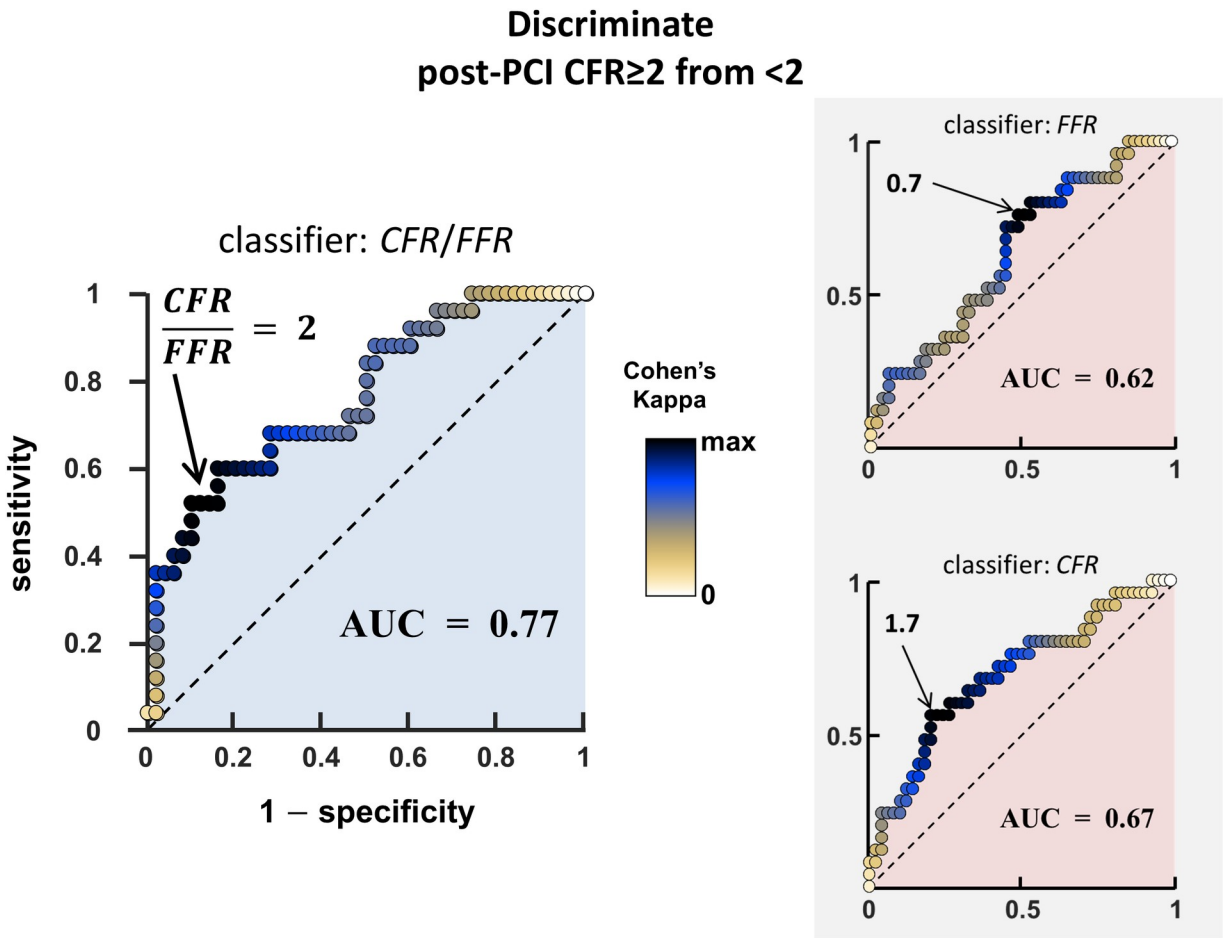

Fig 8. ROC analysis. Accuracy of the CFR-to-FFR ratio to discriminate post-PCI CFR>2 from post-PCI CFR<2. AUC = area under the ROC curve. The colored disks represent the Cohen's kappa statistic. The ROC curves of the FFR and CFR classifiers are also represented for comparison.

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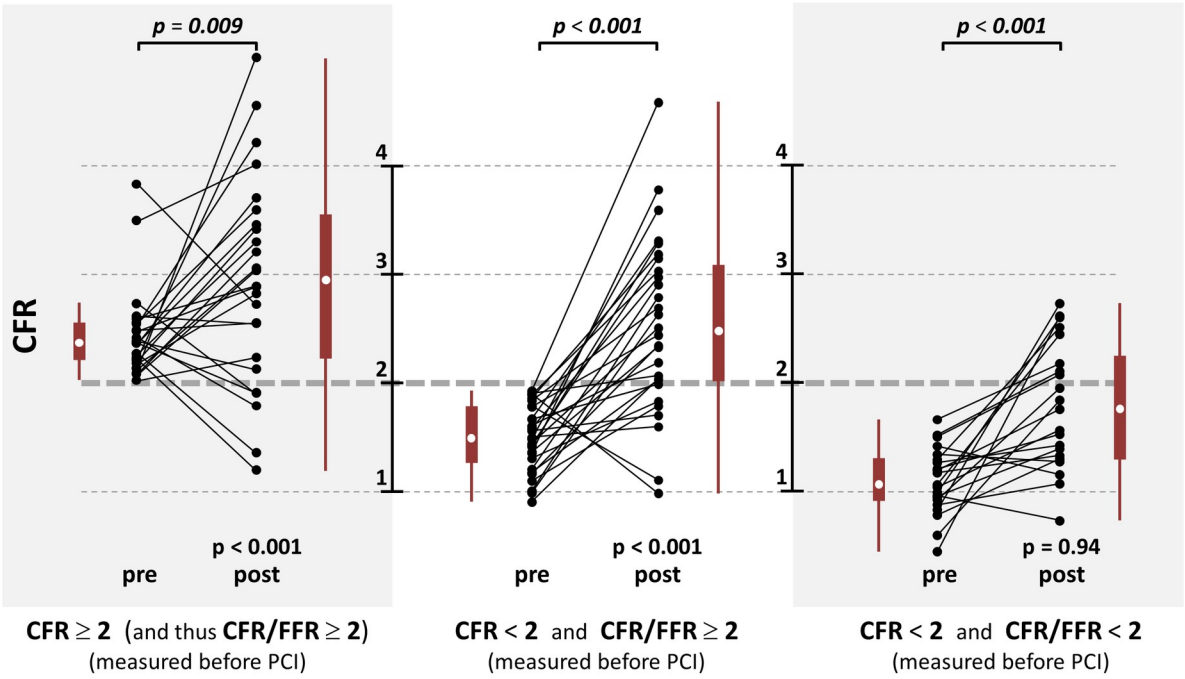

Fig 9. Measured CFR before *vs.* after PCI. The white dots in the boxplots represent the median values. Non-italicized p values (1st rows) refer to the one-sample right-tailed t-tests with the alternative hypothesis that post-PCI-CFR mean was greater than 2. Italicized p values (top) refer to the one-sample right-tailed t-tests with the alternative hypothesis that post-PCI-CFR mean was greater than pre-PCI-CFR mean.

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conflicts between FFR and CFR can actually be predicted from basic hemodynamics. Strictly speaking, there is no discordance as such since FFR and CFR are distinct in nature. These fundamental parameters are rather complementary and it is anticipated that they could jointly contribute to better PCI guidance. We conclude that focal coronary stenoses should be assessed by taking their surrounding environment into account, and their functional assessment should preferentially be based on both CFR and FFR. It is expected that the CFR-to-FFR ratio could be of prognostic relevance in predicting post-PCI CFR and thus has the potential to optimize patient treatment.

Epicardial stenosis and downstream microvascular resistance contribute equally to FFR

The expression relating FFR to the dimensionless Π parameter demonstrates that FFR is governed by the 1) stenotic pressure loss coefficient, 2) downstream hyperemic microvascular resistance and 3) aortic pressure. The involvement of these variables has been already reported [8,10,15]; their impact on FFR, however, was not clearly established since no explicit model was available. Although aortic pressure might influence FFR in particular pathophysiological conditions, such as hypotension [10], its effect was small in our study (Fig 3). Fig 4 further confirmed that FFR was mostly regulated by ζ_L and HMR, both controlling the coronary pressure-flow relationship. The pressure loss coefficient ζ_L depends on the stenotic flow constriction and length [16]: constricted sections induce flow separation, an unstable process that causes irreversible pressure loss; elongated stenoses also make wall friction significant, an additional source of pressure loss. Other factors such as wall curvature and tortuosity can also increase pressure losses [23]. This multifactorial association explains the moderate correlation observed

between the diameter-based severity and ζ_L (Spearman's rank correlation coefficient $|\rho|<0.5$; see dendrogram in Fig 2. See also S1 Fig in the S1 File). Hyperemic microvascular resistance HMR involves the coronary microvasculature downstream from the lesion. It increases in situations such as diffuse coronary disease, acute myocardial infarction [24], cardiac hypertrophy [25] or reduced vasodilatory capacity [26]. Our mathematical model establishes that FFR increases with increasing HMR, all other parameters being equal, as reported by Meuwissen *et al.* [12]. It follows that an epicardial stenosis may appear "less severe" (increased FFR) when significant downstream microvascular dysfunction is present. In this study, HMR and ζ_L contributed equally to FFR modulation around the critical 0.8-threshold. As emphasized in previous clinical investigations, our findings confirm mathematically and experimentally that microvascular resistance, and thus flow or velocity measurements, must be considered when interpreting FFR. As discussed below, this could be achieved by considering CFR in the diagnostic algorithm.

FFR and CFR are interrelated through coronary microvascular resistance

As depicted by Eq 6, the microvascular resistance dictates the relationship between CFR and FFR. We found that CFR can be approximated by {1 + FFR (BMR/HMR-1)}, where BMR and HMR are the basal and hyperemic coronary microvascular resistances. This expression shows that CFR decreases and/or FFR increases as HMR decreases. This is concordant with Meuwissen *et al.* [11] who reported that HMR was lower (1.9 *vs*. 2.4 mmHg/cm/s) in patients with CFR $\geq$ 2 and FFR $<$ 0.75 (*i.e.* CFR/FFR $>$ 2.67) than those with CFR $<$ 2 and FFR $\geq$ 0.75 (*i.e.* CFR/FFR $<$ 2.67). Coronary microvascular resistance is thus in large part responsible for FFR-CFR diagnostic conflicts. Normal-CFR abnormal-FFR situations may occur with high BMR-to-HMR ratios (>2.5) exclusively (Fig 6, left upper quadrant, 22.1% of the patients), whereas abnormal-CFR normal-FFR states are seen only if BMR-to-HMR ratio is low ($<$ 2.5, right lower quadrant in Fig 6, 8.7%). This explains why a so-called discordance between FFR and CFR occurs in roughly 30% of the patients with intermediate stenoses [5,6]. FFR and CFR are often clinically discordant simply because they are not in one-to-one correspondence. An abnormal CFR cannot reliably discriminate significant epicardial stenosis from non-obstructive vascular dysfunction [27]. In like manner, FFR cannot reckon the diffuse disease that may exist concomitantly with a focal stenosis. Since FFR and CFR are both interwove with microvascular resistance, they cannot intend to be alike, but should rather be considered as complementary diagnostic parameters.

Functional assessment based on CFR and FFR

As discussed above, our findings document that there is an interplay of FFR, CFR and microvascular resistance. From our biomechanical reasoning, it is expected that FFR alone should not promote PCI in a number of situations. When assessing the function of a coronary stenosis, the physician must answer two questions: 1) is the coronary lesion likely to induce ischemia?, 2) if so, will a PCI reduce the risk of myocardial ischemia? The well-accepted 0.8 cut-off value for FFR theoretically ensures that a significant increase in CFR can be expected after PCI. If an abnormal FFR is documented with an intermediate lesion, FFR-guided PCI can thus be beneficial and a gain in CFR is to be targeted. This precautionary measure, however, does not ensure ischemia relief if CFR/FFR$<$2 since post-PCI CFR could remain smaller than 2, as reflected by group #3 in Fig 9 (3rd column). This situation may occur for example in diabetic patients [28]. In daily clinical practice, ischemia may not be evaluated before catheterization. In such condition, FFR alone cannot independently foresee the hemodynamic effect of PCI. When coronary flow reserve is relatively preserved, FFR may be misleading as blood flow

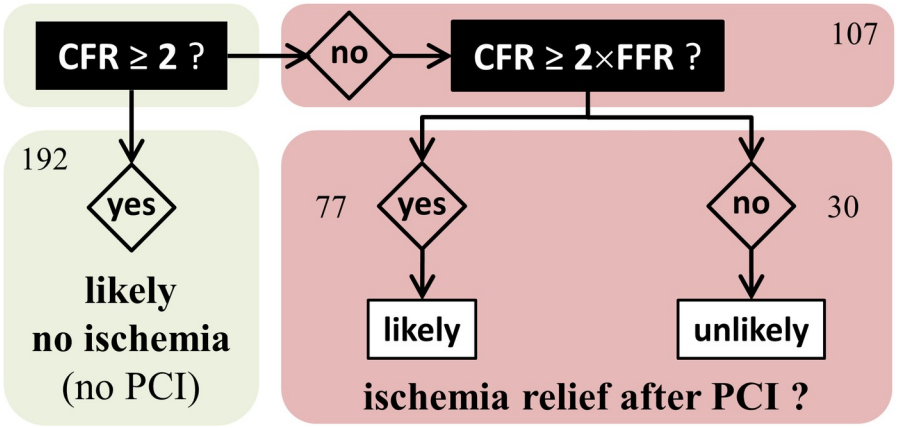

Fig 10. Likelihood of ischemia relief after PCI. This flowchart speculates on ischemia relief by revascularization based on our theoretical and experimental findings. The numbers represent the occurrences among the 299 lesions.

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remains sufficient to meet myocardial demand. It has been concordantly shown that a preserved CFR excludes high-risk CAD with a high negative predictive value [27]. In this circumstance, symptoms are unlikely to be improved after revascularization; revascularization could thus be safely deferred in patients with CFR >2 (group #1 in Fig 9, 1st column). With regard to patients with abnormal CFR (i.e. <2), pre-PCI CFR/FFR should ideally be >2 to substantially relieve ischemia and increase the benefit of PCI (Fig 9, 2nd vs. 3rd column). Significant focal stenosis and vascular dysfunction coexist in patients with CFR/FFR < 2 (group #3 in Fig 9, 3rd column). In such patients, PCI can possibly be of little advantage in terms of ischemia relief, and therapeutic tactics targeting the diffuse disease might be an option. To conclude, a focal stenosis should be assessed by taking its surrounding environment into account, and its functional assessment should preferentially be based on both CFR and FFR (Fig 10). This strategy should be investigated in a prospective outcome study. Interestingly, an ongoing prospective multicenter trial (DEFINE-FLOW, NCT02328820) is evaluating the prognostic value of combined pressure and flow measurements in coronary stenosis. DEFINE-FLOW aims at investigating whether revascularization in low-FFR high-CFR lesions can be deferred. The hypothesis is that lesions with an intact CFR ($\geq$ 2.0) can be reasonably treated with medical therapy despite a reduced FFR ($\leq$ 0.8). Lesions with preserved CFR and reduced FFR will thus receive optimal medical therapy. Only lesions with a reduction in both CFR and FFR will be treated with PCI. In the same vein, and according to our findings (see Figs 8 and 10), we believe that the CFR-to-FFR ratio could be of diagnostic relevance.

Limitations

Although FFR has gained worldwide recognition, it turns out that a critical parameter is still missing to potentially predict post-PCI outcome. In this study, we mathematically confirmed that the missing link is CFR, or alternatively the basal-to-hyperemic vascular resistance ratio. Unfortunately, CFR is rarely measured in clinical practice. To complicate matters, CFR is limited by its dependence upon heart rate [29] and requires reliable Doppler or temperature measures. It is presently challenging and time-consuming to measure coronary flow by Doppler or thermodilution approaches. Efforts thus must be made to design robust technologies to allow clinicians to get reproducible and simultaneous pressure- and flow-based parameters in hopes of better guiding PCI.

The proposed model and the experimental data were based on single stenoses in series with downstream microvascular resistance. Extrapolation of our conclusions to serial stenoses should be treated with caution. We also examined intermediate lesions, as evaluated by coronary angiography. Clinical situations with critical stenoses, endothelial dysfunction or microvascular disease were not investigated. These particular conditions could be considered as extrema within the hemodynamic range observed clinically. Note also that our results were interpreted around FFR = 0.8 and CFR = 2 since we chose the generally accepted cut-off values. Whether other threshold values should be assigned to optimize PCI diagnosis must be investigated prospectively in a large cohort.

Clinical relevance

Despite the clinical importance of FFR and CFR in the assessment of the coronary physiology, their interrelationship and their relationships with other hemodynamic parameters have remained poorly understood. In the present study, we have posed analytical equations to explicate supposedly-conflicting observations that were reported in previous clinical studies. We have explicitly confirmed that the evaluation of epicardial stenosis severity by FFR is in large part disguised by the coronary microvascular resistance. The FFR-CFR relationship that we derived also clearly demonstrates that the pretended discordance between CFR and FFR is governed by the coronary microvascular resistance. These hemodynamic expressions reveal that not only pressure-based but also flow-based measurements should be considered in interventional cardiology practice. In particular, we anticipate that the CFR-to-FFR ratio could be of major clinical relevance in optimizing individual patient treatment.

Conclusion

We demonstrated that both stenosis severity and coronary microvascular resistance modulate FFR and CFR. This study contributes to the growing awareness of the significance of coronary resistance and supports the observations that considering CFR can aid clinical decision-making during coronary angiography. From mathematical and clinical observations, it is anticipated that the CFR-to-FFR ratio may have a substantial prognostic ability in predicting post-PCI ischemia relief. Development of simple tools to measure FFR and CFR simultaneously should be promoted.

Supporting information

S1 File. Mathematical derivations of the hemodynamic formulas.
(DOCX)

S2 File. Matlab (version R2017b) figures. Use the Matlab function "get" to retrieve the original data. Read the Matlab documentation (mathworks.com/help/matlab/ref/get.html) for details.
(ZIP)

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Formal analysis: Damien Garcia, Pierre Lantelme.

Investigation: Damien Garcia, Brahim Harbaoui, Pierre Lantelme.

Methodology: Damien Garcia, Brahim Harbaoui, Pierre Lantelme.

Project administration: Damien Garcia, Pierre Lantelme.

Resources: Tim P. van de Hoef.

Supervision: Brahim Harbaoui, Pierre Lantelme.

Validation: Damien Garcia, Brahim Harbaoui, Pierre Lantelme.

Visualization: Damien Garcia.

Writing – original draft: Damien Garcia.

Writing – review & editing: Damien Garcia, Brahim Harbaoui, Tim P. van de Hoef, Pierre Lantelme.

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5/ Rigidité vasculaire et TAVI

Contexte

Depuis le premier patient traité en 2002 par l'équipe pionnière du Pr Cribier à Rouen, le traitement du rétrécissement aortique a été bouleversé. Le TAVI constitue une révolution dans la prise en charge des patients présentant un rétrécissement aortique. Le succès du TAVI a également été un moteur pour le développement d'autres stratégies de traitement des valves par voie percutanée. Avec l'augmentation de l'espérance de vie et le vieillissement de la population, le nombre de patients présentant un rétrécissement aortique ne cesse d'augmenter et les indications de traitement par TAVI tendent à s'élargir (26). Ceci aboutit déjà à une croissance très importante du nombre de procédures atteignant plus de 400 000 patients traités à travers le monde depuis son invention en 2002. Cependant un nombre encore trop important de patient continue de présenter des événements graves, dont la survenue de décès et d'insuffisance cardiaque dans la première année suivant le TAVI. Le rétrécissement aortique est une pathologie du sujet âgé lié le plus souvent à un processus dégénératif, sa prévalence est dépendante de l'âge (Figure 8). Ce « vieillissement *valvulaire* » s'accompagnera volontiers d'un vieillissement *vasculaire* plus ou moins marqué en fonction des individus, tel que décrit dans la première partie de cette thèse (Figure 9).

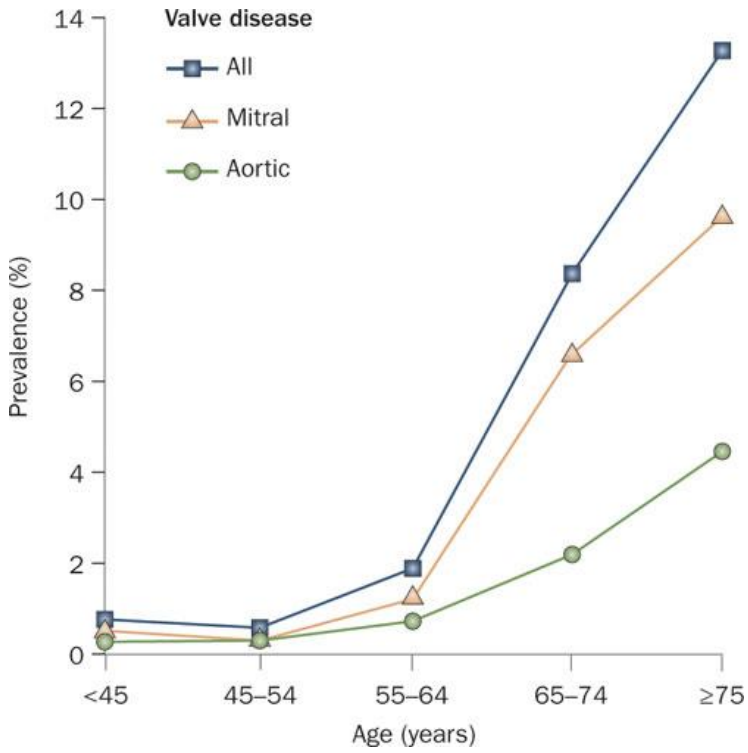

Figure 8 : Prévalence des maladies valvulaires en fonction de l'âge sur 11 911 patients de la population générale. (27)

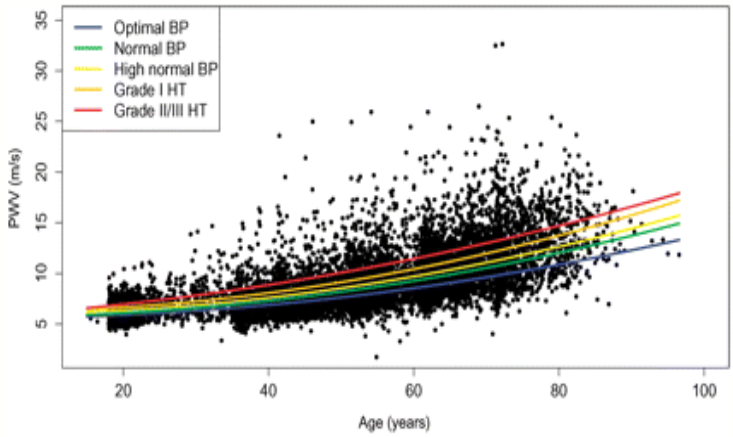

***Figure 9 : Valeurs de la vitesse de l'onde de pouls en fonction de l'âge*. (28)**

Les conséquences de la rigidité vasculaire chez les patients porteurs d'un rétrécissement aortique ont été peu étudiées. Ceci tient probablement du fait que chez ces patients la quantification de la post charge vasculaire est complexe et peu codifiée. En effet la sténose

aortique perturbe les marqueurs de rigidité aortique, qui pour la plupart sont dépendant des conditions hémodynamiques. Briand et al ont proposé un indice permettant de prendre en compte les contingents valvulaire et artériel de la post charge (29). Il s'agit de l'impédance valvulo-artérielle ou Z_{va} dont la formule est la suivante :

$$Z_{va} = \frac{PAS + GM}{VESi} \ (mmHg/\ ml/m^2)$$

PAS est la pression artérielle systolique prise au brassard, GM est le gradient moyen à travers la valve aortique et VES_i est le volume d'éjection indexé par rapport à la surface corporelle.

Cependant ce paramètre a surtout montré son impact pronostique chez des patients porteur d'une sténose aortique asymptomatique.

Le volume de calcifications de l'aorte est un paramètre indépendant des conditions de charge. Il est facilement mesurable par scanner, examen réalisé systématiquement chez les patients traités par TAVI. La corrélation des calcifications de l'aorte avec la VOP a été montrée dans plusieurs groupes de patients. La rigidité vasculaire pourrait constituer un « obstacle vasculaire » une fois « l'obstacle valvulaire » levé et être délétère pour le ventricule gauche.

Ainsi, le volume de calcifications aortiques pourrait être un paramètre intéressant particulièrement chez le patient candidats à un TAVI. Actuellement, les calcifications vasculaires sont surtout étudiées chez ces patients afin de choisir la voie d'abord. En plus d'être un indice de rigidité vasculaire et d'athérosclérose, les calcifications aortiques pourraient être un marqueur de fragilité. Une relation inverse entre les degrés de calcification vasculaire et de minéralisation osseuse a été mise en évidence (30). Ce « calcification paradox » pourrait impliquer des protéines communes agissant sur la résorption et la formation osseuse ainsi que sur la paroi vasculaire. Les travaux de Bucay et al sur un modèle de rongeurs, suggèrent que l'ostéoprogerine pourrait jouer un rôle : les souris knock-out développent une intense

déminéralisation osseuse en même temps qu'elles calcifient leur réseau vasculaire de façon extensive (31). Les calcifications vasculaires sont par ailleurs associées à la sarcopénie (32). Ces éléments pourraient faire des calcifications aortiques un marqueur de risque intégratif chez les patients traités par TAVI.

a) Etude "proof of concept"

Aortic Calcifications Present the Next Challenge After TAVR.

Harbaoui B, Courand PY, Charles P, Dauphin R, Boussel L, Jegaden O, Dubreuil O, De Gevigney G, Lantelme P

J Am Coll Cardiol. 2015 Mar 17; 65(10): 1058-1060

Hypothèse : Le volume de calcifications de l'aorte ascendante, marqueur de rigidité vasculaire, pourrait avoir une implication pronostique chez les patients traités par TAVI.

Objectif : Evaluer l'impact pronostique du volume de calcifications de l'aorte chez les patients traités par TAVI.

Population, Méthodes : Travail monocentrique sur 127 patients consécutifs porteur d'une sténose aortique serrée, traités par TAVI. Mesure du volume de calcifications de l'aorte ascendante sur le scanner systematiquement réalisé avant un TAVI.
L'outcome considéré était un composite de la mortalité cardiaque et hospitalisation pour insuffisance cardiaque.

Résultats :
Le volume de calcification de l'aorte ascendante allait de 0 à 21700 mm^3. La figure 10 représente 3 exemples d'aorte, peu, moyennement et très calcifiée.

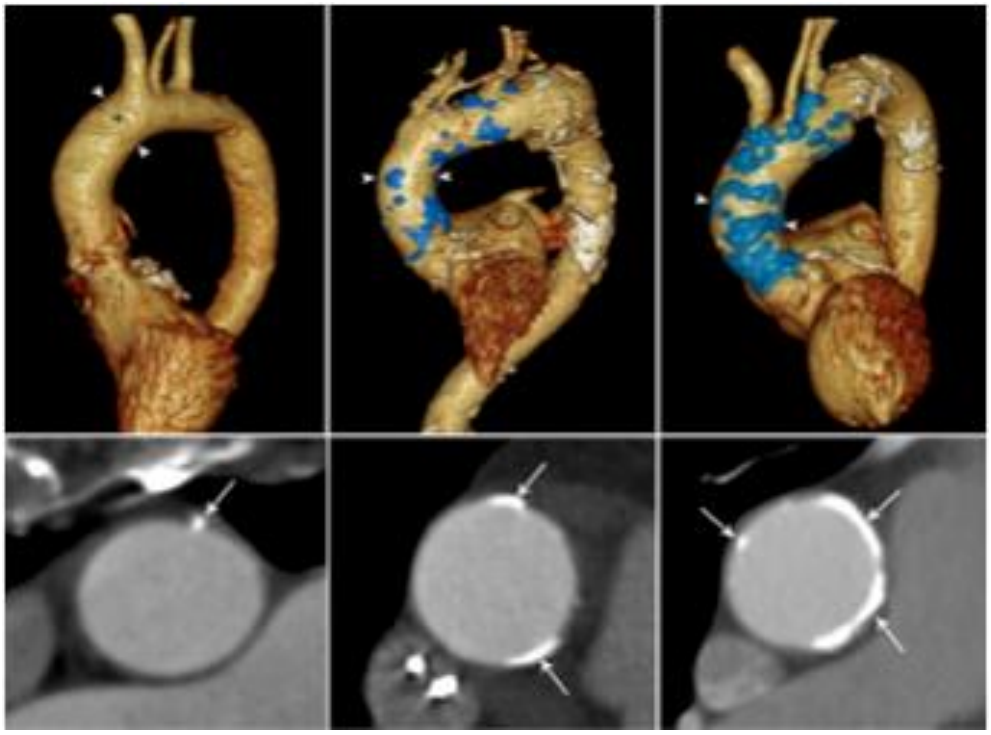

Figure 10: Mesure des calcifications de l'aorte ascendante au scanner.
Illustration de niveaux de calcifications de l'aorte, de gauche à droite peu, moyennement et très calcifié. En bas ; niveau de coupe de l'aorte permettant la mesure du volume.

Après un suivi médian de 907 jours, 24 décès d'origine cardiaque (9 morts subites, 14 insuffisances cardiaques, 1 infarctus du myocarde) et 46 hospitalisations pour insuffisance cardiaque ont eu lieu, donnant 54 événements composites (mortalité cardiaque ou hospitalisation pour insuffisance cardiaque). Après ajustement sur différents facteurs confondants, les calcifications de l'aorte gardaient une puissante valeur pronostique.

Conclusion, discussion :

Le volume de calcifications de l'aorte ascendante est un marqueur de risque de mortalité cardiaque et d'insuffisance cardiaque en post TAVI. L'aorte ascendante joue un rôle majeur dans l'amortissement du volume d'éjection ventriculaire gauche. Une altération de sa rigidité pourrait représenter un obstacle pour le ventricule gauche après la levée de l'obstacle valvulaire (Figure 11).

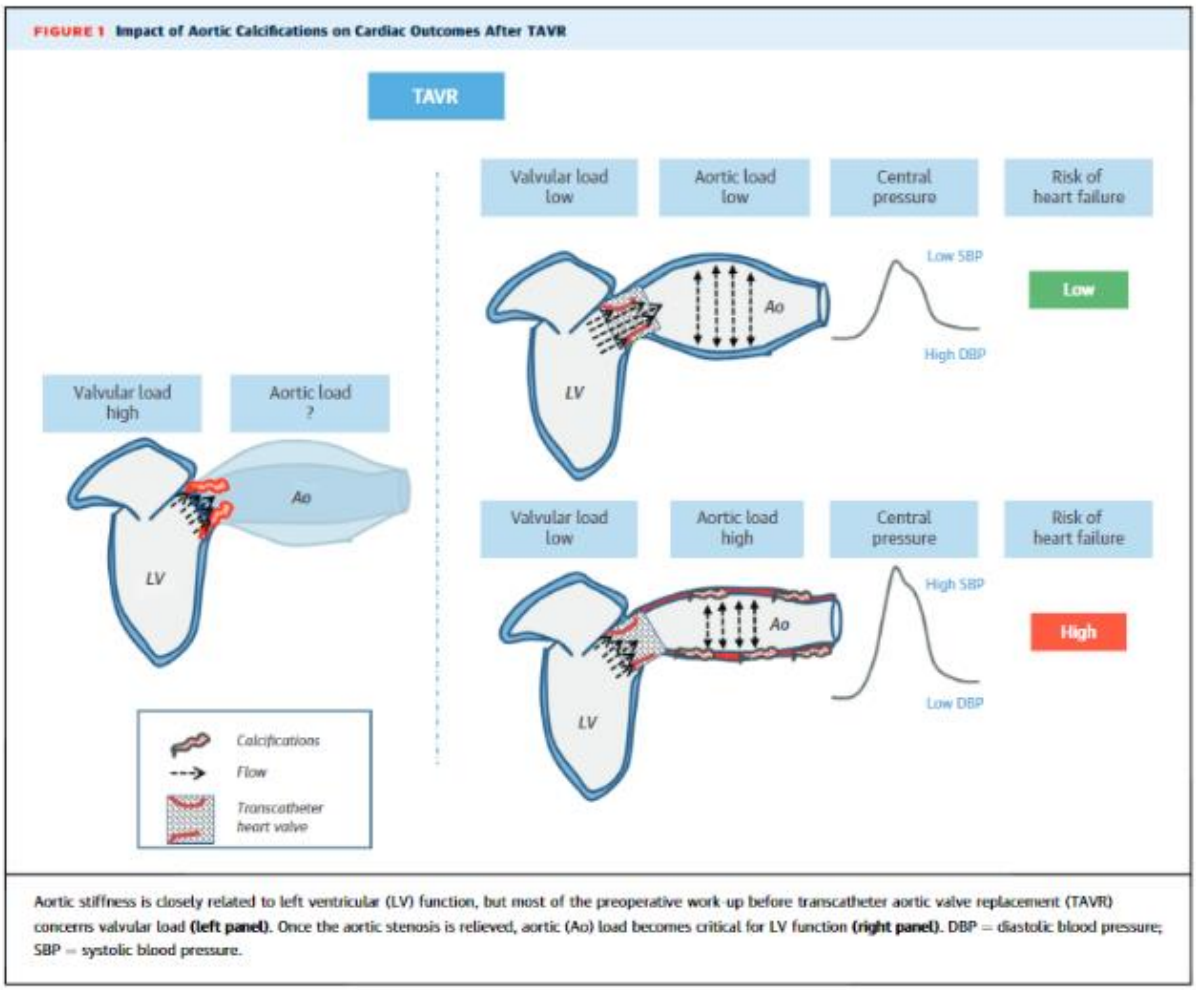

Figure 11 : Impact des calcifications aortique chez les patients traités par TAVI
En présence d'une sténose aortique, la post charge ventriculaire gauche est essentiellement valvulaire. Après un traitement par TAVI, le ventricule gauche fait face à une post charge vasculaire qui en cas de rigidité aortique peut conduire à de l'insuffisance cardiaque.

Perspectives : Afin d'expliquer le lien entre calcifications de l'aorte ascendante et survenue d'insuffisance cardiaque il serait intéressant d'étudier d'autre paramètres évaluant la rigidité aortique. Il serait également intéressant d'étudier la valeur pronostique des calcifications du reste de l'aorte.

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MARCH 17, 2015:1057-63

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Aortic Calcifications Present the Next Challenge After TAVR

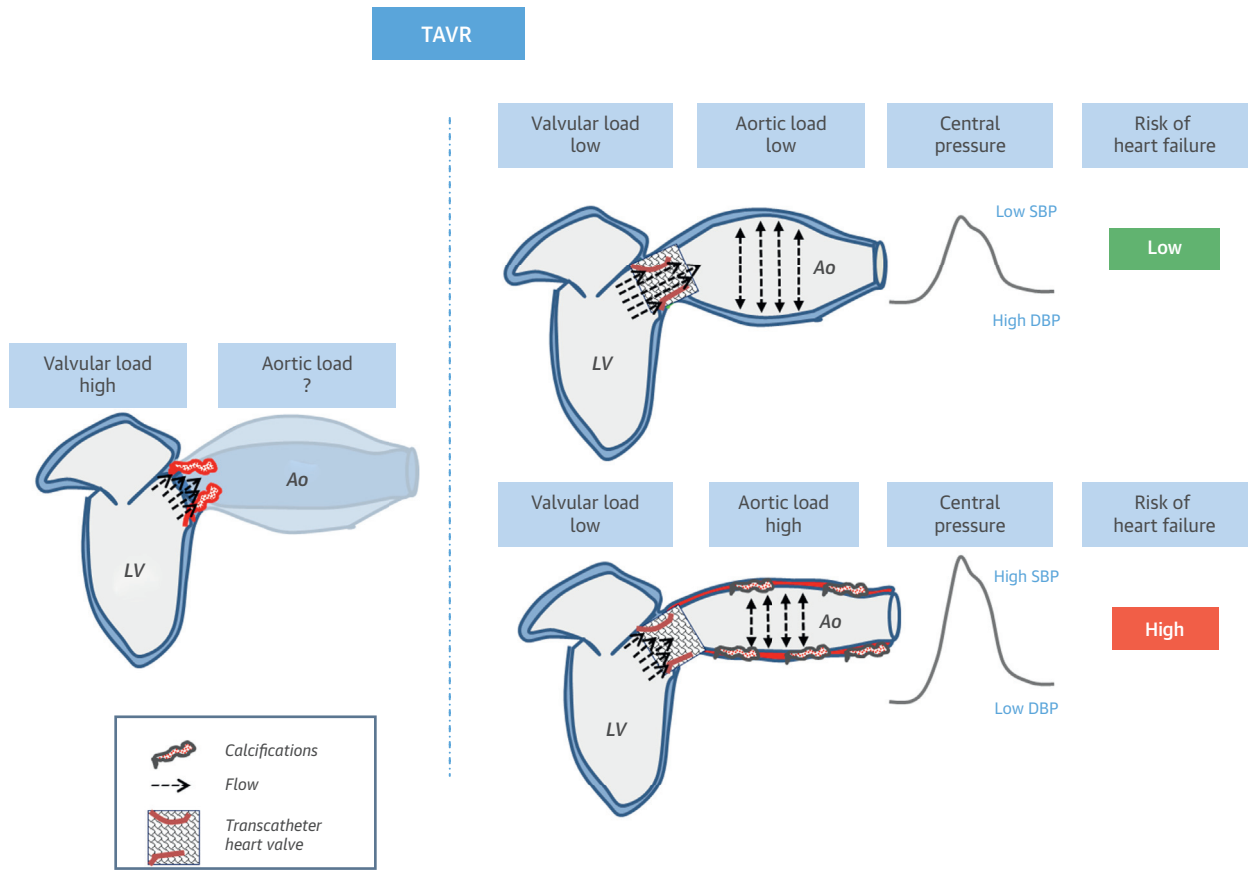
In the presence of aortic stenosis, the left ventricle (LV) faces a double challenge: a valvular load and an arterial load (1). Transcatheter aortic valve replacement (TAVR) has now become a safe and

effective alternative to surgery in patients with a contraindication or at high risk (2). Because patients considered for TAVR are elderly, implying that they often have a markedly remodeled aorta, the arterial component of the LV load is likely to be sizable; yet, the precise impact of aortic remodeling on cardiac outcomes after TAVR has never been tackled. We examined the effect of ascending aortic calcifications (AAC) measured by computed tomography (CT) on a composite endpoint encompassing cardiac mortality (from heart failure [HF], myocardial infarction [MI], or sudden death) and hospitalization for HF following TAVR with Edwards Sapien devices (Edwards Lifesciences, Irvine, California) in 127 consecutive patients. Patients provided written informed consent and the study received ethical committee approval.

Image acquisition was performed on a Brilliance 64-slice CT scanner (Philips, Healthcare, North Andover, Massachusetts). Calcifications of the thoracic aorta were individually delineated from the aortic sinus to the left subclavian artery with a semi-automatic segmentation tool (IntelliSpace Portal, Philips Healthcare) (3). For each patient, the total volume of the delineated AAC was calculated.

AAC was considered in turn as a categorical variable (tertiles) and as a continuous variable for statistical analysis; AAC ranged from 0 to 21,700 mm^3. Transapical approach, peripheral artery disease, and previous coronary artery bypass graft surgery were more frequent with increasing AAC levels. No difference was observed for other variables, in particular comorbidities, Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), or ejection

FIGURE 1 **Impact of Aortic Calcifications on Cardiac Outcomes After TAVR**



Aortic stiffness is closely related to left ventricular (LV) function, but most of the preoperative work-up before transcatheter aortic valve replacement (TAVR) concerns valvular load **(left panel)**. Once the aortic stenosis is relieved, aortic (Ao) load becomes critical for LV function **(right panel)**. DBP = diastolic blood pressure; SBP = systolic blood pressure.

fraction (EF). After a median follow-up of 907 days (range 0 to 1,912 days), we observed 24 cardiac deaths (14 HF, 1 MI, 9 sudden death) and 46 hospitalizations for HF, leading to a total of 54 composite endpoints. Seven patients died during the first week and were considered as periprocedural events.

AAC markedly influenced the occurrence of the outcome in univariable analysis (tertiles 3 and 2 vs. 1 hazard ratio [HR]: 2.61; 95% confidence interval [CI]: 1.31 to 5.20; p = 0.006; +1 Log increment of ACC HR: 1.70; 95% CI: 1.15 to 2.50; p = 0.007). Potential confounders considered were either univariate predictors of events or significant correlates of AAC. In a first multivariable Cox regression model adjusted for arterial approach, peripheral artery disease, and previous coronary artery bypass grafting (or prevalence of coronary artery disease), AAC remained predictive of the outcome (tertiles 3 and 2 vs. 1 HR: 2.50; 95% CI: 1.23 to 5.09; p = 0.001; +1 Log increment of ACC HR: 1.70; 95% CI: 1.10 to 2.61; p = 0.016). Similar findings were observed in 2 other multivariable models, 1 adjusted for EuroSCORE and diabetes and the other adjusted for post-procedural grade 2 aortic regurgitation and calcification of the aortic ring. A sensitivity analysis performed after exclusion of periprocedural events led to similar results.

This study shows that the extent of AAC is a strong independent predictor of cardiac outcome after TAVR. This is not likely to be due to a higher occurrence of MI; indeed, outcome was mainly driven by HF while only 1 fatal MI was observed, which arose in the periprocedural period and was not accounted for in the sensitivity analysis. Furthermore, adjustments for "coronary history" did not change the results. We believe that the worse cardiac prognosis associated with a high AAC score mainly reflects the consequences of aortic stiffening on LV function (**Figure 1**) (4). This is probably critical in TAVR patients, because they often have aged vessels. For the moment, methods to "destiffen" the aorta are limited, and AAC should be considered primarily as a new powerful criterion to refine risk stratification in usually severely ill patients in whom the best option is not easy to determine.

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Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Harbaoui and Courand contributed equally to this work.

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b) Rigidité vasculaire aorte thoracique et aorte abdominale

Aorta Calcification Burden: Towards an Integrative Predictor of Cardiac Outcome After Transcatheter Aortic Valve Implantation

Harbaoui B, Montoy M, Charles P, Boussel L, Liebgott H, Girerd N, Courand PY, Lantelme P

Atherosclerosis; 2016 Jan 11;246:161-168

Hypothèse : La localisation des calcifications le long de l'aorte pourrait ne pas avoir la même valeur pronostique. Les calcifications de l'aorte ascendante pourraient être plus spécifiques de l'insuffisance cardiaque.

Objectif : Evaluer le rôle pronostique des calcifications de l'aorte totale mesurées par scanner en pré-TAVI.

Population, Méthodes : 164 patients consécutifs porteurs d'une sténose aortique serrée traités par TAVI. Mesure du volume de calcifications de l'aorte totale (thoracique ascendante ascendante, thoracique descendante et abdominale) sur le scanner systématiquement réalisé avant un TAVI.

Les outcomes considérés étaient les suivants ;

- Mortalité toutes causes
- Mortalité cardiaque
- Hospitalisation ou décès en lien avec l'insuffisance cardiaque

Résultats :

Le volume de calcifications de l'aorte total était un puissant prédicteur de mortalité cardiaque et de mortalité toute cause. Chaque segment pris séparément prédisait la mortalité cardiaque. Seule les calcifications de l'aorte abdominale prédisait la mortalité toutes causes.

Enfin, nous avons retrouvé que seul le volume de calcifications de l'aorte ascendante était associée à l'insuffisance cardiaque.

Conclusion, discussion :

Le rôle particulier de l'aorte ascendante dans l'insuffisance cardiaque est confirmé. Ainsi le rôle pronostique des calcifications de l'aorte pourrait donc avoir une double origine. Ces calcifications vasculaires peuvent être un marqueur de rigidité vasculaire et augmenter la postcharge ventriculaire gauche, augmentant le risque de survenue d'insuffisance cardiaque : elles jouent alors le rôle de *facteur de risque*. Elles peuvent également être le témoin d'une athérosclérose avancée et signifier que la charge athéromateuse du patient est élevée et représenter dans ces conditions un *marqueur de risque*. Les résultats et conclusion de ce travail ont été résumés dans une figure récapitulative (Figure 12).

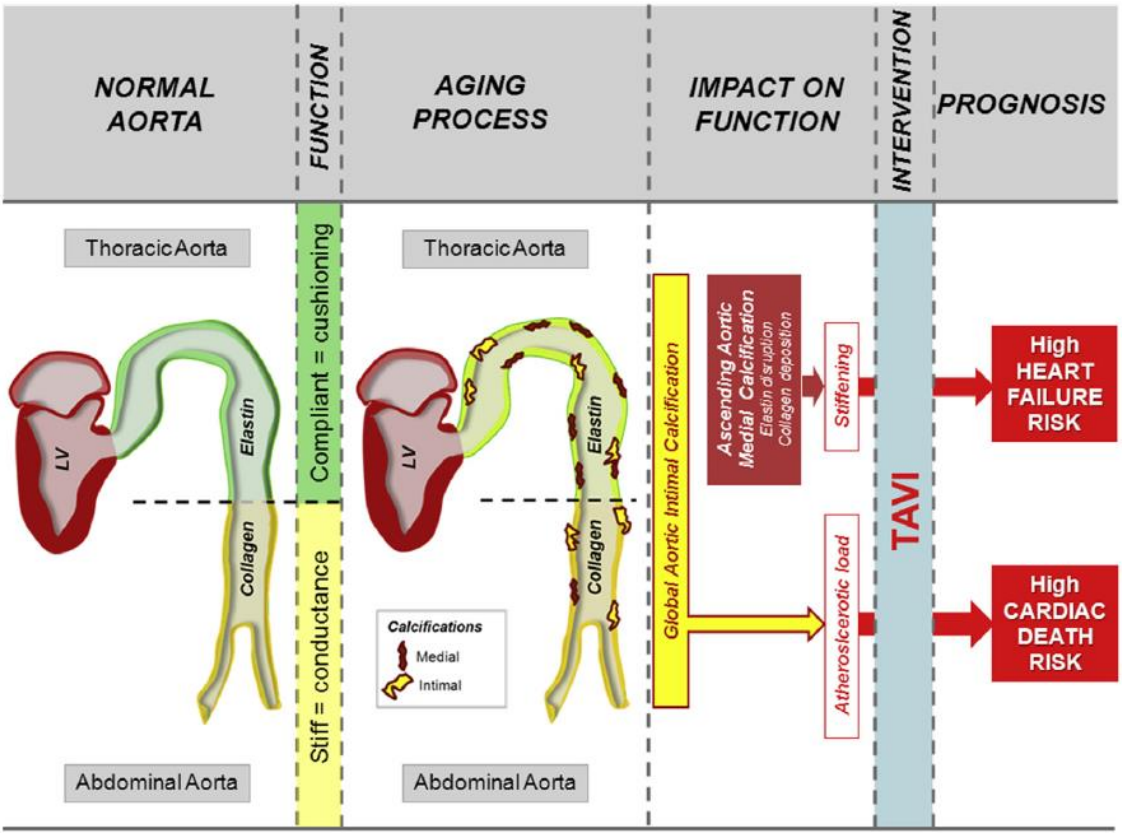

Figure 12 : Localisation des calcifications et implication pronostique.

Avec le vieillissement vasculaire l'aorte va présenter des calcifications. En fonction de la localisation de ces calcifications, l'impact clinique sera différent. Alors que les calcifications de l'aorte complète sont en lien avec la mortalité cardiaque, les calcifications de l'aorte ascendante vont être en plus en lien avec l'insuffisance cardiaque.

Perspectives : Le volume de calcifications de l'aorte pourrait être utilisé de façon plus large afin de prédire le risque des patients candidats à un TAVI. La valeur pronostique du volume de calcifications de l'aorte chez les patients présentant un rétrécissement aortique traité par TAVI a été confirmée sur 2 cohortes internationales indépendantes(3,4).

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Aorta calcification burden: Towards an integrative predictor of cardiac outcome after transcatheter aortic valve implantation

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ABSTRACT

Objective: The principal objective was to determine the effect of total aortic calcification (TAC) burden on outcomes (cardiac mortality, all-cause mortality, and heart failure (HF)) after transcatheter aortic valve implantation (TAVI). The secondary aim was to assess the contribution of each segment of the aorta to these outcomes.
Background: Indications for TAVI are increasing in number. Even after procedural success, however, some patients die soon afterwards, indicating the futility of TAVI in certain cases.
Methods: Aortic calcifications were measured on computed tomography in 164 patients treated by TAVI. TAC, ascending aortic calcification (AsAC), descending aorta calcifications, and abdominal aorta calcifications were expressed as tertiles and their prognostic values were assessed in a multivariable cox analysis adjusted for major confounders including EuroSCORE.
Results: Median duration of follow-up was 565 (interquartile range: 246 to 1000) days. TAC (tertile3 vs. tertile1) was significantly and strongly associated with cardiac mortality (hazard ratio [HR]: 16.74; 95% confidence interval [CI]: 2.21 to 127.05; $p = 0.006$) and all-cause mortality (HR: 2.39; 95% CI: 1.18 to 4.84; $p = 0.015$) but not with HF (HR: 1.84; 95% CI: 0.87 to 3.90; $p = 0.110$). Each segment was associated with cardiac mortality, while only AsAC (tertile 3 vs. tertile 1) appeared predictive of HF (hazard ratio: 2.29; 95% CI: 1.12 to 4.66; $p = 0.023$).
Conclusions: TAC is an integrative predictor of cardiac and all-cause mortality after TAVI. It should be included in the assessment of patients before TAVI in order to predict cardiac outcome after valve replacement and avoid futile interventions.

1. Introduction

Within the past few years, transcatheter aortic valve implantation (TAVI) has become a first-line therapy for inoperable patients with severe aortic stenosis or at high surgical risk [1–4]. More than 150,000 patients have undergone TAVI worldwide [5] since Cribier et al. performed the first implantation in 2002 [6]. Device and technical refinements have led to procedural success in most cases, yet TAVI seems futile for some patients who die rapidly after the procedure or experience only a very small improvement in quality of life [1,2,7–9].

Current risk scores based on heart surgery are not very discriminating in this high-risk population and are not therefore suitable for TAVI [10,11]. Furthermore, the question of long-term benefit is not addressed by any of the current risk models. Thus, optimization of patient selection is a major challenge today in the context of the growing indications for TAVI [12].

We recently reported that ascending aortic calcification (AsAC), a surrogate of aortic stiffness, is a powerful predictor of cardiac outcomes after TAVI [13,14]. In another setting, we found that

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0021-9150/

abdominal aortic remodeling was predictive of coronary events [15]. Thus, total aortic calcification (TAC) burden could represent an integrative marker of cardiac risk encompassing coronary events and heart failure (HF). While the role of aortic biomechanics is often overlooked in the field of cardiology, we present the hypothesis that such an extra-cardiac marker could be of great value and novelty for predicting cardiac outcome after TAVI. Thus, the major objective of this study was to evaluate the effect of TAC burden, measured over the whole aorta by computed tomography (CT), on cardiac mortality, all-cause mortality, and a composite of HF hospitalization or mortality after TAVI. The secondary aim was to assess the contribution of 3 aortic segments (ascending, thoracic descending, and abdominal) on each of these outcomes after TAVI.

2. Methods

2.1. Patient population

From April 2009 through January 2015, 189 patients were scheduled for TAVI in our group of hospitals (Croix-Rousse, Louis Pradel, and Saint-Luc Saint-Joseph, Lyon, France) as part of an ongoing prospective cohort [13]. The multidisciplinary team determined eligibility and vascular access for TAVI on the basis of systematic clinical evaluation, angiographic assessment, CT, and transthoracic echocardiography. An Edwards SAPIEN valve (Edwards Lifesciences LLC, Irvine, CA) was implanted in all eligible patients. Among patients who underwent TAVI, 164 with calcification measureable on at least 1 segment of the aorta on CT **prior to** TAVI were included. All patients provided written informed consent before undergoing the procedure, including consent for anonymous processing of their data. The study received ethical committee approval.

2.2. CT of the aorta

CT acquisition was performed on a Brilliance 64 CT scanner (Philips, Best, Netherlands) in the head-to-feet direction covering the whole thoracic and abdominal aorta, with the following parameters: number of detectors 64, individual detector width 0.625 mm, retrospective electrocardiogram gating, tube voltage/current 120 kV/600 mA s, pitch 0.2, and half rotation reconstruction. Contrast agent (80 ml) (Iomeron 400, Bracco, Italy) was injected at a rate of 3.5 ml/s followed by 50 ml of saline at the same rate. A bolus tracking method on the ascending aorta was used with a threshold of 200 UH. Reconstruction parameters for axial slices were 0.8 mm effective section thickness, 0.4 mm increment, and adapted field-of-view. Retrospective electrocardiogram-gated reconstruction was performed at 0%, 40%, and 75% of the R–R interval.

Analysis was performed with the IntelliSpace Portal (Philips, Best, Netherlands) on the 75% cardiac phase. All calcifications of the aorta were individually delineated from the aortic sinus to the aortic bifurcation with a semiautomatic segmentation tool available in the IntelliSpace Portal based on a level-set method constrained by the Hounsfield units of the delineated structures [16]. The total volume of the delineated aorta calcifications (TAC) and the total aortic volume were first calculated. Then, using 3-dimensional segmentation tools, the volume of aortic calcification was measured for 3 aortic segments: the ascending aorta (AsAC) from the aortic sinus to the left subclavian artery; the descending thoracic aorta (DAC), from the left subclavian artery to the aortic hiatus; and the abdominal aorta (AbAC), from the aortic hiatus to the aortic bifurcation. The same measures were performed for aortic volume. One trained operator blinded to clinical data and outcomes read all the CT scans. Inter-observer and intra-observer reproducibility of TAC were assessed in 2 samples of randomly selected patients. TAC, AsAC, DAC, and AbAC were used both as crude variables and corrected for volume of the corresponding aortic segment.

2.3. Follow-up and outcomes

Patient history and treatment were retrieved from medical files and from review of hospital records. Survival status was obtained by telephone contact with patients, their relatives or carers, or their physicians. The primary outcome was cardiac mortality including sudden death, fatal myocardial infraction, and death from HF. Secondary endpoints were all-cause mortality and a composite of hospitalization for HF or death from HF. Post-procedural aortic regurgitation (PAR) was assessed on the final aortogram or on transthoracic echocardiography when aortography was not available.

2.4. Statistical methods

Qualitative variables are summarized as means ± standard deviations, medians with interquartile ranges, or numbers and percentages, as appropriate. Interobserver and intraobserver reproducibility of TAC measurement was tested by the κ test and by a modified Bland–Altman plotting (mean of the 2 assessments on the x-axis and ratio of the 2 assessments on the y-axis).

Patients were classified according to TAC tertile. One-way analysis of variance, nonparametric analysis of variance (Mann–Whitney test), and the chi-square tests were used, as appropriate, to compare variables between tertiles. The correlations between TAC, AsAC, DAC, and AbAC were assessed with a linear regression analysis (Pearson's coefficient of correlation, r) after logarithmic transformation.

To assess the predictive value of TAC, AsAC, DAC, and AbAC, the different endpoints were first estimated by Kaplan–Meier survival curves (log-rank statistic) according to tertiles. Univariate Cox regressions were performed for putative predictors. A forward stepwise Cox multiple regression analysis was performed to assess the independent predictive value of TAC, AsAC, DAC, and AbAC after adjustment for EuroSCORE, atrial fibrillation, vascular access, estimated glomerular filtration rate, coronary artery disease, and PAR. A backward stepwise Cox multiple regression analysis was also performed for cardiac death. Additional models were used to take into account additional significant univariate predictors not included in the set of variables preselected for adjustment or significant differences in terms of baseline characteristics among tertiles.

To estimate the additional prognostic value of TAC, AsAC, DAC, and AbAC, the accuracy of different multivariable models of prediction was determined by using integrated discrimination improvement and net reclassification improvement (NRI) [17]. A receiver operating characteristic (ROC) curve approach was also used to allow for defining potential prognostic thresholds. The analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, USA) and STATA 12 (Stata Corporation, College Station, USA). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Patient baseline characteristics

Among the 164 patients with an available CT scan, TAC could be assessed in 155 patients, AsAC in 164, DAC in 158, and AbAC in 155. The transfemoral approach was by far the most frequently used (Table 1). Of note, no difference was observed between TAC tertiles for comorbidities or aortic stenosis severity (measured according to

Table 1
Baseline characteristics of the whole cohort and according to tertile of TAC.

TAC	All patients (n = 164)	1st tertile (10.4–6342.4 mm^3) (n = 51)	2nd tertile (6415.6 to 13,750.1 mm^3) (n = 52)	3rd tertile (13,836.2 to 54,081.0 mm^3) (n = 52)	p Value
Age, years	82.3 ± 8.7	79.9 ± 10.7	83.92 ± 6.9	83.5 ± 7.5	**0.031**
Men	47	42.3	42.3	54.9	0.336
Pulse pressure, mmHg	61 ± 18	60 ± 17	58 ± 20	65 ± 19	0.198
Mean blood pressure, mmHg	90 ± 13	90 ± 12	89 ± 15	91 ± 13	0.786
Logistic EuroSCORE, %	20.6 ± 10.5	17.1 ± 9.5	21.7 ± 9.2	22.5 ± 11.6	**0.017**
NYHA class III or IV	63.4	61.4	65.1	60	0.681
TAC, mm^3	11,812.1 ± 9023.1	3106.3 (1912.5–4874.3)	9945.9 (7852.6–11,926.3)	20,128.6 (16,582.3–25,151.3)	–
Calcification of aortic ring, mm^3	1370.3 ± 1010.1	748.7 (479.1–1462.8)	971.9 (559.5–18,23.3)	1624.8 (1023.0–2474.6)	**<0.001**
Approach					
Transfemoral	64.6	72.5	73.1	48.1	**0.01**
Transapical	21.1	15.7	11.5	32.7	**0.017**
Transaortic	15.9	13.5	15.4	19.6	0.687
Medical history					
Hypertension	75.6	65.4	82.7	78.4	0.102
Dyslipidemia	40.2	40.4	44.2	39.2	0.863
Diabetes mellitus	27.4	25.5	21.2	32.7	0.403
Active smoking	3.7	3.8	5.8	1.9	0.605
Obesity	15.2	13.5	17.3	11.8	0.710
Coronary artery disease	57.3	46.2	63.5	64.7	0.101
Previous CABG	15.2	1.9	21.2	23.5	**0.004**
PTCA	32.3	30.8	32.7	35.3	0.887
COPD	30.5	38.5	26.9	21.6	0.154
Stroke	16.5	15.4	15.4	21.6	0.635
Peripheral artery disease	26.2	25.5	17.3	37.3	0.069
Permanent pacemaker	12.2	9.6	15.4	11.8	0.663
Atrial fibrillation	41.5	30.8	51.9	43.1	0.09
eGFR, ml/min	55.7 ± 25	59 ± 24.8	56.9 ± 27.1	51 ± 22.7	0.252
Pre-procedural echocardiographic findings					
Aortic valve area, cm^2	0.63 ± 0.31	0.62 ± 0.31	0.66 ± 0.31	0.61 ± 0.31	0.696
Mean aortic valve gradient, mmHg	44.9 ± 14.2	47.6 ± 14.1	43.7 ± 14.9	42.8 ± 13.8	0.288
Left ventricular ejection fraction, %	54.3 ± 12.3	56.8 ± 11.4	52.7 ± 12.6	53.7 ± 12.9	0.280
Post procedural aortic regurgitation grade ≥2	8.5	7.8	1.9	13.5	0.219

Values are median (interquartile range) or %. CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; TAC = total aortic calcification.

echocardiographic data or left ventricular ejection fraction). Older age, higher EuroSCORE, and previous coronary artery bypass graft (CABG) surgery were more frequent in the 2 highest tertiles. High TAC was also associated with increased aortic ring calcification and a more frequent use of the transapical approach. Concerning peri-procedural complications, there was no significant difference between tertiles except for pacemaker implantation, which was higher in the 2 highest tertiles (tertile 1, n = 4; tertile 2, n = 18; and tertile 3, n = 11; p = 0.04).

3.2. Assessment of TAC with CT

TAC volume ranged from 10.4 mm^3 to 54,081 mm^3. AsAC volume ranged from 0 mm^3 to 19,702.1 mm^3, DAC volume from 0 mm^3 to 33,700 mm^3, and AbAC volume from 10.4 mm^3 to 17,600 mm^3. Correlations between TAC, AsAC, DAC, and AbAC are summarized in Table S1. All segmental calcification loads were correlated but the worse association was found between the 2 extreme segments, *i.e.* between the ascending and the abdominal ones (r = 0.492; p < 0.001).

Intraobserver and interobserver concordance for tertiles of TAC were κ = 1 and κ = 0.83, respectively. Modified Bland–Altman also showed good intraobserver and interobserver reproducibility (Fig. S1).

3.3. Predictors of outcome

After a median follow-up of 565 days (interquartile range: 246 to 1000), we observed 26 cardiac deaths, 52 all-cause deaths, and 55 composite HF endpoints (including 47 hospitalizations for HF). The number and cause of death and composite heart failure endpoint according to tertiles of TAC are summarized in Fig. S2. Age, EuroSCORE, estimated glomerular filtration rate, and PAR were significantly associated with the primary outcome (Table S2). EuroSCORE was also significantly associated with both secondary outcomes. Pulse pressure and pre-TAVI mean aortic gradient were significantly associated with the composite HF endpoint.

3.4. Prognostic value of TAC

In Kaplan–Meier analysis (Fig. 1), cardiac mortality increased with increasing TAC tertile (p < 0.0001). The same results were observed for the secondary outcomes but were non-significant for all-cause mortality (p = 0.071).

In the multivariable Cox model (Table 2), TAC (tertile 3 vs. 1) remained significantly associated with the primary endpoint (HR: 16.74; 95% confidence interval [CI]: 2.21 to 127.05; p = 0.006) and became significantly associated with all-cause mortality (HR: 2.39; 95% CI: 1.18 to 4.84; p = 0.015). A non-significant increase for the composite HF endpoint was observed (HR: 1.84; 95% CI: 0.87 to 3.90; p = 0.110). In another model using age, transapical approach and history of CABG, the results were essentially the same; TAC (tertile3 vs. tertile1) remains an independent predictor of cardiac mortality and of all-cause mortality; in addition, with this adjustment, TAC also predicts the composite heart failure endpoint (Table S3).

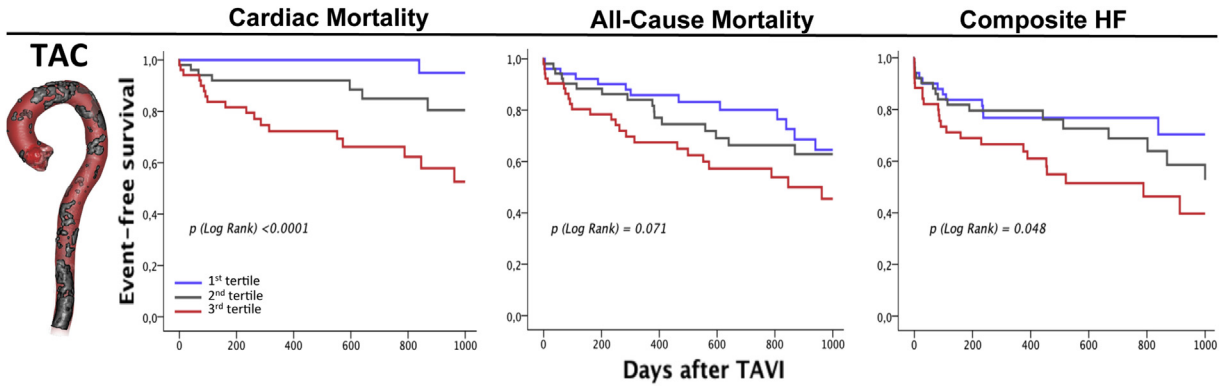

Fig. 1. Kaplan–Meier survival curves for cardiac mortality, all-cause mortality, and the composite of heart failure hospitalization or death, according to TAC tertile. HF = heart failure; TAC = total aortic calcification; TAVI = transcatheter aortic valve implantation.

Table 2
Prognostic value of TAC, AsAC, DAC, and AbC in multivariable Cox regression analyses.[a]

Variable	Cardiac mortality		All-cause mortality		Heart failure (hospitalization/death)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
TAC						
Tertile 2 vs. 1	5.05 (0.60–42.18)	0.135	1.20 (0.55–2.61)	0.642	1.30 (0.59–2.86)	0.522
Tertile 3 vs. 1	16.74 (2.21–127.05)	**0.006**	2.39 (1.18–4.84)	**0.015**	1.84 (0.87–3.90)	0.110
AsAC						
Tertile 2 vs. 1	3.42 (0.72–16.22)	0.122	1.20 (0.56–2.56)	0.634	1.25 (0.59–1.25)	0.568
Tertile 3 vs. 1	7.17 (1.63–31.49)	**0.009**	1.77 (0.89–2.53)	0.105	2.29 (1.12–4.66)	**0.023**
DAC						
Tertile 2 vs. 1	6.28 (0.78–50.76)	0.085	1.06 (0.49–2.28)	0.885	1.39 (0.63–3.06)	0.412
Tertile 3 vs. 1	14.24 (1.87–108.38)	**0.010**	1.75 (0.86–3.56)	0.122	1.51 (0.69–3.30)	0.300
AbAC						
Tertile 2 vs. 1	2.08 (0.40–10.95)	0.388	1.18 (0.56–2.51)	0.661	1.23 (0.57–2.64)	0.596
Tertile 3 vs. 1	7.56 (1.70–33.64)	**0.008**	2.02 (1.01–4.01)	**0.045**	1.27 (0.58–2.77)	0.554

TAC = total aortic calcification; AAC = ascending aortIc calcification; DAC = descending aortic calcification; AbAC = abdominal aortic calcification; HR = hazard ratio.
[a] Adjusted for EuroSCORE, atrial fibrilation, vascular access, estimated glomerular filtration rate, coronary artery disease. and post-procedural aortic regurgitation.

The same results were observed for TAC, corrected for aortic volume (Table S4).

3.5. Prognostic significance of aorta calcification segments

In Kaplan–Meier analysis (Fig. 2), increases in AsAC, DAC, and AbAC were all associated with a reduced event-free survival with respect to cardiac death. For the secondary outcomes, we observed no significant association but only a trend concerning AsAC and the composite HF endpoint (p = 0.074).

In the multivariable Cox model (Table 2), belonging to the highest calcification tertile was associated with an increased hazard for the primary outcome, and this was true for each segment. Similar results were obtained by using a backward stepwise cox regression model (data not shown). Regarding secondary outcomes, tertile 3 of AbAC was significantly associated with all-cause mortality (HR: 2.02; 95% CI: 1.01 to 4.01; p = 0.045) and tertile 3 of AsAC with composite HF endpoint (HR: 2.29; 95% CI: 1.12 to 4.66; p = 0.023). For the composite HF endpoint, adding pre-TAVI mean aortic gradient or pulse pressure did not change the results. The same results were observed were AsAC, DAC, and AbAC corrected for aortic volume (Table S4).

3.6. Improvement in risk stratification by TAC

The addition of TAC into the survival model on top of EuroSCORE, atrial fibrillation, and PAR was associated with a significant improvement in discrimination for cardiac mortality (integrated discrimination improvement: 10%; 95% CI: 1.8–23.5%; p = 0.004; continuous NRI: 41.6%; 95% CI: 13.4–63.3%; p < 0.001). Similarly, the addition of DAC or AbAC to EuroSCORE, atrial fibrillation, and PAR was associated with a significant improvement in discrimination, (with both integrated discrimination improvement and NRI). In contrast, AsAC was not associated with a significant improvement in discrimination.

For the composite HF endpoint and all-cause mortality, none of the calcification variables improved discrimination over EuroSCORE, atrial fibrillation, and PAR (all p > 0.10).

The Area under the ROC curves were rather mitigate, the best values being observed for cardiac mortality and with TAC (Table S5). More specifically, a TAC volume of 17480 mm3 had a 83.3% Sensitivity and a 48.3% Specificity to predict cardiac death.

4. Discussion

The present study demonstrates that calcification burden of the whole aorta is a strong independent predictor of cardiac mortality after TAVI. This is probably because each segment conveys a particular and additive significance, the proximal one being more related to HF. To our knowledge, this is the first study to evaluate quantitatively aortic calcifications of the entire aorta and to highlight the specific prognostic value of each segment of the aorta on mortality and morbidity, with a very robust statistical model.

4.1. Prognostic effect of aortic calcification burden

The main result of the present study was that TAC was a strong independent predictor of mortality after TAVI. The most powerful

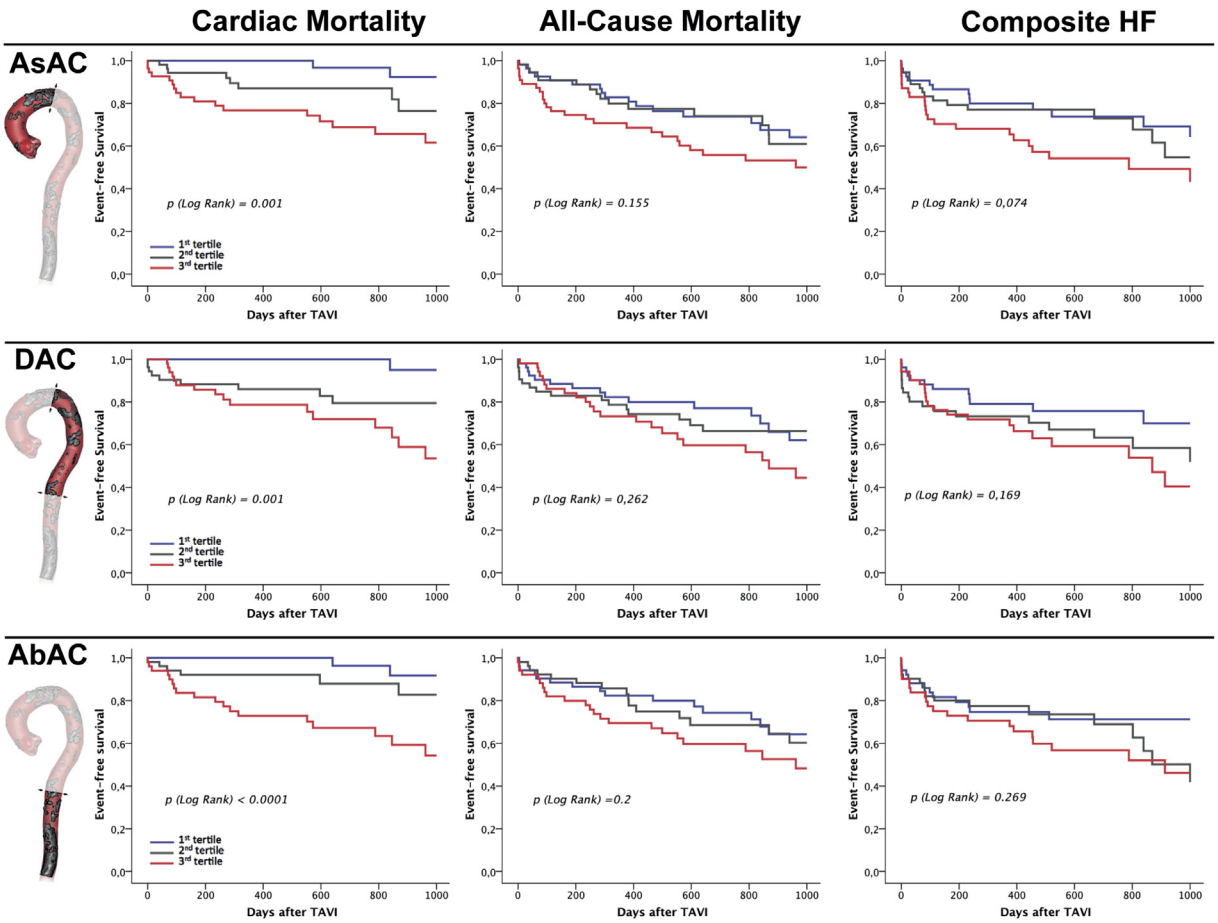

Fig. 2. Kaplan–Meier survival curves for cardiac mortality, all-cause mortality, and the composite of heart failure hospitalization or death according to tertile of each segment of the aorta. AsAC = ascending aortic calcification; DAC = descending aortic calcification; AbAC = abdominal aortic calcification; HF = heart failure; TAVI = transcatheter aortic valve implantation.

association concerned cardiac mortality with an association even after adjustment for major confounders such as EuroSCORE (which include age), atrial fibrillation, vascular access, estimated glomerular filtration rate, coronary artery disease, and PAR. This association was also found when calcifications were considered separately on each aortic segment. NRI and integrated discrimination improvement analyses showed that the best improvement in prediction was obtained with TAC as compared to each individual segment, suggesting a cumulative effect of calcification burden of each part of the aorta for the prediction of cardiac mortality. In addition, a similar association was observed with TAC and all-cause mortality, but was only found with AbAC when segments were analyzed separately.

This contribution of each segment of the aorta to cardiac mortality is consistent with previous reports obtained in different settings. Concerning the ascending aorta, our group has already shown that calcification burden is predictive of cardiac mortality after TAVI [13]. We have also shown in a large cohort of hypertensive patients that abdominal aortic remodeling assessed by angiography is predictive of coronary-related deaths [15]. Abdominal aorta calcification was also found to be an independent predictor of vascular morbidity and mortality when evaluated by lateral lumbar radiograms [18] and predicted all-cause mortality and nonfatal cardiovascular events in hemodialysis patients when evaluated by CT [19]. However, a major limitation of these previous studies is their important heterogeneity concerning both imaging techniques and the fact that only part of the aorta was studied. In this respect, our comprehensive analysis of the aorta shows the improvement in prediction of cardiac outcome by considering the entire aorta as compared with 1 particular segment. This prognostic significance seems of particular relevance in the context of TAVI patients who often have a markedly remodeled aorta. It extends our previous finding [13] and shows that it is possible to further improve prediction by considering the whole aorta. Above all, our study emphasizes the major contribution of the aorta, which is currently somewhat neglected, to cardiac events.

4.2. Aortic calcification is an integrative marker of cardiac events

Each aortic segment appeared associated with cardiac deaths. AsAC was significantly associated with HF after TAVI. At variance with cardiac mortality, the calcification burden of the other segments was not associated with HF. This suggests that AsAC is predictive of both HF and nonheart-failure mortality while DAC and AbAC are mainly predictive of nonheart-failure-related deaths, making TAC an integrative marker of global cardiac mortality. This is likely explained by histological considerations. Vascular calcification occurs at 2 distinct sites within the vessel wall: the intima and the media. The mechanisms leading to these 2 different locations and their clinical consequences are not the same [20]. Intimal calcification is associated with atherosclerosis whereas medial calcification is not; it is closely associated with elastin and vascular smooth muscle cells and thereby promotes aortic stiffening [20]. The wall of the ascending aorta has the highest density in elastic

fibers [21], thereby allowing that it to provide a buffering function during left ventricular ejection. Media calcification burden is proportional to the quantity of intra-parietal elastin, which explains its predominance in the thoracic aorta [22]. Together with elastin disruption and collagen deposition, calcifications at this level will lead to aortic stiffening and to the persistence of a high afterload after TAVI, impaired myocardial perfusion, and, consequently, to HF [23,24]. Aortic stiffness has indeed been related to cardiovascular morbidity or mortality [25] and to HF [26] in other settings. In the context of TAVI, the remaining high vascular load will continue to exert its harmful effect on left ventricular function over the long term [13,27]. This may explain the incomplete regression of left ventricular hypertrophy associated in some high-risk patients with severe aortic stenosis and severe left ventricular hypertrophy undergoing TAVI [28].

On the contrary, calcifications of the intima, albeit present all along of the aorta, mainly affect the abdominal part of the aorta. This is consistent with the worse correlation found between AbAC and AsAC than with DAC in our study. Intimal aortic calcific burden likely reveals global vascular atherosclerotic load thereby being a potent cardiovascular risk marker [22]; this is probably particularly true at the coronary level [29]. Thoracic aorta calcifications are associated with coronary calcium assessed by CT [30] on the one hand, and with the severity of coronary artery disease at angiography on the other [31]. Furthermore, a previous work highlighted that patients with severe aortic stenosis and coexisting coronary artery disease have more extensive arteriosclerotic changes in the thoracic aorta compared to those with aortic stenosis alone [32]. Altogether, this may explain why each segment's calcification is associated with an increased risk of cardiac deaths in our study, with a presumably large contribution of coronary-related deaths. A comprehensive illustration of these concepts and their effect on outcome after TAVI is presented in Fig. 3.

4.3. Clinical implications for prediction of outcome after tavi

For some patients, TAVI can be a futile intervention even after procedural success, which raises ethical and cost-effectiveness concerns. Currently, some patients die shortly after TAVI or show only a very small improvement in quality of life [1,2,7–9]. According to recent registries, between 25% and 30% of the patients die within the first year following TAVI [33,34]. In patients with a contraindication for surgery, almost half die or achieve only a small improvement in quality of life in the same period [1,7]. Easy tools for prediction of outcome after TAVI are lacking. Indeed, traditional surgical risk scores, including the logistic EuroSCORE, EuroSCORE II, and the STS score, have failed to identify patients who would benefit most from TAVI [10,11].

An important aspect is the evaluation of frailty, which appears essential in this elderly population [9]. Concerning cardiac outcome, most efforts have been directed toward “strict cardiac indices” such as NT-pro-B-type natriuretic peptide [35], atrial fibrillation [36], low stroke volume index, low gradient, and low ejection fraction, all of which were associated with higher mortality [37]. We propose to complete this study with an aortic evaluation as it presents a major determinant of cardiac event-free survival, an aspect that is currently neglected in such patients. In addition, assessment of aortic calcification fits very well in the routine work-up of patients before intervention. We do not intend to define a strict threshold based on our results. Aortic calcifications should be regarded as one criteria among a bunch of other ones. Yet, based on the tertile analysis and on the ROC curve approach, one can assume that selecting a TAC threshold somewhere between 14,000 and 17,000 mm^3 would identify a population at very high risk of poor

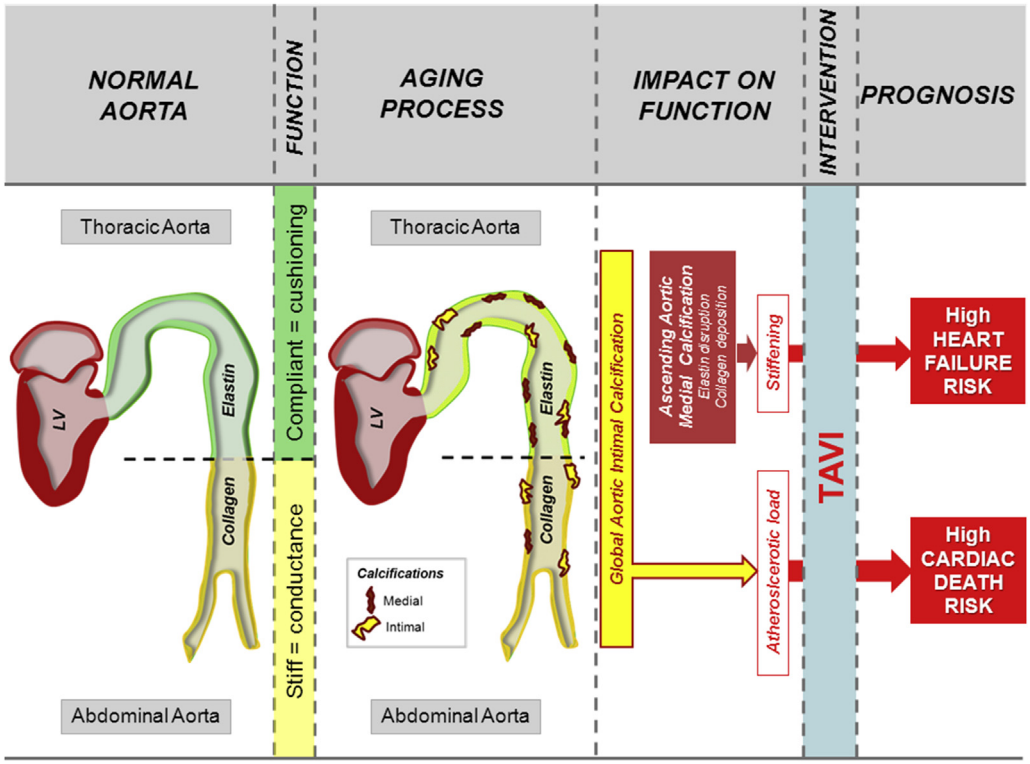

Fig. 3. Segmental aortic calcifications, significance, and consequences after TAVI. Aortic calcifications occur at 2 distinct sites within the vessel wall: the intima and the media. Media calcification burden is proportional to the quantity of intra-parietal elastin; thereby it may explain why it is predominant in thoracic aorta. Both intimal and medial calcifications may play a role on outcomes, as a cardiovascular marker or as a surrogate of stiffness, respectively. LV = Left Ventricle; TAVI = Transcatheter aortic valve implantation.

outcome after TAVI. This threshold should be refined with further studies in larger cohorts. This is particularly important in the context of the growing indications for TAVI [12].

4.4. Study limitations

Although sizeable, our cohort does not include as many patients as in recent registries of TAVI [1,2]. However, almost all of the associations identified in this study are clear and very significant, demonstrating their power. Other mechanisms could be involved in aortic stiffness, especially in elderly people. With aging, vessels contain less elastin and more collagen [38], and calcification burden forms only a part of aortic stiffness. Other ways to assess aortic stiffness may be proposed but may be difficult to obtain in this elderly population presenting severe aortic stenosis with hemodynamic changes [27] and a high prevalence of atrial fibrillation [39]. Thus, TAC offers the advantage of being strictly independent of the hemodynamic condition, as emphasized recently [14]. CT cannot differentiate accurately each type of calcification; however, both types of calcification correlate with significant morbidity and mortality (namely atherosclerosis and aortic stiffness) allowing for a global cardiac risk appraisal.

5. Conclusions

Our results emphasize that TAC is a powerful independent predictor of mortality after TAVI. This new tool is feasible to carry out, with good accuracy and reproducibility and without adding further exams or cost. A new specific “TAVI score risk” should integrate this variable to help physicians in the decision-making process and avoid futile interventions.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.013.

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c) Validation multicentrique et développement d'un score de risque

Development of a Risk Score Based on Aortic Calcification to Predict 1-year Mortality After TAVR.

Lantelme P, Eltchaninoff, Rabilloud M, Souteyrand G, Dupré M, Spaziano M, Bonnet M, Becle C, Riche B, Boussel L, Lefèvre T, **Harbaoui B**

JACC Cardiovasular Img 2019 Jan;12(1):123-132

Hypothèse : Un score de risque utilisant le volume de calcifications de l'aorte ascendante, marqueur de rigidité vasculaire, a une implication pronostique chez les patients traités par TAVI. Un score de risque incluant ce paramètre pourrait aider à prédire la mortalité post TAVI.

Objectif : Développer un score de risque TAVI utilisant les calcifications de l'aorte thoracique (TAC) afin de prédire la mortalité cardiovasculaire et toutes causes à 1 an.

Patients/Méthodes : L'étude multicentrique C4CAPRI (4 Cities for Assessing CAlcification PRognostic Impact) a inclus1 425 patients traités par TAVI entre 2010 et 2014 ainsi qu'une cohorte de test de 311 patients traités en 2015. Une méthode d'automatisation de lecture du volume de calcification de l'aorte a été mise au point avec le laboratoire de recherche Creatis Mesure semi-automatique du volume de calcifications de l'aorte ascendante sur le scanner systématiquement réalisé avant un TAVI. Le score de risques CAPRI a été développé en utilisant des analyses de Cox et a inclus des variables diverse (démographique, comorbidités cardiaques et extracardiaques). Le score CAPRI a été construit et testé dans 2 cohortes indépendantes.

Résultats : La mortalité cardiovasculaire et toutes causes confondues à 1 an était de 13,0 % et 17,9 %, respectivement, dans la cohorte d'entraînement et 8,2 % et 11,8 % dans la cohorte de

test. L'inclusion du TAC dans le modèle a amélioré la prédiction : augmentation de 1 cm3 du TAC était associée à une augmentation de 6 % de la mortalité cardiovasculaire et à une augmentation de 4 % de la mortalité toutes causes confondues. Les prévisions et les probabilités de survie observées étaient fortement corrélées (pentes >0,9 pour la mortalité cardiovasculaire et toutes causes confondues).

Le pouvoir prédictif du modèle était juste (ASC 68% [intervalle de confiance à 95% [IC]: 64-72]) pour la mortalité cardiovasculaire et totale.

Discussions/Conclusions : Le score CAPRI, qui combine la variable TAC avec des facteurs pronostiques classiques, est prédictif de mortalité cardiovasculaire et totale à 1 an. Sa performance prédictive a été confirmée dans une cohorte contemporaine indépendante.

Son utilisation de routine pourrait aider à prévenir les procédures futiles.

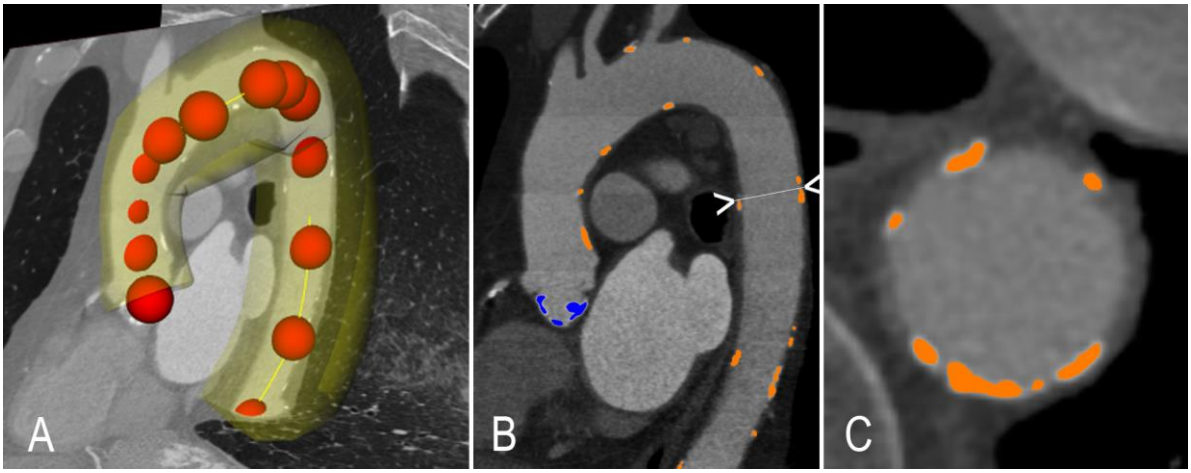

Figure 13: Mesure semi-automatique des calcifications de l'aorte au scanner.

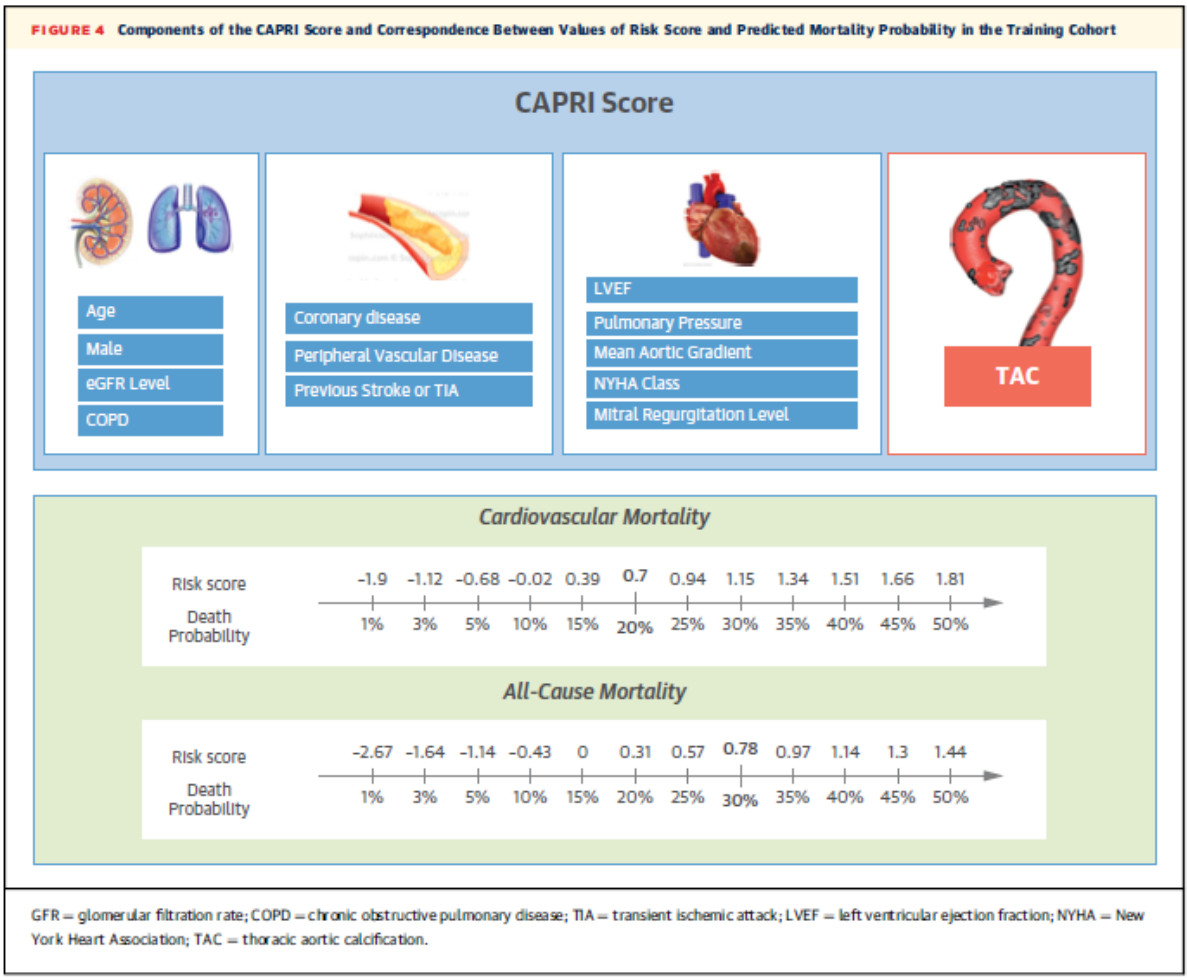

Figure 14 : Paramètres composants le CAPRI Score, valeur du score et probabilité de mortalité totale et cardiovasculaire à 1 an.

Le CAPRI score est calculé à partir de variables démographiques, de paramètres liés à l'athérosclérose, à la fonction cardiaque, à des comorbidités extracardiaques et au TAC.

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ORIGINAL RESEARCH

Development of a Risk Score Based on Aortic Calcification to Predict 1-Year Mortality After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The aim of this study was to develop a new scoring system based on thoracic aortic calcification (TAC) to predict 1-year cardiovascular and all-cause mortality.

BACKGROUND A calcified aorta is often associated with poor prognosis after transcatheter aortic valve replacement (TAVR). A risk score encompassing aortic calcification may be valuable in identifying poor TAVR responders.

METHODS The C_4CAPRI (4 Cities for Assessing CAlcification PRognostic Impact) multicenter study included a training cohort (1,425 patients treated using TAVR between 2010 and 2014) and a contemporary test cohort (311 patients treated in 2015). TAC was measured by computed tomography pre-TAVR. CAPRI risk scores were based on the linear predictors of Cox models including TAC in addition to comorbidities and demographic, atherosclerotic disease and cardiac function factors. CAPRI scores were constructed and tested in 2 independent cohorts.

RESULTS Cardiovascular and all-cause mortality at 1 year was 13.0% and 17.9%, respectively, in the training cohort and 8.2% and 11.8% in the test cohort. The inclusion of TAC in the model improved prediction: 1-cm^3 increase in TAC was associated with a 6% increase in cardiovascular mortality and a 4% increase in all-cause mortality. The predicted and observed survival probabilities were highly correlated (slopes >0.9 for both cardiovascular and all-cause mortality). The model's predictive power was fair (AUC 68% [95% confidence interval [CI]: 64% to 72%]) for both cardiovascular and all-cause mortality. The model performed similarly in the training and test cohorts.

CONCLUSIONS The CAPRI score, which combines the TAC variable with classical prognostic factors, is predictive of 1-year cardiovascular and all-cause mortality. Its predictive performance was confirmed in an independent contemporary cohort. CAPRI scores are highly relevant to current practice and strengthen the evidence base for decision making in valvular interventions. Its routine use may help prevent futile procedures. (J Am Coll Cardiol Img 2019;12:123–32)

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AUC = area under the receiver-operating characteristic curve

CI = confidence interval

COPD = chronic obstructive pulmonary disease

CT = computed tomography

GFR = glomerular filtration rate estimated by the Cockcroft formula

HF = heart failure

IDI = integrated discrimination improvement

HR = hazard ratio

LVEF = left ventricular ejection fraction

ROC = receiver-operating characteristic

TAC = thoracic aortic calcification

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) represents the standard of care for relieving aortic stenosis (AS) in high-risk patients; it is also preferred in symptomatic intermediate-risk patients according to the latest European Society guidelines (1). Although TAVR efficiently normalizes the gradient across the aortic valve, approximately 25% of high-risk patients die within the first year following the procedure (2). Because of the competing risk of noncardiovascular mortality or heart failure (HF), the true benefit of TAVR is difficult to estimate. Although perioperative mortality accounts for a minor part of overall deaths and is diminishing with technical refinement (3), most of this residual risk remains high. This points to a need to better identify potentially poor TAVR responders who would not benefit from the procedure. Lack of benefit may be defined as death and/or absence of functional improvement during a relatively short period after the procedure (6 months to 1 year) (4). Within this time frame, it is likely that adverse outcomes are mainly driven by factors present before the TAVR procedure. Among various candidates (4), predictors of improvement of left ventricular (LV) function are probably highly important but remain insufficiently characterized. Vascular after-load deserves scrutiny as it becomes preeminent after relief of AS (5). Our group recently established the prognostic significance of aortic calcifications assessed manually by computed tomography (CT) on the outcomes after TAVR. In particular, ascending aortic calcification was predictive of HF (6), and total aortic calcification burden was predictive of cardiac mortality (7). This prognostic implication may also concern noncardiovascular mortality (8,9).

SEE PAGE 133

The C_4CAPRI (4 Cities for assessing CAlcification PRognostic Impact; NCT02935491) study aimed at developing a score based on aortic calcification burden combined with classical predictors, to predict 1-year cardiovascular and all-cause mortality after TAVR.

METHODS

This was a multicenter study performed in 4 high-volume French centers. Two different cohorts were considered: a "training cohort" used to develop the risk scores and a "test cohort" in which the predictive value of the model was tested.

PATIENTS. All patients undergoing TAVR for severe AS during the study period were part of the FRANCE 2 (2,10) and of the FRANCE TAVI registries (11). The training cohort encompassed all patients treated by TAVR for severe AS at Clermont-Ferrand University Hospital, Lyon Croix-Rousse University Hospital, Institut Cardiovasculaire Paris Sud and Rouen University Hospital between January 2010, and December 2014. The test cohort comprised all patients implanted from January to December 2015 at the Lyon and Paris centers, reflecting the most recent practices available. Patients were included in the analysis if a pre-operative CT scan was available and thoracic aortic calcification (TAC) was assessed.

The C_4CAPRI study was approved by the Ethical Committee (Comité de Protection des Personnes SUD-EST IV, L16-56) and by the Commission Informatique et Liberté (CNIL N° 16-065). All patients provided written informed consent to anonymous processing of their data.

CALCIFICATION ANALYSIS. CT acquisition was performed on CT scanners with at least a 4-cm z-coverage: Brilliance 64 and iCT (Philips, Best, the Netherlands) or Discovery CT750 HD (GEMS, Waukesha, Wisconsin). For each examination, the whole thoracic aorta was studied. CT scans were performed after intravenous injections of iodine-based contrast agents with electrocardiogram (ECG) gating, tube voltage ranging from 100 to 140 kV, and adapted mAs. Reconstruction parameters for axial slices ranged from 0.625 to 0.8. All images were anonymized, transferred to a core lab, and analyzed by 3 operators who were blinded to outcomes data.

Calcifications were extracted using a semi-automated dedicated software based on an open source environment available at (12). The rater first delineates the ascending, horizontal, and descending thoracic aorta by placing at least 3 points (**Figure 1**). The main axis of the aorta was calculated using a

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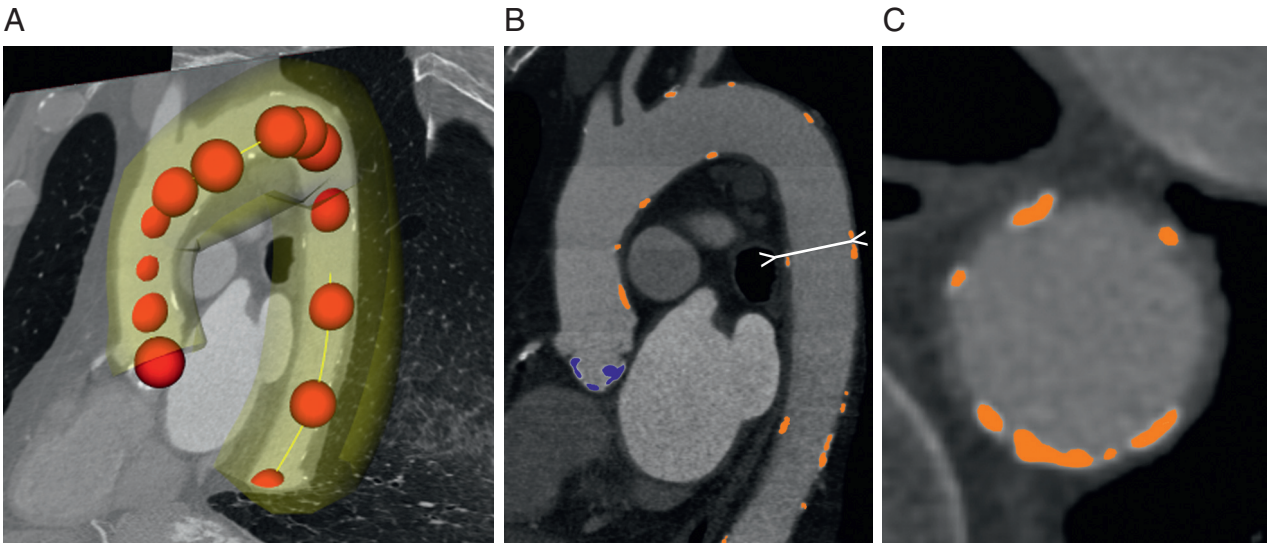
FIGURE 1 Example of Aortic Calcification Measurement



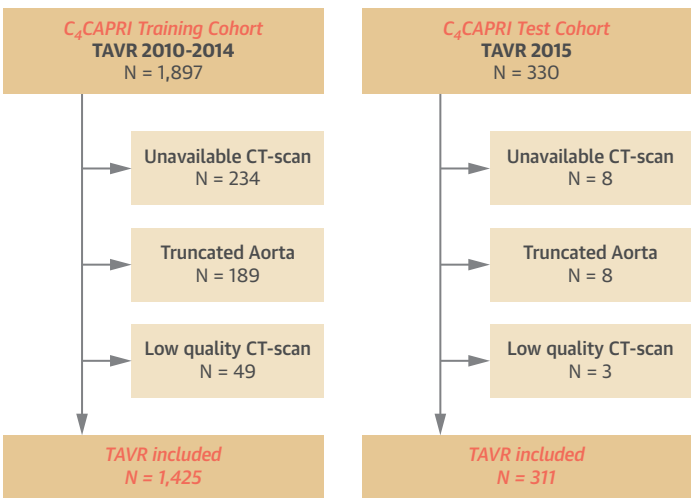
(A) Thoracic aortic segmentation (**red spheres** are used to delineate the ascending, horizontal, and descending thoracic aorta), **(B)** calcification selection (**blue and orange** are for valvular and thoracic aortic calcifications, respectively), **(C) arrows** indicate the level of the corresponding cross sectional image.

third-order b-spline. An adjustable tube embedding the whole aorta was created, and an initial threshold set at 550 UH was applied in the tube to detect calcifications. This threshold could be adapted to improve the performance of the algorithm. The results of the segmentation were visually asserted, and each calcification was manually adjusted (by addition or subtraction) and validated by the user. A connectivity algorithm, based on graph theory, was subsequently applied to segment each calcification. The algorithm is a simple recursive function initialized in the center of each calcification after thresholding. For each pixel, the 28 neighboring pixels were checked, and the algorithm was re-run for each pixel if its value was above the threshold. For each patient, TAC was calculated from the aortic sinus to the aortic hiatus as previously described (7); valvular calcifications were excluded.

Interobserver and intraobserver reproducibility, assessed in a subset of randomly selected patients from the training cohort (N = 50 and 75, respectively), was high with intraclass correlation coefficients estimated, respectively, at 0.997 (95% confidence interval [CI]: 0.994 to 0.998) and 0.997 (95% CI: 0.996 to 0.998).

PROCEDURES. Two TAVR systems were mainly used: a self-expandable prosthesis (Medtronic CoreValve ReValving System, Medtronic, Minneapolis, Minnesota) and a balloon-expandable prosthesis (Edwards SAPIEN valve, Edwards Lifesciences, Irvine, California); various routes (transfemoral, transapical, subclavian) and types of anesthesia were used in the different centers. The variables collected have been described elsewhere (6,10) and encompass demographics, cardiovascular history, biological variables, and echocardiographic variables.

FIGURE 2 Study Flowchart



C_4CAPRI = 4 Cities for Assessing CAlcification PRognostic Impact; CT = computed tomography; TAVR = transcatheter aortic valve replacement.

TABLE 1 Description of Demographic Characteristics, Comorbidities, and Disease Characteristics of the Patients Included in the C_4CAPRI Training and Test Cohorts

	N	Training Cohort	N	Test Cohort
Age, yrs	1,425	83.4 ± 7.1	311	83.3 ± 7.4
Male	1,425	730 (51.2)	311	152 (48.9)
BMI, kg/m^2	1,402	31.5 ± 7.8	304	32.0 ± 9.0
Logistic Euroscore, %	1,407	17.5 ± 10.4	297	17.0 ± 11.6
NYHA functional class III/IV	1,387	868 (62.6)	294	174 (59.2)
GFR, ml/min/1.73 m^2	1,415	50.5 ± 22.9	306	52.1 ± 23.8
Clinical history				
Previous CABG	1,193	144 (12.1)	298	24 (8.1)
Previous PTCA	1,406	379 (27)	398	74 (23.8)
Peripheral vascular disease	1,421	316 (22.2)	305	63 (20.7)
Stroke or TIA	1,421	129 (9.1)	305	27 (8.9)
COPD	1,420	267 (18.8)	305	50 (16.4)
Diabetes	1,425	366 (25.7)	306	86 (28.1)
Atrial fibrillation	1,407	454 (32.3)	297	76 (25.6)
Permanent pacemaker	1,198	155 (12.9)	305	46 (15.1)
Echocardiographic findings				
Mean gradient, mm Hg	1,396	47.1 ± 16.3	287	48.3 ± 16.5
LVEF, %	1,412	56 ± 14	286	54.9 ± 14.9
Moderate/severe MR	1,371	17 (1.2)	278	7 (2.5)
Pulmonary pressure, mm Hg	1,286	44 ± 14	280	43 ± 13
Coronary status				
Number of diseased vessels	1,423		310	
None		781 (54.9)		196 (63)
1		330 (23.2)		70 (23)
2		180 (12.6)		25 (8)
3		132 (9.3)		19 (6)
TAC, cm^3	1,420	3.3 ± 3.2	311	3.1 ± 3.2

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PTCA = percutaneous transluminal coronary angioplasty; TAC = thoracic aortic calcification.

OUTCOMES. The primary endpoint was cardiovascular death at 1 year. Secondary endpoint was all-cause mortality at 1 year. Vital status was obtained by telephone contact with patients, their relatives, caregivers, or physicians and by on-site planned visits. Follow-up was censored at 1 year following TAVR. Cardiovascular deaths were adjudicated by 2 experienced cardiologists, blinded to patient characteristics and TAC. Cardiovascular deaths were defined according to the VARC-2 criteria (13). Data collection was performed through dedicated web-based case report forms in each center, which were merged for analysis. Range checks to identify extreme values and assessments of internal consistency were applied during upload.

CONSTRUCTION OF CAPRI RISK SCORE. The characteristics of the cohorts were described using the absolute and relative frequencies for the qualitative characteristics and the mean and the standard deviation for the quantitative characteristics. TAC was considered as a 3-class variable defined according to the tertiles for the analysis using the Kaplan-Meier method and as a continuous variable in the model used to build the risk score. In addition to the continuous TAC, the risk score was constructed from known prognostic mortality factors according to the literature (2,10,14-16) and expert opinion, split into 3 groups: 1) demographic and comorbidities; 2) atherosclerotic disease; and 3) cardiac function (Supplemental Appendix). Nonredundant factors were selected in each group after estimating correlations among factors by Spearman coefficient, tetrachoric, or polychoric coefficients according to the nature of the factors. Cox regression models were used to quantify the effects of the retained factors on mortality hazard. The prediction improvement linked to the added factors was tested using the likelihood ratio test as recommended (17) and quantified using the integrated discrimination improvement (IDI) index (18). The calibration of the final model was estimated by plotting observed survival probabilities against deciles of prediction and its discriminative performance by using the cumulative/dynamic area under the ROC curve (AUC). The bootstrap method was used to quantify and correct the optimism of the estimated AUCs. The risk scores of mortality were computed using the linear combination of the factors included in the Cox model, weighted by the regression coefficients. The same strategy of analysis was applied to cardiovascular and all-cause mortality. The predictive performance of the risk scores was evaluated on the independent test cohort by assessing its calibration and estimating the AUC.

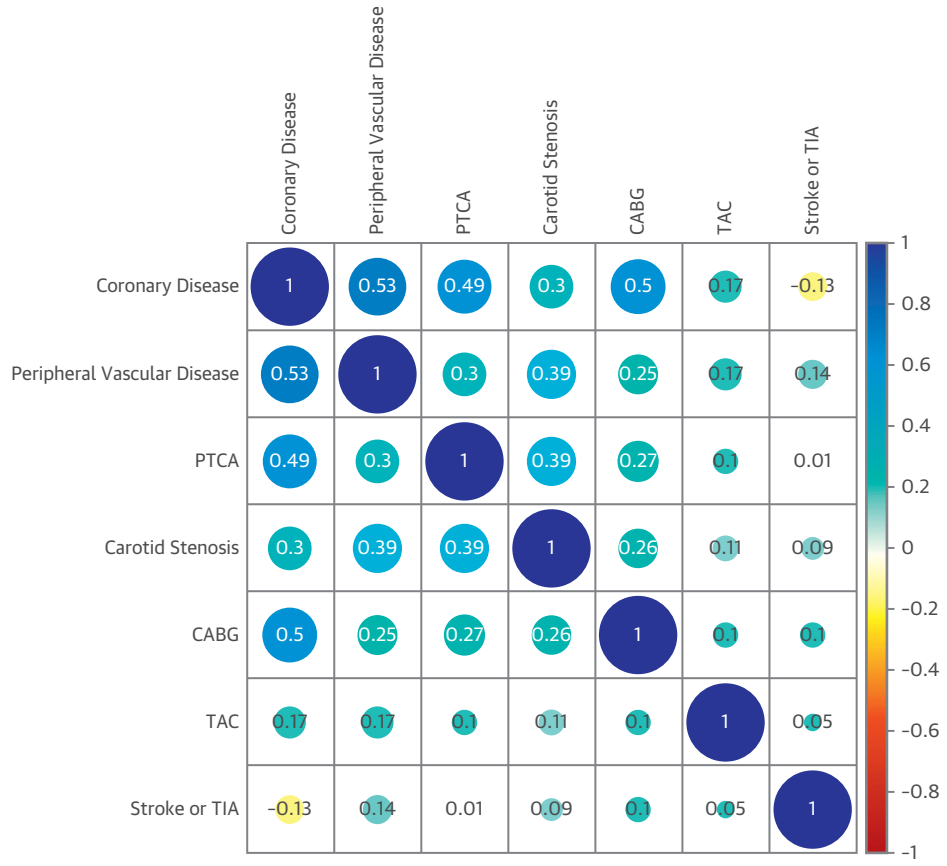
To illustrate the impact of the risk scores on the identification of potentially futile TAVR, futility thresholds corresponding to the expected 1-year mortality (between 15% and 25% for cardiovascular mortality and between 25% and 35% for all-cause mortality) of a medically treated population (19) were estimated in the training cohort. These thresholds were used in the test cohort to give an estimate of potentially futile TAVR: that is, those patients in whom the mortality probability after TAVR would be equal to or greater than that without intervention (Supplemental Appendix).

The analysis was performed using the statistical software SAS version 9.3 (SAS Institute Inc., Cary, North Carolina), and R version 3.3.1. (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

CHARACTERISTICS OF PATIENTS AND PROCEDURES. The flow of patients is shown in Figure 2. The characteristics of the training and of the test cohorts

FIGURE 3 **Correlations Between the Factors Linked to Atherosclerotic Disease and TAC**



The size and the color of the circles are indicative of the direction and the strength of the correlation, respectively (legend on the right). CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; TAC = thoracic aortic calcification(s); TIA = transient ischemic attack.

were similar concerning risk profile, route for TAVR, type of prosthesis, echocardiographic parameters, and TAC (**Table 1,** Supplemental Table 1). There were no substantial differences to the excluded patients (Supplemental Table 2). The rate of procedural success was high, and a marked decrease of transaortic gradient accompanied by a small increase of left ventricular ejection fraction (LVEF) was observed (Supplemental Table 1).

In the training cohort, 237 deaths were observed during the first year following TAVR, 170 of which were from cardiovascular causes. The 1-year cardiovascular and all-cause mortalities in the training cohort were estimated at 13.0% (95% CI: 11.2% to 14.8%) and 17.9% (95% CI: 15.9% to 19.1%), respectively. In the test cohort, 30 deaths—21 from cardiovascular causes—were observed. Cardiovascular and all-cause mortalities in this group were thus 8.2% (95% CI: 4.7% to 11.6%) and 11.8% (95% CI: 7.7% to 15.7%).

CORRELATION BETWEEN FACTORS BELONGING TO THE SAME GROUP AND TAC. For all 3 groups of risk factors, the correlations with TAC were low (**Figure 3,** Supplemental Figure 1). The highest correlation was between TAC and peripheral vascular disease or coronary disease, with coefficients estimated at 0.17.

PREDICTIVE POWER OF TAC FOR CARDIOVASCULAR AND ALL-CAUSE MORTALITY. The survival curves of the 3 classes of TAC were significantly different for cardiovascular and all-cause mortality, respectively (Supplemental Figure 2), with a survival much lower for the patients with a TAC above the second tertile in comparison with the 2 other classes of TAC.

Among demographic variables and comorbidities, age, sex, glomerular filtration rate (GFR), and chronic obstructive pulmonary disease (COPD) were included in the Cox model. The inclusion significantly improved the prediction of cardiovascular and

TABLE 2 Hazard Ratios and Corresponding Coefficients of the Risk Score Estimated in the Training Cohort Using a Cox Model for Predicting 1-Year Cardiovascular Mortality

	Hazard Ratio	95% CI	p Value	Coefficient
Demographic factors and comorbidities				
Age, yrs	1.03	0.998–1.06	0.07	0.026
Male	1.05	0.74–1.49	0.77	0.051
GFR level*	1.32	1.05–1.66	0.02	0.277
COPD	1.27	0.79–1.87	0.24	0.236
Atherosclerotic disease factors				
Coronary artery disease	0.89	0.64–1.25	0.50	−0.116
Peripheral vascular disease	0.92	0.61–1.38	0.69	−0.084
Previous stroke or TIA	1.34	0.81–2.23	0.26	0.294
Cardiac function factors				
LVEF, %	0.99	0.98–1.003	0.16	−0.008
Pulmonary pressure, mm Hg/10	1.13	1.02–1.26	0.02	0.126
Unknown pulmonary pressure	1.68	0.74–3.80	0.21	0.519
Mean gradient, mm Hg	0.99	0.98–1.001	0.07	−0.010
Dyspnea†	1.61	1.23–2.10	<0.01	0.475
Mitral regurgitation level‡	0.87	0.79–1.09	0.23	−0.136
TAC, cm^3	1.06	1.02–1.11	<0.01	0.059

*GFR in 4 ordinal levels, i.e., 1: <15 ml/min/1.73 m^2; 2: 15- 30 ml/min/1.73 m^2; 3: 30- 60 ml/min/1.73 m^2; 4: 60-90 ml/min/1.73 m^2; 5: ≥ 90 ml/min/1.73 m^2. †Dyspnea in 2 ordinal levels, i.e., 0: NYHA functional class I/II; 1: NYHA functional class III/IV. ‡Mitral regurgitation in 5 ordinal levels, i.e., 0: absence; 1: light; 2: moderate; 3: important; 4: severe.

CI = confidence interval; TIA = transient ischemic attack, other abbreviations as in Table 1.

all-cause mortality compared with the model without covariates (p = 0.002, p < 0.0001, respectively). Inclusion of the atherosclerotic disease factors (coronary artery disease, history of stroke or transient ischemic attack, or history of peripheral vascular disease) did not significantly improve the predictive power of the model (p = 0.75 for cardiovascular and p = 0.16 for all-cause mortality). Addition of factors linked to cardiac function (LVEF, pulmonary pressure, mean gradient, dyspnea [New York Heart Association functional class], mitral regurgitation) to the 2 previous groups improved the prediction of cardiovascular and all-cause mortality significantly (p = 0.0001, p < 0.00001, respectively).

Adding TAC to the other factors improved the prediction of cardiovascular and all-cause mortality significantly (p < 0.01 and p = 0.04, respectively). An increase of 1 cm^3 was associated with a 6% increase in cardiovascular mortality (hazard ratio [HR]: 1.06, 95% CI: 1.01 to 1.10) (Table 2) and a 4% increase in all-cause mortality (HR: 1.04, 95% CI: 1.00 to 1.08) (Table 3).

CALIBRATION AND DISCRIMINATION OF THE FINAL MODEL. The calibration of the model including the 3 groups of factors and the TAC was good for cardiovascular (Supplemental Figure 3A) and all-cause mortality (Supplemental Figure 3B). Slopes were 0.90 for cardiovascular and 0.95 for all-cause mortality, respectively. The IDI index measuring the improvement of the discrimination ability of the model by adding the TAC was significant: estimated at 0.006 (95% CI: 0.000 to 0.025) for cardiovascular mortality and at 0.004 (95% CI: 0.000 to 0.018) for all-cause mortality (Supplemental Figures 4A and 4B). The AUC for cardiovascular mortality was 68% (95% CI: 64% to 72%); that for all-cause mortality was 68% (95% CI: 64% to 72%). The optimism of the AUC of the final models was low: estimated at 0.04% for cardiovascular mortality and 0.07% for all-cause mortality.

In comparison, the Euroscore performed less well for cardiovascular and all-cause mortality, with AUCs estimated at 56% (95% CI: 52% to 60%) and 57% (95% CI: 53% to 61%), respectively. It is interesting that adding TAC to the Euroscore was also able to improve its discrimination ability with an estimated IDI at 0.007 (95% CI: 0.001 to 0.021) for cardiovascular mortality and at 0.006 (95% CI: 0 to 0.018) for all-cause mortality (Supplemental Figures 4C and 4D). The AUCs of TAC combined with Euroscore were estimated at 59% (95% CI: 55% to 62%) and 58% (95% CI: 54% to 62%), respectively.

RISK SCORES AND THRESHOLDS. Tables 2 and 3 present the coefficients of the risk scores constructed on the training cohort for predicting cardiovascular and all-cause mortality, respectively. Figure 4 presents the components of the risk scores and the correspondence between risk scores and predicted mortality in the training cohort. The threshold of risk

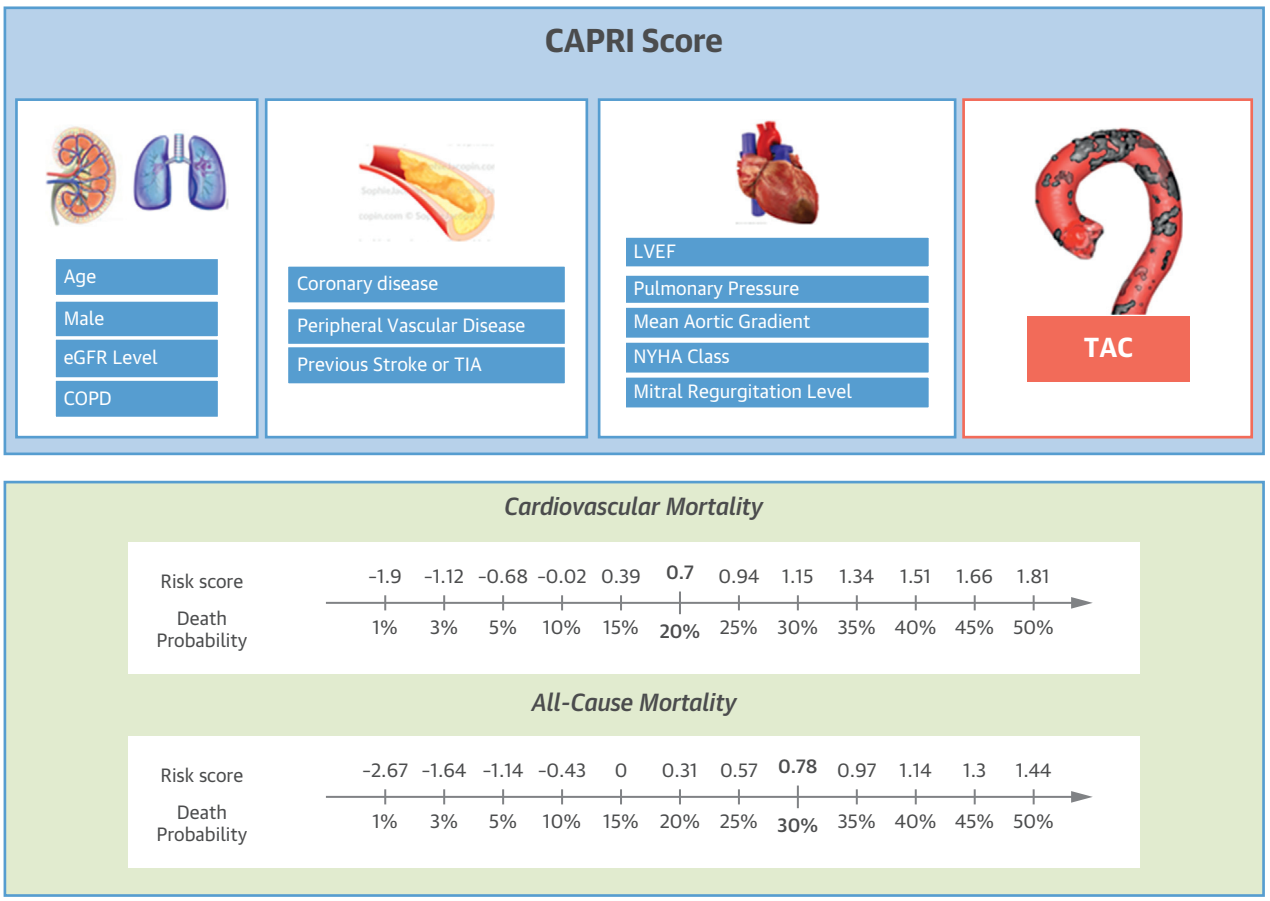
TABLE 3 Hazard Ratios and Corresponding Coefficients of the Risk Score Estimated in the Training Cohort Using a Cox Model for Predicting 1-Year All-Cause Mortality

	Hazard Ratio	95% CI	p Value	Coefficient
Demographic factors and comorbidities				
Age, yrs	1.03	1.002–1.05	0.03	0.026
Male	1.12	0.84–1.50	0.44	0.114
GFR level*	1.40	1.16–1.70	<0.01	0.333
COPD	1.21	0.87–1.68	0.26	0.190
Atherosclerotic disease factors				
Coronary artery disease	1.07	0.81–1.41	0.65	0.064
Peripheral vascular disease	1.31	0.96–1.79	0.09	0.269
Previous stroke or TIA	1.14	0.73–1.79	0.55	0.135
Cardiac function factors				
LVEF, %	0.99	0.98–1.00	0.06	−0.010
Pulmonary pressure, mm Hg/10	1.15	1.05–1.26	<0.01	0.140
Unknown pulmonary pressure	2.36	1.22–4.55	0.01	0.858
Mean gradient, mm Hg	0.99	0.98–1.002	0.11	−0.007
Dyspnea†	1.54	1.23–1.94	<0.01	0.435
Mitral regurgitation level‡	0.93	0.78–1.12	0.43	−0.076
TAC, cm^3	1.04	1.002–1.08	0.04	0.040

*GFR in 4 ordinal levels, i.e., 1: <15 ml/min/1.73 m^2; 2: 15–30 ml/min/1.73 m^2; 3: 30–60 ml/min/1.73 m^2; 4: 60–90 ml/min/1.73 m^2; 5: ≥ 90 ml/min/1.73 m^2. †Dyspnea in 2 ordinal levels, i.e., 0: NYHA functional class I/II; 1: NYHA functional class III/IV. ‡Mitral regurgitation in 5 ordinal levels, i.e., 0: absence; 1: light; 2: moderate; 3: important; 4: severe.

Abbreviations as in Tables 1 and 2.

FIGURE 4 Components of the CAPRI Score and Correspondence Between Values of Risk Score and Predicted Mortality Probability in the Training Cohort



GFR = glomerular filtration rate; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TAC = thoracic aortic calcification.

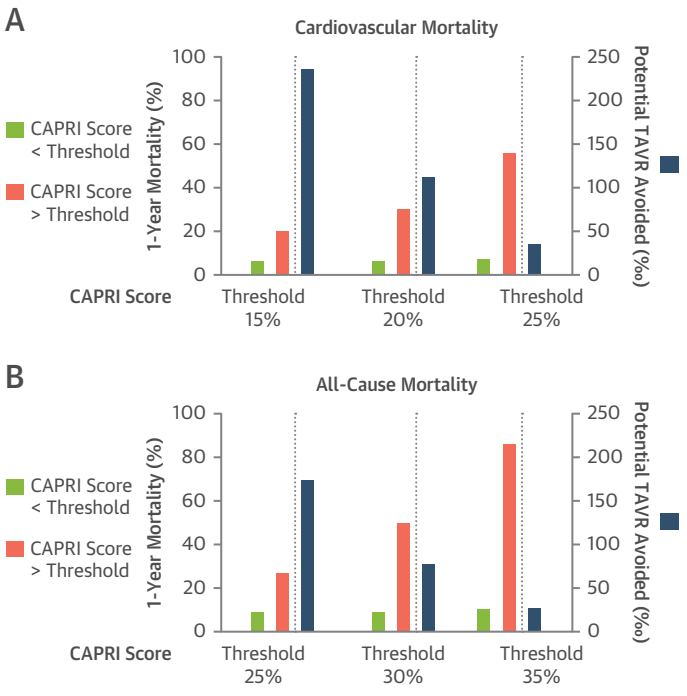
score corresponding to a predicted cardiovascular mortality of 20% was estimated at 0.7 (Supplemental Table 3). The associated sensitivity and specificity were estimated at 33.4% and 87.5%, respectively. The threshold of risk score corresponding to a predicted all-cause mortality of 30% was estimated at 0.78. The associated sensitivity and specificity were estimated at 27.8% and 90.8%, respectively.

PREDICTIVE PERFORMANCE OF THE RISK SCORES ON THE TEST COHORT. The calibration of the risk scores on the test cohort was good (Supplemental Figures 3C and 3D), with slopes estimated at 0.92 and 0.95 for cardiovascular and all-cause mortality, respectively. The AUCs were estimated at 66% (95% CI: 65% to 67%) and 67% (95% CI: 65% to 67%) for cardiovascular and all-cause mortality, respectively. For patients with risk scores above the 20% mortality threshold, cardiovascular mortality probability at 1 year was estimated at 29.6%, compared with 6% for patients with risk scores below or equal to the threshold. For all-cause mortality, the 1-year probability of death in patients with risk scores above the 30% threshold was estimated at 50%, versus 8.5% in patients with risk scores below or equal to the threshold. This corresponds to 112 and 77 of 1,000 patients, respectively, in whom TAVR would potentially be futile. The stringency of the criteria may be varied, as illustrated in **Figure 5**.

DISCUSSION

The CAPRI score is a newly developed, dedicated score encompassing an original and meaningful variable—TAC—in addition to classical variables representative of comorbidities and atherosclerotic

FIGURE 5 Impact of CAPRI Score to Identify Potentially Futile TAVR



Mortality estimations for patients of the test cohort with a CAPRI score below or above a threshold corresponding to a predicted mortality of 15%, 20%, or 25% for the cardiovascular mortality **(A)** and of 20%, 25%, or 30% for the all-cause mortality **(B)**, and expected numbers of avoided transcatheter aortic valve replacement (TAVR) per 1,000 patients. The thresholds correspond to the expected mortality in a similar population treated medically (i.e., not receiving TAVR), based on the literature.

and cardiac factors. A 1-cm^3 increase in TAC predicted a 6% increase in cardiovascular mortality and a 4% increase in all-cause mortality. The CAPRI score has a good discriminative ability for 1-year cardiovascular and all-cause mortality after TAVR.

THE CAPRI SCORE COMPONENTS AND PERFORMANCE. The identification of patients in whom non-modifiable factors will predispose to adverse outcomes post-TAVR is of utmost importance, both for ethical and economical reasons. The CAPRI score performs well when predicting cardiovascular and all-cause mortality. The validation process strictly followed recommendations (20) and represents the most ambitious attempt so far to develop a risk model for TAVR candidates. As prediction models tend to perform better on the data from which they were constructed than on new data, strategies of bootstrapping were used for internal validation to limit the optimism bias. External validation was also used as a confirmatory step to assess the predictive performance of the scores. The CAPRI score included 3 groups of meaningful factors: demographic and comorbidities, atherosclerotic disease, and cardiac function (Figure 4). The components of these 3 groups have been largely found to have an important prognostic value among patients undergoing TAVR, although differences exist according to different settings (4). Although comorbidities and cardiac function were mostly strongly associated with mortality, the inclusion of other factors makes the scores less dependent on the training cohort and more extendable to other settings (20). The model is based on preprocedural factors only and can therefore be used prospectively to inform clinical decision making. Importantly, the score is based on contemporary practice and not on cohorts from earlier trials (16,21), which is relevant with respect to the continuing extension of indications for TAVR.

Based on our previous analyses (6,7), we added TAC to the predictive variables. We used continuous TAC because categorization of a continuous variable is usually associated with a loss of power and inaccurate estimation of the effect of the covariate (22,23). TAC significantly increased the predictive ability of the model as shown by the likelihood test (17) and further highlighted by the IDI index (18). TAC appeared poorly correlated with other markers of atherosclerosis or risk factors in keeping with the Multi-Ethnic Study of Atherosclerosis (24). This suggests that TAC, a surrogate of aortic stiffening and vascular aging, may predict future HF after TAVR, in keeping with our previous reports (6,7). Only thoracic aortic calcification was assessed, as our previous study showed that most of the prognostic information was embedded there (7) and also because not all centers performed whole aorta CT scans. TAC is precisely computable, highly reproducible, and may also encompass some aspect of frailty including fragility fracture (8), muscle loss (25), and cerebrovascular events (9). As frailty is complex to assess with no unequivocal definition (26), this additional facet of TAC may be interesting.

The score was well calibrated for cardiovascular and all-cause mortality in both cohorts, and its prognostic discriminative performance was also good. A score with a good calibration means that the model has a good ability to predict risk of poor outcome with the intervention.

The CAPRI score appears highly relevant for objective decision making in individual patients. Although no formal decision threshold can be proposed, we tried to estimate a meaningful threshold corresponding to the probability of 1-year death with medical treatment. In a cohort comparable to C_4CAPRI, the probability of dying was 23.7%, which could increase to >35% in the presence of symptoms (19). As in our study, most deaths were attributable to

cardiovascular causes. In our cohort, CAPRI scores predicted a 1-year cardiovascular and all-cause mortality risk after TAVR similar to or greater than that without the intervention in a substantial number of patients (**Figure 5**). For example, CAPRI scores above 0.70 and 0.78 for cardiovascular and all-cause mortality, respectively, indicate a 50% risk of all-cause death and a 30% risk of cardiovascular death within the first year after TAVR, markedly higher than the estimated risk without intervention. On top of other markers (frailty or cognitive function), such a level of risk may represent an important argument against further proceeding with TAVR. Thus, the CAPRI score represents an objective way for the heart team to improve patient selection and for the patient to make an informed decision.

OTHER RISK SCORES. Many scores are dedicated to perioperative mortality prediction such as the surgical scores Euroscore, Euroscore II, or the STS score. Their discriminative ability for 1-year mortality is poor (14), in keeping with our study. The same applies to the France 2 score, which has also been proposed to predict early post-TAVR mortality (15). The PARTNER and the TARIS scores have been proposed to predict mid-term all-cause deaths (27). These scores mainly represent various combinations of the same variables collected in registries or study cohorts. Despite the addition of some specific variables of functional and cognitive capacity, the discrimination of the PARTNER score remains moderate (21): much lower than the CAPRI score. The addition of "frailty syndrome" to the other risk factors appears not to improve 1-year predictions of the score (16). Importantly, these previous scores are based on extreme-risk and high-risk patients for standard aortic valve surgery; thus, their performance in lower-risk patients remains unknown. In this respect, the CAPRI score is at present the only score that has been validated in lower-risk patients (test cohort).

STUDY LIMITATIONS. The training cohort comprised patients treated between 2010 and 2014 and may not be representative of today's populations and technologies. It is conceivable that technological refinement and inclusion of patients with lower-risk profiles may improve outcome further in the future. In this respect, it is notable that the mortality rate in the test cohort, treated in 2015, was dramatically lower than in the training cohort. However, the CAPRI scores had very similar performance (AUC) in these more recently treated patients. The outcomes assessed in the C_4CAPRI multicenter study were limited to cardiovascular and all-cause mortality; its usefulness in predicting other relevant outcomes, such as residual HF and quality of life, is untested. The score would need to be prospectively evaluated for its power to predict functional improvement and/or persisting HF.

The model might have been improved by the inclusion of frailty-associated variables such as daily-life activities. However, such markers were not available in the C_4CAPRI cohorts, and their prognostic impact remains to be determined.

CONCLUSIONS

Objective, evidence-based decision making is critical to avoid futile interventions and to make optimal use of finite medical resources. The current study proposes a new specific TAVR-risk score based on pathophysiological variables. The inclusion of TAC, an independent unbiased variable, markedly increased the predictive power of the score. The implementation of a TAC-based score into daily practice is facilitated by the fact that CT scans are systematically performed before TAVR. This study also emphasizes the critical role of aortic biomechanics in determining outcomes after TAVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A substantial number of patients exhibit a poor outcome despite TAVR; they should be identified. TAC is associated with mortality after TAVR.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The CAPRI score, which encompasses TAC combined with classical prognostic factors, has a good ability to predict 1-year cardiovascular and all-cause mortality. Calculation of CAPRI scores should be part of the initial work-up for a more personalized evaluation of the patients who are candidates for TAVR procedures.

TRANSLATIONAL OUTLOOK: The impact of aortic biomechanics and vascular aging on the outcome after TAVR are important but overlooked. Additional research is warranted in this field.

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KEY WORDS aortic stiffness, mortality, outcome, risk stratification, TAVR

APPENDIX For an expanded Methods section and supplemental tables, figures, and references, please see the online version of this paper.

d) Score de risque CAPRI et insuffisance cardiaque après TAVI

Significance of the CAPRI risk score to predict heart failure hospitalization post-TAVI: The CAPRI-HF study.

Harbaoui B, Durand E, Dupré M, Rabilloud M, Souteyrand G, Courand PY, Boussel L, Lefevre T, Eltchaninoff H, Lantelme P.

Int J Cardiol. 2019 Dec 1;296:98-102.

Hypothèse : Le score de risque CAPRI pourrait prédire le risque d'hospitalisation pour insuffisance cardiaque en post TAVI sachant qu'il comporte plusieurs variables potentiellement impliquées dans la survenue d'insuffisance cardiaque notamment les calcifications de l'aorte, reflet de la post charge vasculaire. Cela pourrait avoir un intérêt chez les patients à bas gradient qui souvent ont une post charge vasculaire élevée.

Objectif : Vérifier si le score CAPRI est capable de prédire l'hospitalisation pour insuffisance cardiaque en post TAVI, plus particulièrement chez les patients avec rétrécissement aortique à bas gradient.

Population, Méthodes : Etude ancillaire de C4CAPRI incluant les patients de Rouen et Lyon. 409 patients traités par TAVI entre 2010 et 2014 ont été inclus.

L'outcome considéré était l'hospitalisation pour insuffisance cardiaque.

Résultats : Parmi les 409 patients, 14 décès péri procéduraux et 3 perdus de vue ont été exclus. 392 patients ont finalement été concerné par l'analyse. A 1 an de suivi, 78 (19.9%) patients ont eu au moins 1 hospitalisation pour insuffisance cardiaque. Durant le suivi, 60(15.3%) patients

sont décédés, 28(35.9%) parmi les 78 qui avaient présentés une hospitalisation pour insuffisance cardiaque et 32(10.2%) patients parmi les autres, $p < 0.001$. La figure 15 montre les courbes d'incidences cumulées en fonction des 3 groupes définis selon les tertiles de CAPRI score pour toute la population puis en fonction du gradient moyen. Les patients appartenant aux groupes de score CAPRI les plus élevés ont présenté plus d'hospitalisation pour insuffisance cardiaque que ceux avec un score bas. La même tendance est observée chez les patients à bas gradient transvalvulaire aortique p=0,007. Chez les patients à haut gradient, il n'y avait plus de différence significative.

Conclusion, discussion : Cette étude montre que le CAPRI score initialement développé pour prédire la mortalité à 1 an est capable de prédire l'hospitalisation pour insuffisance cardiaque. Ainsi les patients les patients présentant un score de risque CAPRI élevée devraient bénéficier d'un suivi rapproché en post TAVI.

Perspectives : Une réflexion sur la futilité de la procédure en cas de score CAPRI élevé devrait avoir lieu compte tenu du risque de mortalité, d'insuffisance cardiaque et d'absence d'amélioration de la qualité de vie.

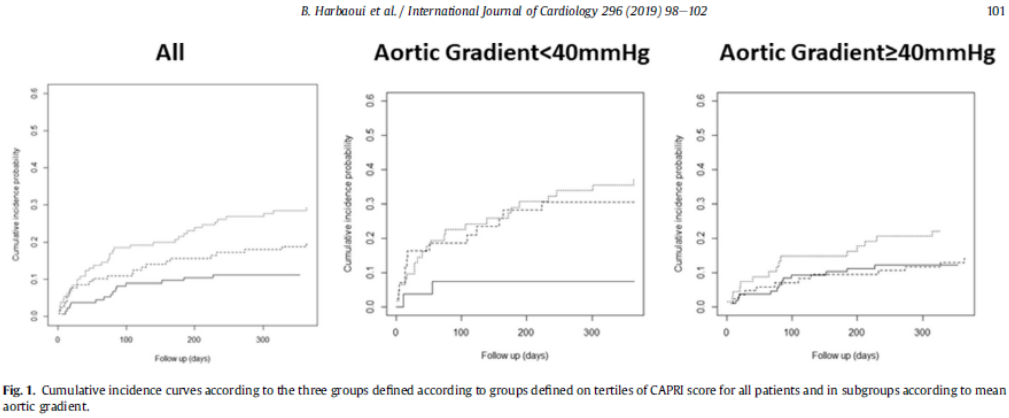

Fig. 1. Cumulative incidence curves according to the three groups defined according to groups defined on tertiles of CAPRI score for all patients and in subgroups according to mean aortic gradient.

Figure 15 : Courbes d'incidences cumulées d'hospitalisation pour insuffisance cardiaque en fonctions des tertiles de Score CAPRI.

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Significance of the CAPRI risk score to predict heart failure hospitalization post-TAVI: The CAPRI-*HF* study

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ABSTRACT

Background: Predictors of heart failure (HF) hospitalization after transcatheter aortic valve implantation (TAVI) are not well defined. CAPRI is a score for predicting 1-year post-TAVI cardiovascular and all-cause mortality. The aim of the present study is to assess the prognostic significance of the CAPRI score for HF hospitalization 1 year after TAVI.

Methods and results: CAPRI-*HF* is an ancillary study of the C4CAPRI trial, analyzing 409 consecutive patients treated by TAVI. The primary outcome was hospitalization for HF during the first year post-intervention. The prognostic value of the CAPRI score was assessed by multivariable analysis adjusted for diabetes, atrial fibrillation, vascular route, pacemaker implantation, post-TAVI aortic regurgitation, transfusion and pulmonary artery systolic pressure. A subanalysis focused on patients with low-gradient aortic stenosis (LGAS). At 1 year, HF hospitalization occurred in 78 (19.9%) patients. Patients with HF were more prone to have diabetes, atrial fibrillation, renal dysfunction, lower mean aortic gradient, higher logistic EuroSCORE and higher CAPRI score ($p < .05$ for all associations).

In the multivariable analysis, CAPRI score was the sole predictor of HF: hazard ratio (HR) for each 0.1 CAPRI score increase was 1.065, 95% confidence interval (CI) 1.021–1.110. This was confirmed when adjusted for EuroSCORE: HR 1.066, 95% CI 1.024–1.110. The predictive power of the CAPRI score increased for LGAS: HR 1.098, 95% CI 1.028–1.172.

Conclusions: CAPRI score helps predict HF post-TAVI. Including the score in the decision-making process may help selecting candidates for TAVI and identifying patients who need close monitoring post-procedure.

1. Introduction

The number of transcatheter aortic valve implantation (TAVI) procedures is increasing due to the recent extension of indications to patients at lower risk [1]. However, a substantial number of patients do not benefit from the procedure and rates of early death and repeated readmissions for heart failure (HF) remain an issue [2,3]. Outcomes can be improved by improving patient selection to avoid futile interventions and by improving treatment strategies in those patients at high residual risk of HF [4].

Predictors of HF hospitalization after TAVI are not well defined. Few studies have tackled this issue [2] and no standardized score is available to predict HF after TAVI. We have recently developed the CAPRI score to predict 1-year post-TAVI cardiovascular and all-cause mortalities [5]. This dedicated score includes thoracic aortic

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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calcification (TAC) volume (assessed by CT scan) in addition to cardiac, vascular, and comorbid conditions. Our demonstration that TAC is predictive of mortality after TAVI independent of classical variables [6,7] has recently been confirmed by other groups [8].

We hypothesized that CAPRI score could also predict 1-year post-TAVI HF hospitalization since it encompasses several variables potentially involved in HF. Residual HF after TAVI is an even greater concern in low-gradient aortic stenosis (LGAS) patients [2]. There is a need for predictors in this population since classical cardiac and valvular parameters have failed to predict clinical outcomes after AS relief [9]. Because the CAPRI score includes TAC, a surrogate of aortic stiffness, it may be particularly relevant for LGAS which is often associated with high vascular load [10].

The aim of the present study was to assess the prognostic significance of the CAPRI score to predict HF hospitalization during the first year after TAVI in a consecutively treated population. We also tested the prognostic significance in a subset of patients with LGAS.

2. Methods

CAPRI-*HF* was an ancillary study of the C4CAPRI trial (4 Cities for assessing CAlcification PRognostic Impact NCT02935491), which was a multicenter study, performed in 4 high volume French centers [5].

2.1. Patients

The present study included 409 consecutive patients from 2 out of the 4 centers (Rouen and Lyon University hospitals), undergoing TAVI between 2010 and 2014 and for whom follow-up data on HF was available. The C4CAPRI cohort has been described elsewhere [5]. Patients were indicated for TAVI in the presence of severe AS when surgical aortic valve replacement was either contraindicated or deemed too high risk by the multidisciplinary Heart Team. To be included in the C4CAPRI cohort, patients had to have a pre-operative CT-scan for TAC assessment and CAPRI score calculation. For the main analysis patients were analyzed according to whether they had undergone HF hospitalization. For the subanalysis, LGAS was defined as a mean aortic gradient <40 mm Hg [11].

2.2. Outcomes

The primary outcome was HF requiring hospitalization during the first year after TAVI. Follow-up was censored at 1 year following TAVI. Patients deceased during the first year were not considered as having experienced the primary outcome unless a hospitalization for HF had been recorded. Data collection was performed through dedicated web-based case report forms in each center, which were merged for analysis. Range checks to identify extreme values and assessments of internal consistency were applied during upload.

2.3. Calculation of CAPRI score

The score has been described elsewhere [5]. Briefly, CAPRI score encompasses TAC burden assessed by CT scanner of the whole thoracic aorta as previously described [5]; cardiac (left ventricle ejection fraction (LVEF); mean aortic gradient, mitral regurgitation, pulmonary systolic artery pressure (PSAP), coronary artery disease), vascular (vascular disease), and comorbid (renal function, and chronic obstructive pulmonary disease) conditions. We adapted the score for cardiovascular mortality and for all-cause mortality by adjusting the coefficient of each variable for the specific outcome.

2.4. Statistical analysis

Variables are summarized as means ± standard deviations, medians with interquartile ranges, or numbers and percentages, as appropriate. CAPRI score was considered as a categorical variable (tertiles) or a continuous variable as appropriate. For the purpose of this study (predicting HF hospitalization during the first year after TAVI), we used the *cardiovascular mortality CAPRI score* in the main analysis. The performance of the *all-cause mortality CAPRI score* was used in a sensitivity analysis (presented in the Supplementary materials).

The prognostic value of the CAPRI score was first assessed by building the cumulative incidence curves of HF hospitalization for the three groups defined according to the terciles of CAPRI score, using the Aalen-Johansen estimator in order to take into account the competing risk corresponding to death. The three curves were compared using the Gray's test. The prognostic value of CAPRI score considered as a continuous variable was further quantified and tested in univariable and multivariable Cox regression analysis in order to estimate its cause-specific effect.

Several models were built according to the existent literature [2,3,12].

- Model 1 adjusted for Logistic EuroSCORE.
- Model 2 adjusted for significant differences in terms of baseline characteristics. (excluding variables included in the CAPRI score) between the groups of patients with and without HF hospitalization.
- Model 3 adjusted for vascular access, post TAVI aortic regurgitation, post TAVI PASP, post TAVI transfusion, and post TAVI pacemaker implantation.
- Model 4 adjusted for the variables in models 2 and 3.

The interaction between mean aortic gradient and CAPRI score was tested and found significant at $p < .05$. This justified the subanalysis in LGAS patients.

Further sensitivity analysis was performed after exclusion of patients who didn't have a transfemoral TAVI.

Finally, in order to assess the ability of the CAPRI score to predict recurring HF hospitalization ordinal multivariate regression analyses were performed at 3 levels; no HF (reference subgroup), 1 HF occurrence, ≥2 HF occurrences. A similar analysis was performed for the CAPRI score for all-cause death.

All analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, USA and R software, version 3.6.1). A p value <.05 was considered statistically significant.

3. Results

3.1. Baseline data

Among the 409 patients, 14 peri-procedural deaths and 3 patients lost to follow-up were excluded. Thus, 392 patients were included in the study. 78 (19.9%) patients experienced at least one HF hospitalization. 60(15.3%) patients died during the follow-up, respectively 28(35.9%) patients of the 78 who experienced HF hospitalization and 32(10.2%) patients of the 314 who didn't experience HF hospitalization, $p < .001$. Table 1 summarizes the characteristics of the cohort as well as according to the hospitalization of HF. On average, patients were 83.7 ± 7.3 years old, 183 (46.7%) were men, mean LVEF was 59.1 ± 14.3% and mean aortic gradient was 45.9 ± 15.6 mm Hg. TAVI was performed with femoral access in 339 (86.5%) patients. Patients with HF hospitalization were more prone to have diabetes, atrial fibrillation, renal dysfunction, lower mean aortic gradient, higher PSAP and higher logistic EuroSCORE ($p < .05$ for all associations). Though levels of TAC and several individual variables in the CAPRI score (LVEF, coronary artery disease, vascular disease, and chronic obstructive pulmonary disease) did not differ significantly between patients with HF and without HF, the CAPRI score was significantly higher in patients who experienced HF ($p < .05$).

Table S1 summarizes patients' characteristics according to mean aortic gradient. LGAS patients were more often women and had higher rates of diabetes atrial fibrillation, peripheral vascular disease or pacemaker use. The CAPRI score was higher in LGAS patients, $p < .001$; the same trend was noticed for the EUROSCORE, $p = .048$.

3.2. Prognostic power of the CAPRI score

At the 1-year follow-up, 78 (19.9%) patients recorded one or more HF hospitalizations. Fig. 1 displays the cumulative incidence curves according to the three groups defined according to the terciles of CAPRI score for all patients and according to aortic gradient. CAPRI score ranges were −2.288 to −0.188 for group 1; −0.188 to 0.344 for group 2 and 0.344 to 1.685 for group 3. Higher CAPRI scores were associated with greater risk of HF hospitalization, $p < .001$ (Fig. 1). Analyzing subgroups according to mean aortic gradient, the same trend was found in LGAS patients, $p = .007$. In patients with mean aortic gradient ≥40 mm Hg, cumulative incidence curves did not differ significantly between the three groups ($p = .1$).

Table 2 summarizes univariate and multivariate Cox analyses in all patients and in LGAS patients. CAPRI score was predictive of HF hospitalization in all models. In the model adjusted for logistic

Table 1
Patient's baseline characteristics (CAPRI HF cohort).

	All	No hospitalization for HF	Hospitalization for HF	p
Number of patients	392	314	78	
Demographic characteristics				
Age (years)[a]	83.7 ± 7.3	83.7 ± 7.6	83.9 ± 6.3	0.79
Male sex n (%)	183 (46.7)	153 (48.7)	30 (38.5)	0.104
BMI (kg/m^2)[a]	26.4 ± 5.6	26.4 ± 5.6	26.5 ± 5.4	0.94
Clinical history				
Diabetes n (%)	110 (28.1)	80 (25.5)	30 (38.5)	**0.022**
Hypertension n (%)	296 (75.7)	237 (75.7)	59 (75.6)	0.989
Smoker n (%)	74 (18.9)	62 (19.8)	12 (15.4)	0.372
Dyslipidemia n (%)	221 (56.5)	180 (57.5)	41 (52.6)	0.431
Atrial fibrillation n (%)	157 (40.2)	115 (36.7)	42 (53.8)	**0.006**
CAD n (%)	143 (36.6)	120 (38.3)	23 (29.5)	0.146
PVD n (%)	59 (15.1)	43 (13.7)	16 (20.5)	0.132
Previous stroke or TIA n (%)	37 (9)	26 (8.3)	8 (10.3)	0.579
Pace maker n (%)	50 (12.8)	40 (12.7)	10 (12.8)	0.985
COPD n (%)	88 (22.4)	71 (22.6)	17 (21.8)	0.877
NYHA 3/4 n (%)	260 (66.5)	204 (65.2)	56 (71.8)	0.268
Pre-TAVI TTE parameters				
Mean LVEF %[a]	59.1 ± 14.3	59.8 ± 14.2	56.5 ± 14.6	0.069
Mean aortic gradient (mm Hg)[a]	45.9 ± 15.6	47.1 ± 15.4	40.9 ± 15.6	**0.002**
LGAS n (%)	132 (33.7)	94 (29.9)	38 (48.7)	**0.002**
Aortic valve area (cm^2)[a]	0.71 ± 0.22	0.71 ± 0.23	0.70 ± 0.19	0.806
Moderate/severe MR n (%)	8 (2)	4 (1.3)	4 (5.1)	**0.032**
PASP (mm Hg)[a]	42.7 ± 15	41.5 ± 14	47.7 ± 15	**0.002**
Aortic calcifications				
LogTAC (cm^3)[a]	0.327 ± 0.48	0.317 ± 0.48	0.365 ± 0.50	0.441
Renal function				
GFR (mL/min/1.73 m^2)[a]	51.1 ± 26	52.5 ± 27.2	45.3 ± 19.9	**0.028**
Risk scores				
Euroscore[a]	17.27 ± 9.7	16.76 ± 9.4	19.26 ± 10.4	**0.041**
CAPRI cardiovascular[a]	0.0593 ± 0.631	0.0042 ± 0.635	0.2811 ± 0.567	**<0.001**
CAPRI all causes[a]	0.024 ± 0.638	−0.0306 ± 0.649	0.2444 ± 0.5449	**0.001**
Procedural and peri-procedural data				
Femoral access n (%)	339 (86.5)	277 (88.2)	62 (79.5)	**0.044**
Balloon expendable valve n (%)	382 (97.4)	305(97.1)	77(98.7)	0.67
Blood transfusion n (%)	68 (17.3)	49 (15.6)	19 (24.4)	0.068
Aortic regurgitation >2 n (%)	11 (2.9)	9 (3)	2 (2.6)	0.882
PASP				0.283
≤60 n (%)	254 (64.8)	205 (65.3)	49 (62.8)	
Nonmes n (%)	117 (29.8)	95 (30.3)	22 (28.2)	
>60 n (%)	21 (5.4)	14 (4.5)	7 (9)	
New pacemaker implantation	52 (13.5)	41 (13.1)	11 (15.1)	0.657

HF, heart failure; BMI, body mass index; GFR, glomerular filtration rate; CAD, coronary artery disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; TTE, transthoracic echography; LVEF, left ventricular ejection fraction; LGAS, low gradient aortic stenosis; MR, mitral regurgitation; TAC, thoracic aortic calcifications, nonmes, non-measurable; PASP pulmonary artery systolic pressure.
[a] Mean ± sd.

EuroSCORE, the CAPRI score considered as a continuous variable was the sole predictor of HF hospitalization. The hazard ratio (HR) for each 0.1 CAPRI score increase was 1.066, 95% confidence interval (CI) 1.024–1.062. In the adjusted multivariate Cox analysis only CAPRI score was predictive of HF: HR for each 0.1 CAPRI score increase 1.068, 95% CI 1.021–1.065. The results were similar in LGAS patients (Table 2).

When restricting the analysis to patients with transfemoral TAVI, results remained very similar (Table S2).

Similar results were obtained with the CAPRI score for all-cause death when performing the cox regression analysis (Supplementary data, Table S3).

4. Discussion

The present study demonstrates that the CAPRI score designed to predict one-year mortality after TAVI also predicts HF hospitalization. CAPRI score has been shown to be valuable for risk stratification before TAVI [5], and the present analysis indicates its utility in the follow-up of patients at risk of HF.

Despite procedural success, the risk of developing HF remains high after TAVI: HF hospitalization was experienced by 19.9% of patients in the present study and by up to 40% in other studies [2,3]. HF reduces patients' wellbeing and prognosis, especially in older people like those typically treated with TAVI [2,3,13]. It is further associated with depression [14], lower quality of life [15], and increased mortality [2]. In the present study we again stress the association of HF and mortality. Improved identification of patients at high risk of HF would help focus management efforts on those patients post-TAVI who need the greatest vigilance, as well as reduce the risk of futile procedures.

Many factors are involved in HF [16] and some predictors have been identified in other studies, notably new pacemaker implantation [12] mitral regurgitation, low LVEF, atrial fibrillation, blood transfusion or renal insufficiency [2,3]. Some of these variables are part of the CAPRI score which includes cardiac, vascular and co-morbid conditions, e.g., renal insufficiency, which is more prevalent in patients with HF and is an independent prognostic factor in diastolic and systolic dysfunction [17]. The CAPRI score is unique in that it includes TAC, a surrogate of aortic stiffness and consequently high afterload, and impaired myocardial perfusion. This suggests a pathophysiological role for TAC in HF, especially HF with preserved LVEF [18,19]. In the present cohort no significant difference of TAC was observed between HF and non-HF patients conversely to what

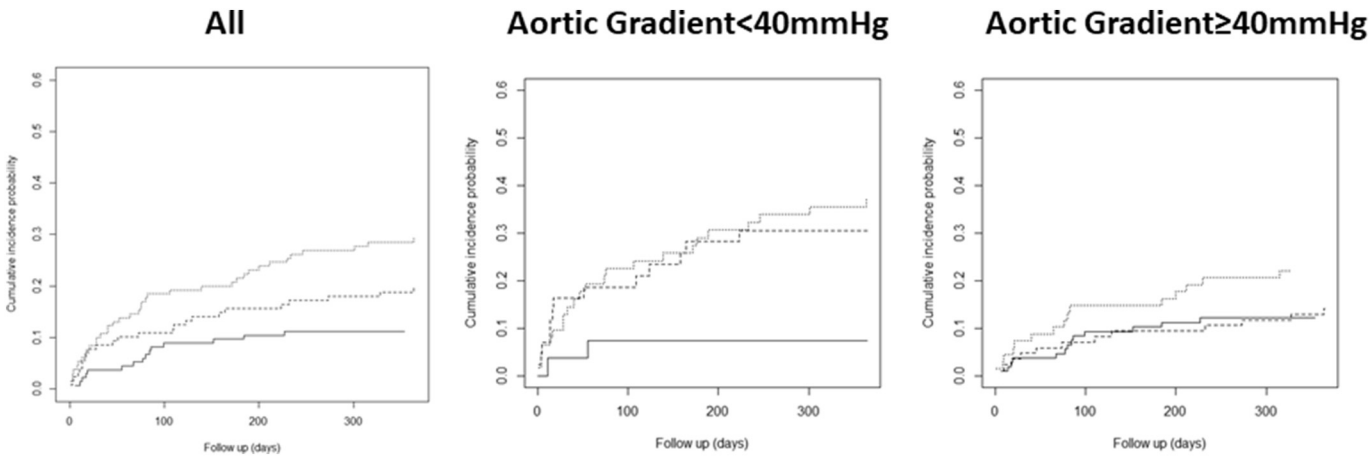

Fig. 1. Cumulative incidence curves according to the three groups defined according to groups defined on tertiles of CAPRI score for all patients and in subgroups according to mean aortic gradient.

has been previously observed with a longer follow-up of 1000 days. Yet, a greater proportion or heavily calcified patients (third tercile) are represented in the HF than in the non-HF subgroups (data not shown) [7]. Aortic stiffness has also been linked to HF [18] in other settings. Post-TAVI, high vascular load will continue to exert a detrimental effect on LV function [6,7,20] contributing to HF.

Other post TAVI parameters may promote HF such as PASP >60 mm Hg, aortic regurgitation, vascular access, or pacemaker implantation [2,3,12]. Yet taking these variables into account in the multivariate model did not reduce the prognostic value of the CAPRI score. In contrast, the EUROSCORE, which was developed for patients undergoing cardiac surgery and not calibrated on TAVI patients [21], did not predict HF, further confirming the value of the CAPRI score.

Predicting outcomes may be particularly important in LGAS patients since they are known to be at higher risk of morbidity and mortality than non-LGAS patients [7–9] and are more prone to suffer from HF after TAVI [2,3]. LGAS is a complex condition, in which the valvular impediment may be intertwined with other pathophysiological determinants such as systolic and diastolic dysfunction [22] and high vascular load [10]. This makes the prediction of outcomes based on classical parameters, mainly valvular criteria, extremely challenging [9]. Possibly because of the multifactorial pathophysiology, CAPRI score seems to be particularly adapted to predict HF after TAVI in LGAS patients.

4.1. Clinical implications

Calculation of CAPRI score may be a useful addition to the initial work-up for a more personalized evaluation of candidates for a TAVI procedure [23,24]. For some patients, TAVI can be a futile intervention even after procedural success. In patients with a high CAPRI score in whom TAVI is still considered necessary, close monitoring and intensification of medical treatment after the procedure may be indicated. This may be even truer in LGAS patients.

A high CAPRI score may be defined as higher than 0.7 as it corresponds to the mortality cut-off proposed in the pivotal trial [5] and as it also selects patients belonging to the tertile associated with the highest risk of HF.

5. Study limitations

HF hospitalization wasn't assessed in 2 of the 4 centers involved in the CAPRI study, however the number of patients included in the CAPRI HF study and the number of events allowed a robust analysis. The diagnosis of HF may be challenging [25]. However retaining only HF requiring hospitalization has certainly strengthened the robustness of the outcome. It has allowed us to check that the clinical judgment and the paraclinical tests were consistent with this diagnosis. Natriuretic peptides would have been interesting in this respect but unfortunately they were not available in this

Table 2
Relative risk of HF hospitalization in unadjusted and adjusted Cox regression models.

	Hospitalization for HF All N = 392		Hospitalization for HF LGAS N = 132	
	HR [95% CI]	p	HR [95% CI]	p
CAPRI score + 0.1 unit[a]	1.072 [1.032–1.112]	<0.001	1.084 [1.022–1.149]	0.007
CAPRI score + 0.1 unit[b]	1.066 [1.024–1.110]	0.002	1.080 [1.012–1.151]	0.020
CAPRI score + 0.1 unit[c]	1.060 [1.019–1.101]	0.003	1.085 [1.021–1.152]	0.008
CAPRI score + 0.1 unit[d]	1.072 [1.030–1.115]	0.001	1.097 [1.028–1.170]	0.005
CAPRI score + 0.1 unit[e]	1.065 [1.021–1.110]	0.003	1.098 [1.028–1.172]	0.005

HF, heart failure; HR, hazard ratio; CI, confidence interval; LGAS, low gradient aortic stenosis.
[a] Unadjusted.
[b] Model 1 adjusted for Euroscore.
[c] Model 2 adjusted for pre-TAVI parameters: diabetes, atrial fibrillation.
[d] Model 3 adjusted for post-TAVI parameters: vascular access (femoral Y N), blood transfusion or severe vascular access leakage, aortic regurgitation >2, pulmonary systolic blood pressure (high, low, undefined), new pacemaker implantation.
[e] Model 4 adjusted for both pre and post TAVI parameters: diabetes, atrial fibrillation, vascular access (femoral Yes, No), blood transfusion, aortic regurgitation >2, pulmonary artery systolic pressure (high, low, undefined), new pacemaker implantation.

cohort. Yet, in the particular setting of TAVI patients, the diagnostic value of NT-proBNP remains uncertain because of the numerous confounders that may alter its significance (left ventricular hypertrophy, atrial fibrillation, renal failure…) and because of the lack of unequivocal threshold [25]. A more precise classification of HF would have been valuable but this was not assessed. It would have been interesting to assess the stroke volume index in order to better categorize LGAS patients.

6. Conclusions

The CAPRI score is predictive of HF hospitalization after TAVI, including LGAS patients. Calculation of CAPRI scores may be valuable as part of the initial work-up for a more personalized evaluation of TAVI candidates. The score allows a better identification of poor responders to a TAVI procedure as well as of patients at high residual HF risk post-procedure.

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None to disclose.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.08.033.

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e) Impact pronostic différentiel des calcifications de l'aorte et de la valve aortique chez les patients avec RA serré à bas et haut gradient trans-aortique

Prognostic significance of vascular and valvular calcifications in low- and high-gradient aortic stenosis.

Harbaoui B, Ghigo N, Boussel L, Liebgott H, Souteyrand G, Durand E, Eltchaninoff H, Lefevre T, Courand PY, Lantelme P.

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Hypothèse : Dans le rétrécissement aortique à bas gradient, la postcharge vasculaire est probablement élevée. Les calcifications vasculaires de l'aorte thoracique (TAC) sont un reflet de la post-charge vasculaire et les calcifications valvulaires aortiques (VAC) sont corrélées au gradient transvalvulaire aortique. Ainsi TAC et VAC pourraient avoir une signification pronostique différente chez les patients à bas (LGAS) et haut gradient transvalvulaire aortique (HGAS).

Objectif: Décrire et comparer les contributions respectives du TAC et du VAC sur la mortalité cardiovasculaire (CV) à 3 ans post TAVI chez les patients LGAS et HGAS.

Population/Méthode: 1396 patients consécutifs ont été inclus. Le TAC et le VAC ont été mesurés sur le scanner pré-TAVI. L'analyse de mortalité a été réalisée par régression logistique multivariée de Cox ajustée sur les facteurs confondants.

L'outcome considéré était la mortalité cardio-vasculaire à 3 ans

Résultats: 435(31,2%) patients avaient des LGAS et 961 (68,8 %) HGAS. Les patients du groupe LGAS étaient plus susceptibles d'être diabétique, coronarien, en fibrillation auriculaire (FA) et d'avoir une fraction d'éjection ventriculaire gauche (FEVG) plus basse, $p<0,05$. Durant

p<0,05. Durant les 3 années post TAVI, 245 (17,8%) patients ont présenté un décès de cause cardiovasculaire, 92 (21,6%) patients LGAS et 153 (16,2%) patients HGAS, p = 0,018. L'analyse multivariée ajustée sur l'âge, le sexe, le diabète, la FA, la coronaropathie, la FEVG, la fonction rénale, l'accès vasculaire et l'insuffisance aortique a montré que TAC mais pas VAC était associé à la mortalité cardiovasculaire chez les patient LGAS, HR 1,085 IC [1,019-1,156], p = 0,011 , et HR 0,713 IC [0,439–1,8], p = 0,2 ; l'inverse a été observé chez les patients HGAS, VAC mais pas TAC était associé à la mortalité CV, HR 1,342 IC[1,034–1,742], p = 0,027, et HR1,015 IC[0,955–1,079], p =0,6.

Discussions Conclusions: TAC joue un rôle pronostique majeur chez les patient LGAS tandis que le VAC joue ce rôle chez les patients HGAS (Figure 16). Cela confirme que le rétrécissement aortique à bas gradient est une maladie vasculaire et valvulaire complexe.

Perspectives : Ce travail permet de mieux appréhender la physiopathologie de l'atteinte des calcifications vasculaires et vasculaires chez les patients présentant un rétrécissement aortique en fonction de leur gradient. Ces données pourraient permettre le raffinement du score de risque C4CAPRI en l'adaptant le plus possible au patient, une sorte de médecine personnalisée. Ces données pourraient facilement s'intégrer dans un score reposant intelligence artificielle par « machin learning ».

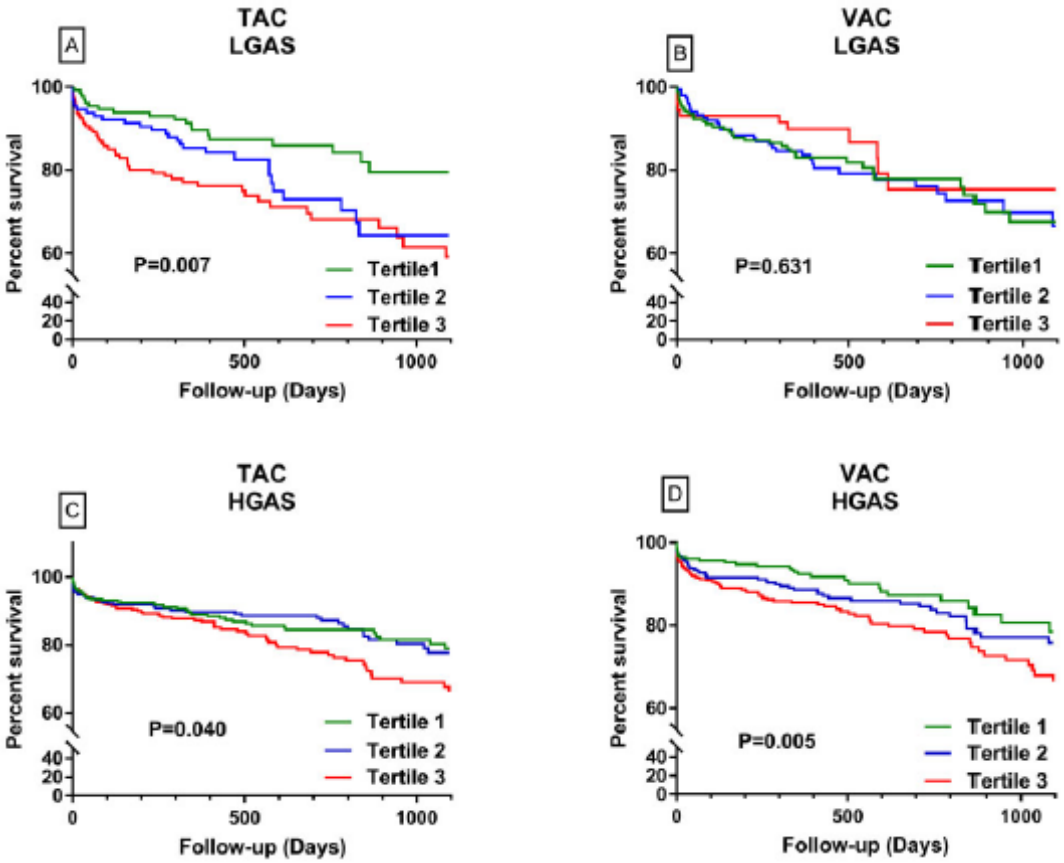

Figure 16 : *Analyse de survie de Kaplan-Meier pour la mortalité cardiovasculaire à 3 ans selon les groupes définis sur les terciles de TAC et VAC chez les patient à bas (LGAS) et haut (HGAS) gradient transvalvulaire aortique. HGAS, rétrécissement aortique à haut gradient (gradient aortique moyen ≥ 40 mmHg); LGAS, rétrécissement aortique à bas gradient (gradient aortique moyen <40mmHg); TAC, calcifications de l'aorte thoracique; VAC, calcifications valvulaires aortique.*

ESC European Society of Cardiology

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Prognostic significance of vascular and valvular calcifications in low- and high-gradient aortic stenosis

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Aims In low-gradient aortic stenosis (LGAS), the high valvulo-arterial impedance observed despite low valvular gradient suggests a high vascular load. Thoracic aortic calcifications (TACs) and valvular aortic calcifications (VACs) are, respectively, surrogates of aortic load and aortic valvular gradient. The aim of this study was to compare the respective contributions of TAC and VAC on 3-year cardiovascular (CV) mortality following TAVI in LGAS vs. high-gradient aortic stenosis (HGAS) patients.

Methods and results A total of 1396 consecutive patients were included. TAC and VAC were measured on the pre-TAVI CT-scan. About 435 (31.2%) patients had LGAS and 961 (68.8%) HGAS. LGAS patients were more prone to have diabetes, coronary artery disease (CAD), atrial fibrillation (AF), and lower left ventricular ejection fraction (LVEF), $P<0.05$ for all. During the 3 years after TAVI, 245(17.8%) patients experienced CV mortality, 92(21.6%) in LGAS and 153(16.2%) in HGAS patients, $P=0.018$. Multivariate analysis adjusted for age, gender, diabetes, AF, CAD, LVEF, renal function, vascular access, and aortic regurgitation showed that TAC but not VAC was associated with CV mortality in LGAS, hazard ratio (HR) 1.085 confidence interval (CI) (1.019–1.156), $P=0.011$, and HR 0.713 CI (0.439–1.8), $P=0.235$; the opposite was observed in HGAS patients with VAC but not TAC being associated with CV mortality, HR 1.342 CI (1.034–1.742), $P=0.027$, and HR 1.015 CI (0.955–1.079), $P=0.626$.

Conclusion TAC plays a major prognostic role in LGAS while VAC remains the key in HGAS patients. This confirms that LGAS is a complex vascular and valvular disease.

Keywords TAVI • TAVR • aortic stiffness • vascular stiffness • outcome

Introduction

Low-gradient aortic stenosis (LGAS) is being more and more recognized as a peculiar form of aortic stenosis (AS); it currently represents 30–50% of patients with severe AS.[1,2] The prognosis of LGAS is worse than that of high-gradient aortic stenosis (HGAS), the explanation being uncertain.[2] In HGAS, the primary abnormality is valvular impediment represented by mean aortic gradient ≥40 mmHg, a surrogate of which may be valvular aortic calcifications (VACs).[3,4] Despite a lower mean transaortic gradient, LGAS patients often exhibit a higher left ventricle afterload assessed by valvulo-arterial impedance.[5,6] We have shown that thoracic aortic

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calcifications (TACs), which reflects vascular impediment, are of prognosis significance after transcatheter aortic valve implantation (TAVI)[7,8]; since our initial publications, this has been confirmed by other groups in other countries.[9] We hypothesize that the contribution of VAC and TAC to the post-TAVI outcome may differ depending on aortic gradient: from a prevailing valvular disease in HGAS to a more complex valvular and vascular disease in LGAS.

Thus, the objective of this study was to compare the respective contribution of TAC and VAC on 3-year cardiovascular (CV) mortality following TAVI in LGAS as compared with HGAS patients.

Methods

Patients

Among the 1425 patients of the multicentric C4CAPRI study recruited between 2010 and 2014, 1396 patients with both an available pre-operative CT-scan and a measurement of mean aortic gradient were included. The C4CAPRI cohort has been described elsewhere.[10] Patients were indicated for TAVI in the presence of severe AS when surgical aortic valve replacement was either contraindicated or deemed at too high risk by the multidisciplinary Heart Team. Severe AS was defined by an aortic valve area <1.0 cm^2 (or 0.6 cm^2/m^2) and/or a mean transaortic pressure gradient >40 mmHg and/or a peak aortic jet velocity (*V*max)>4 m/s. Mean aortic gradient was obtained with transthoracic echography (TTE). TTE was performed by a senior cardiologist, using continuous Doppler in the most appropriate window among five apical chamber view, right parasternal, and suprasternal views. LGAS was defined as a mean aortic gradient<40 mmHg and HGAS as a mean aortic gradient≥40 mmHg.[2] The C_4CAPRI study was approved by the ethics committee (Comité de Protection des Personnes SUD-EST IV, L16-56) and by the Commission Informatique et Liberté (CNIL N° 16-065). All patients provided written informed consent to anonymous processing of their data.

Patient and public involvement

Before undergoing the TAVI procedures, patients were asked to give and sign an informed consent to participate to the registry.

Patients were not involved in the design of the study.

Outcomes

The primary outcome was CV mortality (according to the VARC-2 criteria[11]) occurring within a 3-year follow-up period after TAVI. Vital status was obtained by telephone contact with patients, their relatives, carers or physicians, and by on-site planned visits. A follow-up was censored at 3-year following TAVR. Two experienced cardiologists blinded to TAC, VAC, and to patient characteristics adjudicated CV mortality according to the VARC-2 criteria.[11]. Data collection was performed through dedicated web-based case report forms in each centre, which were merged for analysis. Range checks to identify extreme values and assessments of internal consistency were applied during upload.

Measurement of TAC AND VAC

The way measurements were performed has been described elsewhere.[10] Briefly, both TAC and VAC were extracted using semi-automated dedicated software from the CT scanner of the valve and the whole thoracic aorta with a very good reproducibility as previously described.[10] For each patient, TAC was calculated from the aortic sinus to the aortic hiatus while excluding VAC, and VAC was measured including valve leaflets and annular calcification while ignoring non-valvular calcification in the left ventricular outflow tract, aortic sinus, coronary arteries, and mitral annulus. *Figure 1* shows an example of VAC and TAC measurements.

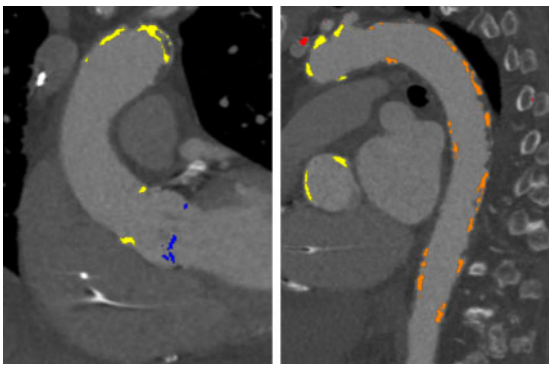

Figure 1 Example of calcifications measurement. Blue, yellow, and orange are for valvular, ascending, and descending thoracic aortic calcifications, respectively. Red calcifications do not belong to the aorta and have been excluded.

Statistical analysis

Variables are summarized as means±standard deviations, or numbers and percentages, as appropriate. Comparisons between LGAS and HGAS patients were performed using χ^2 test, unpaired *t*-test, or non-parametric test as appropriate. Both TAC and VAC were considered as categorical variables (three groups according to terciles of TAC and three groups according terciles of VAC) or continuous variables. Correlates of TAC and VAC were assessed using univariate and multivariate linear regression. Comparisons of distributions of TAC and VAC among LGAS and HGAS, patients were performed using a Mann–Whitney non-parametric test and illustrated using box plots.

The prognostic value of the TAC and VAC was first assessed by building Kaplan–Meier curves of cardiovascular mortality for the three groups defined according to the terciles of TAC and VAC. The three curves were compared using the log-rank test.

The prognostic value of both TAC and VAC considered as a continuous variable was further quantified and tested in univariate and multivariate Cox regression analysis.

Several models were built according to the existent literature.

- Model 1 adjusted for age and gender.
- Model 2 adjusted for Logistic EuroSCORE.
- Model 3 adjusted for age, gender, diabetes, atrial fibrillation, coronary artery disease, left ventricular ejection fraction (LVEF), and renal function.
- Model 4 adjusted for age, gender, diabetes, atrial fibrillation, coronary artery disease, LVEF, renal function, vascular access, and aortic regurgitation.
- Model 5 adjusted for age, gender, diabetes, atrial fibrillation, coronary artery disease, LVEF, renal function, vascular access, aortic regurgitation, and TAC or VAC as applicable.

Table 1 Patient's baseline and procedural characteristics according to mean aortic gradient

	LGAS Gradient<40 mmHg	HGAS Gradient≥40 mmHg	*P*
Number of patients	**435**	**961**	
Demographic characteristics			
Age (years)[a]	82.7 (±7.5)	83.7 (±6.7)	**0.01**
Men, *n* (%)	267 (61.4%)	448 (46.6%)	**<0.001**
BMI (kg/m^2)[a]	26.1 (±4.7)	26.4 (±5.3)	0.3
Clinical history, *n* (%)			
Diabetes	129 (29.7%)	232 (24.1%)	**0.035**
Hypertension	248 (71.7%)	589 (71.5%)	1
Smokers	66 (19%)	126 (15.2%)	0.1
Dyslipidaemia	180 (52%)	438 (53.2%)	0.7
Atrial fibrillation	159 (36.8%)	287 (30.2%)	**0.018**
CAD	222 (51.3%)	408 (42.5%)	**0.002**
PVD	110 (25.3%)	200 (20.8%)	0.07
Previous stroke or TIA	45 (10.4%)	79 (8.2%)	0.2
COPD	90 (20.7%)	176 (18.4%)	0.3
NYHA 3/4	268 (63.7%)	582 (61.8%)	0.5
TTE parameters			
LVEF (%)[a]	51.3 (±16.1)	58.8 (±12.4)	**<0.001**
LVEF <50%, *n* (%)	179 (41.3%)	196 (20.5%)	**<0.001**
Mean aortic gradient (mmHg)[a]	30.3 (±6.6)	54.7 (±13.4)	**-**
Aortic valve area (cm^2)[a]	0.74 (±0.21)	0.63 (±0.17)	**<0.001**
Aortic valve area (cm^2/m^2)[a]	0.42 (±0.12)	0.36 (±0.09)	**<0.001**
Moderate/severe MR, *n* (%)	7 (1.6%)	10 (1.1%)	0.4
PASP (mmHg)[a]	43.7 (±15)	43.8 (± 14)	0.8
Renal function			
GFR (mL/min/1.73 m^2)[a]	47.6 (±21.3)	50.2 (±22.5)	**0.05**
Euroscore[a]			
	19.18 (±11.6)	16.77 (±9.79)	**<0.001**
Procedural and hospitalization			
Femoral access *n* (%)	306 (70.5%)	684 (71.3%)	0.7
Balloon expandable valve (*n* %)	278 (64.1%)	593 (68.1%)	0.2
Aortic Regurgitation >2 (*n* %)	3 (0.7%)	14 (1.5%)	0.3
Tamponade or annulus rupture (*n*%)	6 (1.4%)	33 (3.5%)	**0.03**
New pacemaker implantation	66 (18.6%)	136 (16.3%)	0.3

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HGAS, high-gradient aortic stenosis; LGAS, low-gradient aortic stenosis; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PVD, peripheral vascular disease; TIA, transient ischaemic attack; TTE, transthoracic echography.
[a]Values are expressed as mean±SD or percentages.
Bold values *P*<0.005.

All analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, IL, USA). A *P*-value<0.05 was considered statistically significant.

Results

Baseline data

Table 1 summarizes the characteristics of the cohort according to mean aortic gradient. Patients with LGAS were more prone to have diabetes, atrial fibrillation, renal dysfunction, coronary artery disease, lower LVEF, and higher logistic EuroSCORE (*P*<0.05 for all associations). HGAS patients experienced more procedural tamponade or annulus rupture than LGAS patients (*P*=0.03).

Supplementary data online, *Figure S1* displays the distributions of TAC and VAC volumes among LGAS and HGAS patients. TAC was higher in LGAS patients (*P*<0.001) compared with HGAS patients while VAC was higher in HGAS compared to LGAS patients (*P*=0.027).

Correlates of TAC AND VAC

Table 2 summarizes the correlates of TAC and VAC in univariate and multivariate analyses.

Table 2 Correlates of TAC and VAC: univariate and multivariate linear regression analysis

Variables	TAC				VAC			
	Univariate		Multivariate		Univariate		Multivariate	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Age (+1year)	0.080	**0.003**	0.098	**0.005**	0.044	0.107		
Gender (men)	0.082	**0.002**	0.090	**0.004**	0.234	**<0.001**	0.317	**<0.001**
Hypertension (yes)	0.174	**<0.001**	0.149	**<0.001**	-0.053	0.081		
Diabetes (yes)	0.069	**0.01**	0.028	0.353	-0.071	**0.011**	-0.05	0.08
Dyslipidemia (yes)	0.085	**0.004**	0.051	0.102	0.025	0.417		
Smoking (yes)	0.05	0.086			0.068	**0.023**	0.001	0.980
Coronary artery disease (yes)	0.150	**<0.001**	0.089	**0.004**	-0.043	0.118		
Peripheral vascular disease (yes)	0.170	**<0.001**	0.123	**<0.001**	-0.061	**0.028**	-0.068	**0.019**
Atrial fibrillation (yes)	0.033	0.217			0.005	0.844		
Estimated glomerular filtration rate (+1 mL/min)	-0.111	**<0.001**	-0.086	**0.013**	0.022	0.441		
Left ventricular ejection fraction (+1%)	-0.028	0.290			-0.005	0.868		
Aortic-valve area (+1 cm^2)	0.040	0.139			-0.096	**0.001**	-0.055	0.075
Mean aortic valve gradient (+1 mmHg)	-0.056	**0.037**	0.017	0.590	0.217	**<0.001**		**<0.001**
LogTAC (+1 cm^3)					0.022	0.435		
LogVAC (+1 mm^3)	0.022	0.435						

TAC, thoracic aorta calcifications; VAC, valvular aortic calcifications.
Bold values *P*<0.005.

In multivariate analyses, the correlates of TAC were age, gender, hypertension, coronary artery disease, peripheral vascular disease, and renal function, *P*<0.05 for all. In multivariate analyses, the correlates of VAC were gender, mean aortic gradient, and to a lesser extent peripheral vascular disease, *P*<0.05 for all.

Prognostic value of TAC AND VAC

After 3 years of follow-up, 23 (1.6%) patients were lost to follow-up and 245 (17.8%) patients experienced CV mortality, 92 (21.6%) in LGAS patients, and 153 (16.2%) in HGAS patients, respectively, pLogRank=0.018 (*Figure 2*).

Figure 3 displays the Kaplan–Meier curves according to the three groups defined according to the terciles of TAC and VAC according to mean aortic gradient. TAC ranges were 0–1.359 cm^3 for Group 1, 1.36–3.616 cm^3 for Group 2, and 3.619–22.33 cm^3 for Group 3. VAC ranges were 0–573.6 mm^3 for Group 1, 573.7–1077 mm^3 for Group 2, and 1078–4517.28 mm^3 for Group 3. In LGAS patients, the survival curves of the three groups defined according to terciles of TAC were significantly different for CV mortality (pLogRank=0.007) (*Figure 3A*) with a survival much lower for patients belonging to the third group; conversely, no difference of the survival curves of the three groups defined according to terciles of VAC (*Figure 3B*) was observed. In HGAS, the survival curves of the three groups defined according to terciles of both TAC and VAC were significantly different for CV mortality (pLogRank=0.04 and 0.005, respectively) (*Figure 3C and D*). Again the survival was lower for patients belonging to the third groups defined according to terciles of TAC or VAC.

Table 3 summarizes univariate and multivariate Cox analyses in LGAS and HGAS patients.

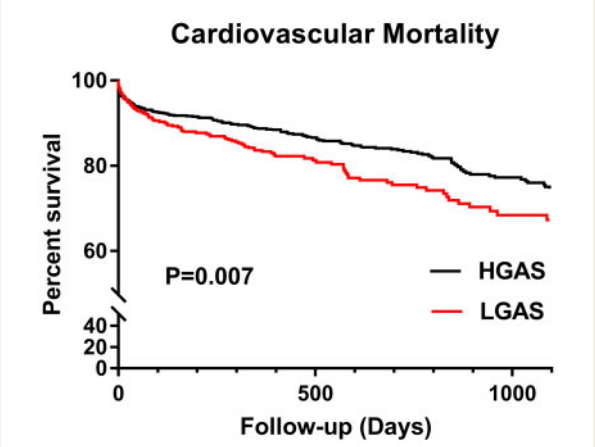

Figure 2 Kaplan–Meier analysis of 3-year cardiovascular mortality-free survival according to according to mean aortic gradient. HGAS, high-gradient aortic stenosis (mean aortic gradient ≥40 mmHg); LGAS, low-gradient aortic stenosis (mean aortic gradient<40 mmHg).

In LGAS patients, TAC was associated with CV mortality in univariate analysis and in all multivariate models while VAC was not. In HGAS patients, TAC remained only associated with CV mortality in univariate analysis and after adjustment for age and gender but not in other multivariate models, while VAC was associated with CV mortality in univariate and in all multivariate models.

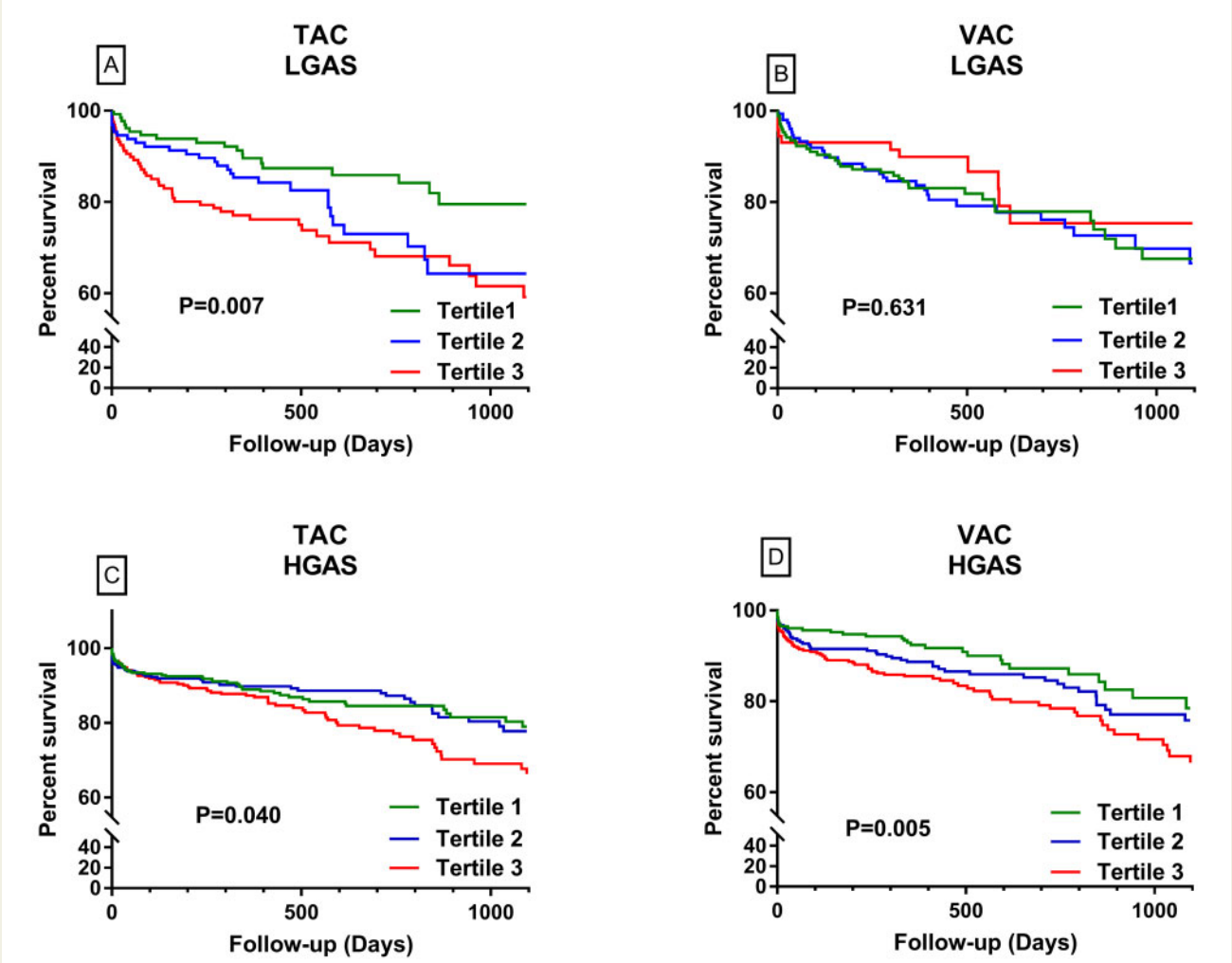

Figure 3 Kaplan–Meier analysis of 3-year cardiovascular mortality-free survival according to groups defined on terciles of TAC and VAC in LGAS and HGAS patients. HGAS, high-gradient aortic stenosis (mean aortic gradient≥40 mmHg); LGAS, low-gradient aortic stenosis (mean aortic gradient<40 mmHg); TAC, thoracic aortic calcifications; VAC, valvular aortic calcifications.

Discussion

By considering the prognostic influence of VAC and TAC on post-TAVI outcomes, we highlighted some pathophysiological differences between LGAS and HGAS patients; while the prognosis of the classical HGAS form is mainly driven by valvular aspects, which of LGAS is more complex, being related to vascular features. This explains, at least in part, why both AS forms do not benefit to the same extent from a TAVI procedure and suggest that TAC and VAC should be considered for risk stratification.

This study confirms that LGAS and HGAS patients are different with respect to some important clinical characteristics and comorbidities. LGAS also have a worse prognosis than HGAS after valve replacement in line with previous reports.[12] The course of the disease could be influenced by factors that may differ between LGAS and HGAS patients. Traditional AS is characterized by a severe reduction of aortic valve area, correlated to both a high VAC and a high gradient,[3,4] as confirmed in this study. HGAS is an unequivocal valvular disease as emphasized by the major prognostic significance of VAC in this this situation. This is consistent with previously published studies in patients with AS, treated by TAVI or surgery, demonstrating that VAC was associated with mortality.[13] The mechanisms underlying the association of VAC with post-TAVI outcomes may be linked to an increased rate of periprocedural complications, device failure, pacemaker implantation, or paravalvular leak.[14,15] AS severity, and thus VAC, is also correlated with myocardial fibrosis,[16] which is mostly irreversible and influences post-operative mortality[17] and heart failure.[18] This may explain that VAC continued to have a prognostic significance over the long run, i.e. after AS relief.

In LGAS patients, TAC but not VAC represents a major risk factor for CV mortality. Albeit TAC and VAC share some common pathways,[19] both being linked with atherosclerotic risk factors, they are not tightly related suggesting different significance. TAC seems more integrative, being related to CV factors, CV disease, and renal function. In this respect, the prognostic impact of TAC in LGAS is in line with a more diffuse disease encompassing cardiac, vascular, and

Table 3 Risk of 3-year cardiovascular mortality in unadjusted and adjusted Cox regression models

	LGAS (n=435)		HGAS (n=961)	
	HR (95% CI)	P	HR (95% CI)	P
$TAC^{3a}_{+1\ cm}$	1.078 (1.030–1.129)	**0.001**	1.052 (1.005–1.101)	**0.028**
$VAC^{3a}_{+1\ cm}$	0.788 (0.506–1.227)	0.291	1.299 (1.044–1.616)	**0.019**
$TAC^{3b}_{+1\ cm}$	1.097 (1.046–1.152)	**<0.001**	1.049 (1.001–1.100)	**0.044**
$VAC^{3b}_{+1\ cm}$	0.703 (0.437–1.1290)	0.145	1.276 (1.010–1.612)	**0.041**
$TAC^{3c}_{+1\ cm}$	1.030 (1.014–1.047)	**<0.001**	1.047 (1.000–1.097)	0.052
$VAC^{3c}_{+1\ cm}$	0.790 (0.511–1.220)	0.287	1.288 (1.033–1.606)	**0.024**
$TAC^{3d}_{+1\ cm}$	1.085 (1.024–1.149)	**0.005**	1.035 (0.981–1.091)	0.205
$VAC^{3d}_{+1\ cm}$	0.780 (0.478–1.273)	0.320	1.336 (1.048–1.703)	**0.019**
$TAC^{3e}_{+1\ cm}$	1.073 (1.010–1.141)	**0.023**	1.023 (0.966–1.083)	0.443
$VAC^{3e}_{+1\ cm}$	0.738 (0.447–1.218)	0.235	1.335 (1.031–1.728)	**0.028**
$TAC^{3f}_{+1\ cm}$	1.085 (1.019–1.156)	**0.011**	1.015 (0.955–1.079)	0.626
$VAC^{3f}_{+1\ cm}$	0.713 (0.439–1.8)	0.235	1.342 (1.034–1.742)	**0.027**

CI, confidence interval; HGAS, high-gradient aortic stenosis; HR, hazard ratio; LGAS, low-gradient aortic stenosis; TAC, thoracic aortic calcifications; VAC, valvular aortic calcifications.
[a]Unadjusted.
[b]Model 1 adjusted for age and gender.
[c]Model 2 adjusted for Logistic EuroSCORE.
[d]Model 3 adjusted for: age, gender, diabetes, atrial fibrillation, coronary artery disease, left ventricular ejection fraction, renal function.
[e]Model 4 adjusted for: age, gender, diabetes, atrial fibrillation, coronary artery disease, left ventricular ejection fraction, renal function, vascular access (femoral Y N), aortic regurgitation >2.
[f]Model 5 adjusted for model 4+TAC and VAC.
Bold values P<0.005.

kidney damages. Moreover, TAC represents a surrogate of vascular afterload[20]; it has been shown that the negative prognosis impact of an increased vascular load was even worse in the presence of low LVEF or low stroke volume.[5,6] In the setting of TAVI, the high residual vascular load will continue to exert its detrimental influence on left ventricular function over the long time.[7,8,21] This is in line with a lower left ventricle mass regression and a lower LVEF improvement at 1-year follow-up in AS patients with a high calcification burden of the thoracic aorta.[22] TAC has recently been incorporated in a dedicated TAVI risk score, the CAPRI score, that predicts 1-year mortality[10] and hospitalization for heart failure.[23]. The fact that VAC was not of prognostic importance in this setting, reinforces the view that, valvular disorder is not the sole component of LGAS.

Clinical implications

The present multicentric study highlights the pathophysiological differences existing between LGAS and HGAS patients. The pre-TAVI CT-scan provides some crucial prognostic information by quantifying the calcification load of both the thoracic aorta and the valve. On top of these pathophysiological insights, this study has important prognostic consequences. TAC may be crucial to consider for risk stratification, particularly in the setting of LGAS to foresee the post-TAVI outcome. On top of being associated with peri-procedural complications, VAC will still influence outcome after restoration of transvalvular flow in HGAS patients. Nowadays, VAC and TAC are easily measurable with CT-scan, and artificial intelligence will probably allow to fully automatize their measurements as it is already the case for coronary calcifications. Therefore, together with other predictors of outcomes, VAC and TAC may help in the decision-making process during the TAVI work-up with the aim of selecting patients with a high probability of poor outcome after the procedure.

Limits

The present ancillary study of C4CAPRI study is a registry, even though the completeness of data entered is high,[10] we may not exclude that some information may not have been available in the database. For example, the repeatability of Doppler data was not assessed.

With the improvement of aortic valve bioprosthesis, and the evolution of TAVI indications, the patients treated nowadays by TAVI may not fully match in terms of risk with those included in the present study, i.e. between 2010 and 2014, questioning the generalizability of the study results. Still, valvular and aortic calcifications are common findings in the AS setting and will still be encountered in lower risk patients. VAC and left ventricle outflow tract calcifications have been associated with more aortic regurgitation and more pacemaker implantation after TAVI. While new generation prosthesis has partly addressed these drawbacks, it is unlikely that their use would lessen the prognostic significance of VAC; indeed the rate of aortic regurgitation is already low in the study population, and, in any case, not different between the more calcified HGAS patients than in the LGAS ones. Thresholds of VAC volume have been proposed in order to stratify the severity of AS with a special attention to gender. However, these thresholds have been determined on a different CT-Scan protocol. In our work, the aim was not to define a threshold as all patients were considered to have a severe AS. The aim was to highlight the differential prognostic value of TAC and VAC in HGAS and LGAS patients. It would have been interesting to assess the

stroke volume index in order to better categorize LGAS patients; however, in this study, we only have the LVEF which is to some extent a surrogate. Finally, a lack of statistical power in HGAS patients (less events) may explain the absence of prognostic value of TAC in the full adjusted model.

Conclusions

TAC and VAC should be carefully analysed and quantified during the pre-TAVI CT-scan since they carry specific prognostic information in LGAS and HGAS patients, corresponding to partly different underlying pathological mechanisms.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Data availability

Possible, please send an email to the corresponding author with the purpose of your demand.

Conflict of interest: No conflict of interest regarding the present work.

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f) Impact pronostic des calcifications de l'anneau mitral après TAVI

Significance of quantitative mitral annular calcifications volume to predict mortality after TAVI

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En cours de soumission

Hypothèse : Les données concernant l'impact pronostique des calcifications de l'anneau mitral (MAC) en post TAVI sont rares et contradictoires. Ces contradictions pourraient venir du fait que sa définition est équivoque et que MAC a souvent été considéré qualitativement. MAC peut être mesuré précisément au scanner, ainsi sa quantification précise et objective pourrait être évaluée dans la prédiction de la mortalité en post TAVI.

Objectif : Evaluer l'impact pronostique sur la mortalité à 1 mois et 1 an post TAVI de MAC considéré de façon quantitative (cm^3), indexé sur la surface corporelle (MAC index cm^3/m^2) et qualitative (sévère/non sévère).

Population, Méthodes : Etude ancillaire de C4CAPRI, 1493 patients porteur d'une sténose aortique serrée, traités par TAVI entre 2010 et 2014 ont été inclus.

MAC a été mesuré de façon semi-automatique (Figure 17) et considéré selon 3 modalités : continue en cm^3, MAC indexé sur la surface corporelle en cm^3/m^2 et qualitative (sévère/non sévère, un MAC sévère correspondant aux patients ayant un volume de MAC supérieur à la borne inférieure du $10^{ème}$ décile, soit un MAC $\geq 2cm^3$.

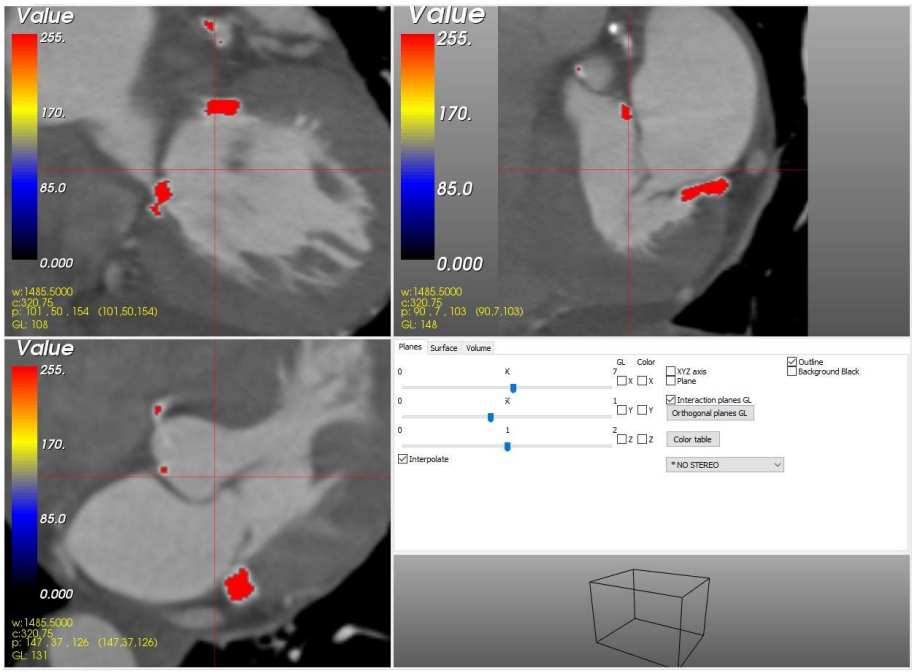


Figure 17 *: Détection et mesure semi-automatique des calcifications de l'anneau mitral*

L'outcome considéré était la mortalité totale et cardiovasculaire à 1 an

Résultats : À 1 mois de suivi, 86(5,9%) patients sont décédés, respectivement 70(5,3%) dans le groupe absence de MAC sévère et 16(10,7%) dans le groupe MAC sévère, p Log-Rank = 0.007. À 1 an de suivi, 245 patients (17 %) sont décédés, 211/1293 (16. 3%) dans le groupe absence de MAC sévère et 34/149 (22,8%) chez les patients présentant un MAC sévère (p Log-Rang= 0. 027). Après ajustement sur les principaux facteurs confondants, la présence d'un MAC sévère reste associée à la mortalité à 1 mois et 1 an, le MAC considéré en continue également, pour une augmentation de 1 cm^3 du volume de MAC; HR 1,195 IC [1,078–1,324], p=0. 001, et HR 1,118 IC [1,036–1,206], p=0. 004. Les résultats étaient similaires en ce qui concerne le MAC index. La valeur de pronostic des 3 modalités de MAC était similaire avec la mortalité cardiovasculaire, p<0,05 pour tous les modèles.

Conclusion, discussion : MAC est fortement associé à la mortalité quelle que soit la modalité considérée. Cet impact pronostic peut s'expliquer par plus de décès péri-procéduraux comme en témoigne la mortalité à 1 mois mais également par le fait que MAC est un marqueur de

risque intégratif. En effet, MAC est associé à de nombreuses comorbidités (insuffisance rénale chronique, fibrillation auriculaire, maladies de la valve mitrale, troubles de conduction intracardiaque, maladie coronarienne, insuffisance cardiaque, endocardite, embolie systémique et accidents vasculaires cérébraux ischémiques) Figure 18.

Perspectives : MAC est actuellement considéré par le cardiologue interventionnel pour la planification de la procédure, le type de valve, la profondeur d'implantation. MAC pourrait jouer un rôle dans la stratification du risque en post TAVI en étant intégré dans un score de risque TAVI. Nos résultats justifient une surveillance plus étroite au cours du premier mois après TAVI. Aussi MAC est facilement et précisément mesurable au scanner et se prête donc bien à une analyse complétement automatique via le machin learning.

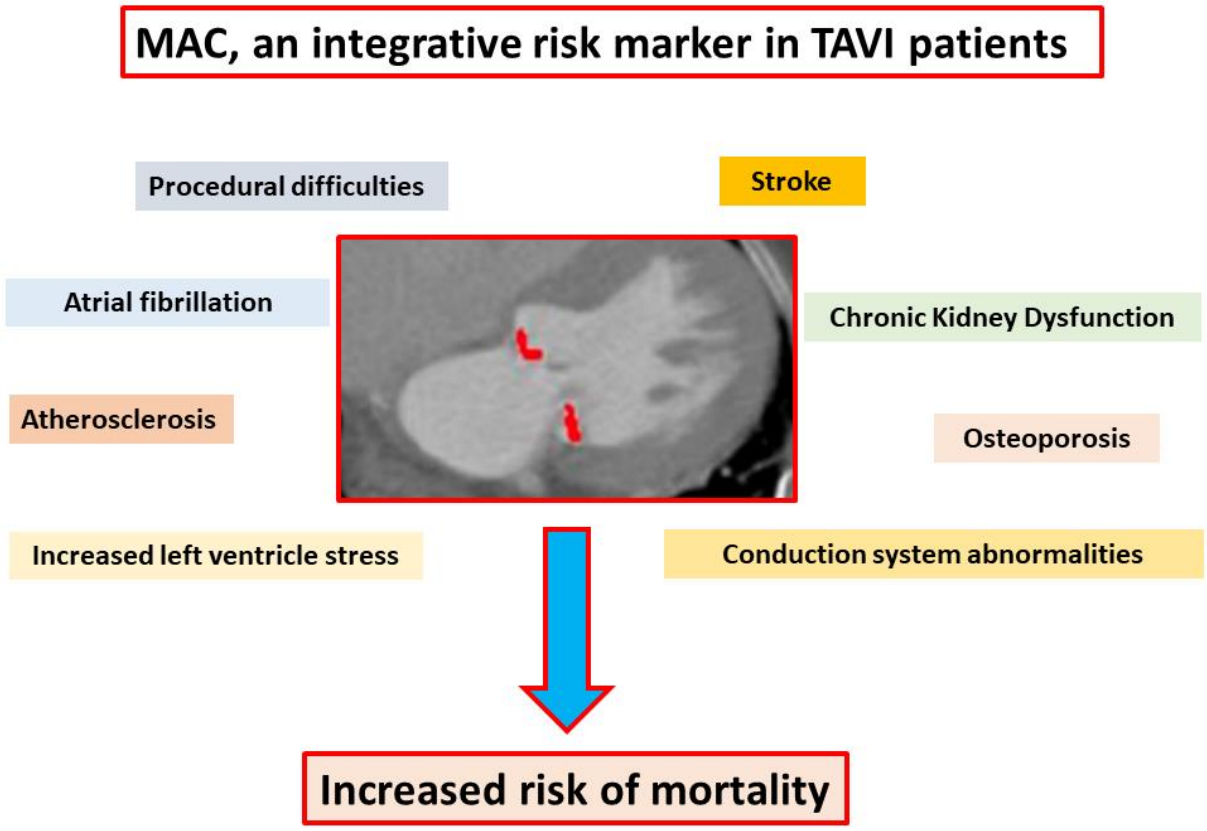


Figure 18 : *MAC est un marqueur de risque intégratif de mortalité après TAVI*

6/ Perspectives, présentation du projet de recherche envisagé à moyen terme

Le point commun des travaux exposé dans ce manuscrit est de nous aider à mieux appréhender la physiopathologie des pathologies prise en charge en cardiologie interventionnelle afin d'en permettre une meilleure prise en charge et d'améliorer la pertinence des soins.

Nous allons poursuivre cette thématique de recherche originale autour de la rigidité vasculaire en cardiologie interventionnelle. Cela passera par la poursuite d'encadrements de travaux de thèses d'université et d'exercice, le développement de notre start-up i-COR technologies et la réponse aux appels à projets afin de pouvoir obtenir les financements nécessaires.

Axe valvulaire

Afin d'amplifier l'effort de recherche autour des calcifications de l'aorte, nous travaillons avec le service d'imagerie du Pr Boussel et CREATIS à une automatisation complète de la mesure de ce paramètre par « deep learning ». Une automatisation et standardisation des mesures permettraient une utilisation universelle de ce permettre. Aussi, le score CAPRI pourrait être amélioré en intégrant d'autres biomarqueurs scanographiques tel que le volume de calcifications de l'anneau mitral (Mitral Annular Calcifications, MAC). Ce paramètre semble prometteur puisque les patients les plus « calcifiés » au niveau mitral sont différents des plus « calcifiés » au niveau aortiques : ces deux types de calcifications pourraient être complémentaires et améliorer la prédiction du risque comme montré dans un abstract accepté au congrès Journées Européenne de la Société Française de Cardiologie 2021.

Abstract Journée Européennes de la SFC 2021
Cumulative impact of mitral annular calcifications and thoracic aortic calcifications on 1-year mortality after TAVI

Background

Prognostic markers after TAVI are lacking. Mitral Annular Calcifications (MAC) and Thoracic Aortic Calcifications (TAC) measured on multi detector CT scan are two original strong predictors of outcome after TAVI. The cumulative prognostic value of both MAC and TAC has never been assessed.

Purpose

In the present multicenter study, we sought to evaluate the cumulative prognostic value of high MAC and high TAC in patients with aortic stenosis and treated with TAVI on 1-year all-cause and cardiovascular mortalities.

Methods

Between January 2010, and December 2014, in 4 high volume centers, consecutive patients with severe aortic stenosis and with a measurable MAC and TAC on multi detector CT scan were included. Patients with mechanical mitral valve were excluded. Both MAC and TAC were measured with semi-automatic software. Based on previous reports high MAC was defined as a MAC volume $\geq 2cm^3$ and high TAC was defined as belonging to the third tertile of TAC. 3 groups of patients were therefore considered; group 1 low MAC and low TAC, group 2 high MAC or high TAC, and group 3 high MAC and high TAC.

Kaplan Meier graphs and PLogRank test were used to compare 1-year all-cause and cardiovascular mortalities among the 3 groups.

Multivariable Cox regression analysis was therefore used to assess the prognostic value of high MAC and high TAC. 2 models were performed: Model 1 adjusted for EUROSCORE, and Model 2 for age, gender, atrial fibrillation, coronary artery disease, left ventricle ejection fraction (LVEF), mean aortic gradient, renal function, peripheral vascular disease, history of stroke, renal function, chronic obstructive pulmonary disease, and vascular access.

Results

1382 patients met the inclusion criteria. The main characteristics were as follows: 677 (49%)women, mean age 83.5 +/-7.1 years, mean euroscore 17.44 +/- 10.4; mean LVEF 56.4±14.1% and mean renal function 50.44+/-22.9ml/min/m^2. 839 (60.7%)patients had low MAC and low TAC (group 1), 492(35.6%)patients had high MAC or high TAC (group2), and 51 (3.7%) patients high MAC and high TAC (group 3). There was no difference among groups regarding age, gender, LVEF, renal function. Patients belonging to groups 2 and 3 had a higher EUROSCORE, and were more prone to have a history of atrial fibrillation and stroke.

At 1-year post TAVI, 25 patients were lost to follow-up and 230 (16.6%) died, among them 164(11.9%) died from cardiovascular causes. Figure 1 displays Kaplan Meier graphs for all-cause and cardiovascular mortalities according to the 3 groups. We observed an increased mortality rate from group 1 to group 3. Patients from groups 1, 2, and 3 experienced respectively 123 (14.9%), 93(19.3%), and 14(28%) deaths, PLogRank=0.005, and respectively 83 (10.1%), 71(14.7%), and 10(20%) cardiovascular deaths, PLogRank=0.005.

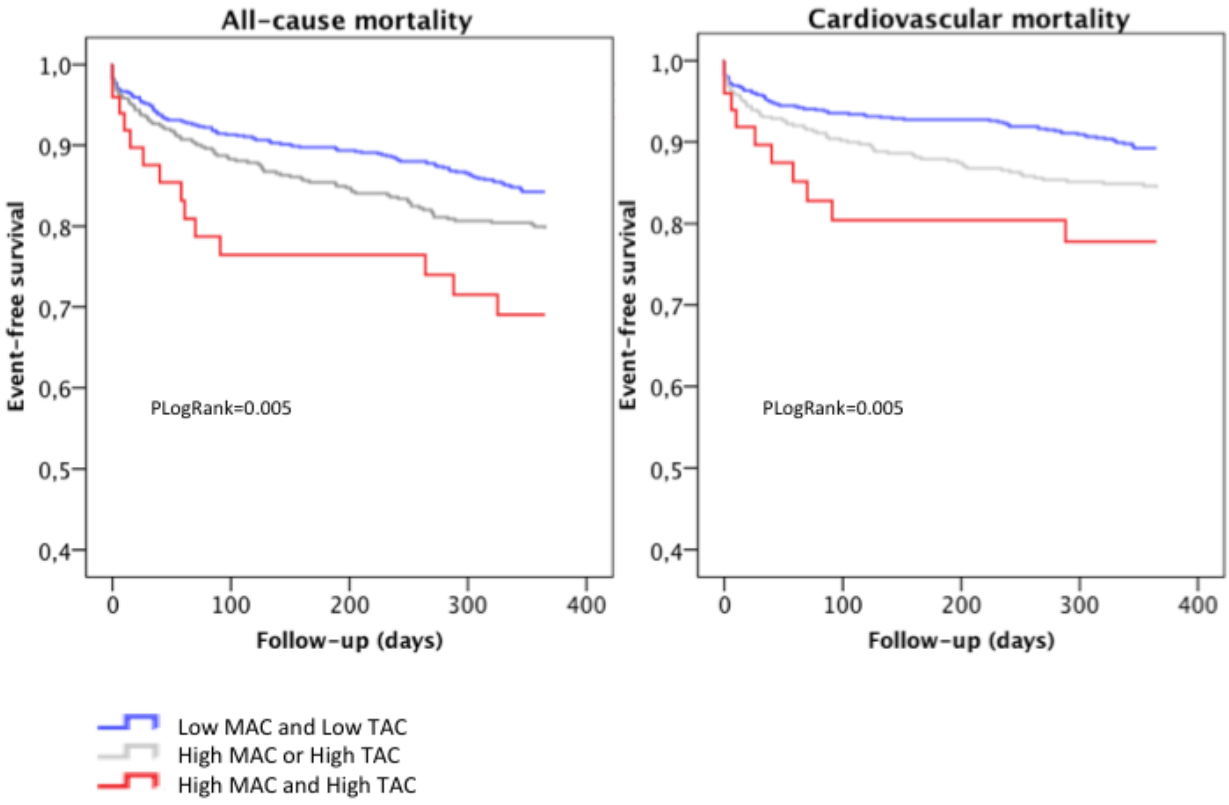
Taking group 1 as a reference, unadjusted cox regression analysis showed an increased risk of mortality of groups 2 and 3; group 2 *vs* group1 Hazard Ratio 1.331 Confidence Interval (1.017-1.742), p=0.037, and group 3 *vs* group1 HR 2.204 CI (1.268-3.831), p=0.005. Results were similar for cardiovascular mortality with an increased risk for groups 2 and 3; group 2 *vs* group 1 HR 1.500 CI (1.093-2.060), p=0.012, and group 3 *vs* group 1 HR 2.292 CI (1.189-4.418), p=0.013.

In model 1, group 3 still had an excess of mortality compared to group 1 HR 2.215 CI (1.274-3.851), p=0.005, while it was no more significant for group 2 *vs* group1 HR 1.264CI (0.963-1.660), p=0.091. Regarding cardiovascular mortality, both groups 2 and 3 showed an increased risk compared to group 1; group 3 *vs* group 1 HR 2.293 CI (1.190-4.421), p=0.013, and group 2 *vs* group1 HR 1.414CI (1.026-1.949), p=0.034.

In model 2, group 3 experienced an excess of mortality compared to group 1 HR 2.058 CI (1.177-3.601), p=0.011, while it was not significant for group 2 *vs* group1 HR 1.155 CI (0.871-1.533), p=0.091. Regarding cardiovascular mortality group 3 showed an excess of mortality compared to group 1 HR 2.139CI (1.101-4.156), p=0.025, while it was not statistically significant for group 2 *vs* group1 HR 1.376CI (0.987-1.918), p=0.059.

Conclusion

The present study demonstrates that patients with high MAC and high TAC experience a dire outcome compared to others while patients with low MAC and low TAC experience the best outcome. MAC and TAC are easily assessable on multi detector CT scan and should be systematically considered for risk stratification during the pre-TAVI workup. Further studies are needed in order to include MAC and TAC in TAVI dedicated risk scores.



Parallèlement, nous avons pour projet de construire un score de risque TAVI complètement basé sur le scanner le pré-TAVI utilisant l'intelligence artificielle. Ce score de risque inclura le volume de calcification de l'aorte et d'autres paramètres tels les calcifications valvulaires aortique et de l'anneau mitrale. Il pourra facilement être implémenté sur d'autres centres de cardiologie interventionnelle et fera l'objet d'une étude de large ampleur.

Aussi, je viens de mettre en place la cohorte monocentrique CALCITAVI gérée par la DRCI des HCL : elle a pour originalité d'inclure des marqueurs de rigidité vasculaire (calcifications de l'aorte, vitesse de l'onde de pouls aortique, pression pulsée) en plus d'autres paramètres clinico-biologiques classiques. Nous prévoyons d'inclure 1000 patients d'ici 4 ans en raison de l'extension des indications de TAVI et du nombre croissant de procédures. Par ailleurs, nous projetons d'étudier la corrélation de la vitesse de l'onde de pouls carotido-fémorale avec le volume de calcifications de l'aorte et avec une nouvelle méthode échographique mise au point au laboratoire CREATIS, « l'Ultrafast Echo », technologie permettant littéralement « d'imager » l'onde de pouls qui chemine le long de l'artère. En utilisant une sonde convexe nous pourrions déterminer la vitesse de l'onde de pouls au niveau de l'aorte abdominale. Cela ouvrira de nouvelles perspectives de recherche en utilisant des moyens non invasifs.

Axe coronaire

- Développement de la VOP coronaire (VOPc). L'objectif est de fabriquer, via la start-up i-COR technologies, une plateforme dédiée permettant d'obtenir facilement la VOPc. Plusieurs étapes sont à venir et le développement de notre start-up nous permettra d'avancer sur ce projet. Dans cette optique les succès récents aux appels d'offre nous encouragent à poursuivre cette politique de développement. Un des objectifs à court terme est la fabrication d'un prototype de guide coronaire capable de mesurer facilement la VOPc. Nous menons

actuellement des travaux in-vitro de perfectionnement de la méthode de mesure de la VOPc, cela fait l'objet du mémoire de master 2. Les étapes suivantes sont de développer un prototype de guide permettant d'obtenir facilement la VOPc en relation avec un industriel. Ensuite, nous entreprendrons les démarches nécessaires pour obtenir le marquage CE et le droit d'utilisation chez l'homme. Nous réaliserons alors une validation des mesures en reproduisant notre travail princeps en monocentrique. Par la suite, nous mènerons des études prospectives multicentriques d'évaluation de la valeur pronostique de ce nouveau paramètre en candidatant à un PHRC. De nombreux centres sont déjà demandeurs de participer à ce travail.

- Etude COREYE. Actuellement 80 patients sont inclus sur 200 de prévus. Ce travail original qui corrèle les paramètres physiologiques oculaire et coronaires constitue l'essentiel d'une thèse d'Université en cours. Lors de son Master 2 et pendant les 12 premiers mois de sa thèse d'Université, le doctorant s'est focalisé sur le traitement d'images ophtalmologiques acquises par imagerie oculaire OCT en utilisant des techniques de « deep learning » pour apprécier la micro-circulation oculaire. En parallèle nous réalisons les acquisitions coronaires invasives afin de déterminer les pressions intracoronaires, les résistances microvasculaires et le débit coronaire. L'hypothèse est qu'en étudiant les paramètres oculaires nous puissions obtenir un reflet des paramètres coronaires sans avoir à pratiquer un examen invasif et donc comportant des risques. L'ophtalmologue pourrait ainsi dépister une maladie coronaire et permettre une prise en charge de la pathologie cardiaque à un stade plus précoce possiblement accessible à la prévention.

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