MUST Project: A Quantitative MRI Evaluation of Structural and Functional Changes in Myocardial and Skeletal Muscles Induced by Ultra-Endurance Running

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Ultra-endurance trail: An outstanding model to challenge qMRI in the study of the adaptive responses to extreme load and stress conditions

A post-industrial, technology-based society is leading, on the one hand, to an increasingly sedentary lifestyle, and on the other, to a growing interest in endurance sports. An example of this is participation in ever longer trail or ultra-marathon running races. However, whilst moderate exercise is clearly an important therapy for cardiovascular health [1], the effects of more extreme physical exercise are still unclear. An ultra-endurance trail is any running/walking event longer than the 42.195 km (26.2 miles) marathon distance, on footpaths or trails with various positive/negative slopes, elevations and conditions (mountain, desert, etc.). Some ultra-marathons require several days for completion, adding the stress of sleep deprivation to the exercise-induced physical difficulty. Ultra-trailers participating in such an extreme mountain ultra-marathon (MUM) can reach significant levels of inflammation and fatigue [2] that raise a very understandable interest within the scientific community [3]. Indeed, an ultra-marathon represents a unique and outstanding reversible model to study acute consequences of extreme load and stress on human organs. Moreover, with each subject being his or her own control, this model offers a window to screen the inter-individual susceptibility to injuries and limits of the adaptive responses. Therefore, given the fascination...
as inflammatory mechanisms in these muscles, have indeed never been explored using novel advanced quantitative MRI (qMRI) techniques. Such MRI findings will allow us to better understand the time-course of degeneration and regeneration of myocardial and skeletal muscle tissues caused by several days of extreme physical load as well as the differences between the two types of muscles. Ultra-trail hence represents a ‘real-life’ and longitudinal model for assessing quantitative non-invasive and local (organ-specific) imaging biomarkers on a wide range of tissue changes – from acute intense to subtle subclinical changes – and for correlating them with advanced blood biomarkers.

An on-site research lab at the foot of Mont-Blanc in Courmayeur, Italy
The whole project of performing an international study on a cohort of ultra-trailers before, immediately after, and three days after, the race, required the logistical achievement of installing a 30 m long, 45 tons truck containing a whole-body MRI scanner within the beautiful city of Courmayeur, in Italy’s Aosta Valley. A biochemistry laboratory for on-site immediate conditioning of all biomedical samples at all time-points was also needed. Thanks to the mutual interests of Siemens Healthcare, Swiss engineers and the medical team of the Aosta public hospital, it was possible to have our favorite 1.5T cardiac MR system (MAGNETOM Avanto) within an Alliance medical truck for 3 weeks in the center of Courmayeur, less than 100 m from the finishing line of the world’s most extreme mountain ultra-marathon: The ‘Tor des Géants’. Our team of scientists would also like to pay tribute to the incredible welcome given to our project by the organizers and medical team in
charge of the event’s safety and research management.

330 km, 24,000 m positive elevation, ~100-150 hours running, 4-10 hours sleeping, 3 x 90 min MR scans, 50 athletes

The ‘Tor des Géants’ is an extreme MUM, famous for being the longest distance for such events (330 km), and boasting the highest positive elevation (24,000 m). All participating ultra-trailers also point to the unmatched atmosphere of this event within an extraordinary landscape at the feet of the highest mountains in the Alps.

Our team of scientists would also like to highlight the incredible and unique welcoming encountered by our project among the organizers and the medical team in charge of the safety and research management. Fifty ultra-trailers volunteered for a non-invasive and longitudinal quantitative MRI exploration performed prior to, during, and after the ‘Tor des Géants’.

Cardiac and skeletal muscle, as well as brain examinations, were conducted in three 90-minute MR sessions and three-step examinations. The study protocol has been approved by the Aosta Valley Ethics Committee. At the cardiac level, the 30 min imaging protocol included standard Cine-bSSFP imaging, but also MR-tagging to investigate changes of both global and regional function changes after the event and after recovery. Magnitude short- and long-axis CSPAMM images [4, 5] were processed using InTag post-processing toolbox (Creatis, Lyon, France) implemented in OsiriX software (Geneva, Switzerland) to perform quantitative myocardial strain analysis. Motion estimation is based on the Sine Wave Modeling approach [6]. Cine bSSFP images will also be processed by feature tracking analysis and regional and global peak circumferential (Ecc), longitudinal (EIl) strains as well as peak rotation and torsion will be derived using both techniques. Quantitative T1 mapping [7], T2 mapping [8, 9] and diffusion (multiple b values and multiple directions for both DTI and IVIM modeling) MRI sequences were further more acquired to evaluate the sensitivity of these new

3 Myocardial mid short-axis tagged image (CSPAMM) with superimposed displacement maps (left) and end-systolic peak circumferential strain (right) at basal (top) and apical levels (bottom) illustrating the basal clockwise rotation and counter-clockwise rotation of the apex. At the bottom, typical curves of the circumferential strain over time in AHA segments (inTag, OsiriX, Creatis, Lyon: www.creatis.insa-lyon.fr/inTag).
quantitative indexes in addition to potential biomarkers to explore changes occurring in myocardium.

The second step was a 30 min skeletal muscle examination, including a full quadriceps multi-echo isotropic 3D Dixon sequence (two-point Dixon, in and out of phase images, fat (F) and water (W) calculated images), a 3D multi-echoes (eight echoes), multi-flip-angle Dixon sequence for T2*, T1, fat fraction (FF), fat (F) and water (W) image calculation [10]. A STEAM diffusion sequence was also realized to screen any mean diffusion (MD), apparent diffusion coefficient (ADC), fraction of anisotropy (FA) as well as IVIM parameters (D, D* and f) exercise induced physiological variations. A multi-echoes T2 spin-echo sequence was also acquired for advanced T2 compartmental analysis.

Finally, a 15 min head examination concluded the series of tests, including a diffusion scan, and T2-weighted imaging using a standard 3 mm T2 TSE as well as a T2 multi-echo sequence.

**Preliminary results and discussion**

The redistribution of water into the muscle, in particular, has never been scrutinized using advanced quantitative MRI techniques such as T1, T2 and diffusion mapping, but also fat (F) and water (W) fraction mapping, immediately following extreme MUM and a few days of recovery. Our goal was to investigate the sensitivity and specificity of these quantitative MR derived parameters to follow-up the kinetics of the potential inflammatory phenomena caused by the ultra-trail and their links to the physiological processes involved in this controlled and reversible model of myocardial tissue stress. This study should provide new insights into the physiological mechanisms involved during ultra-endurance, and also during the recovery, at the cardiac and peripheral muscle level.
Leg muscle damage is frequently reported by the trailers after eccentric loading conditions such as in extreme MUM. Under these circumstances, muscles that provide most of the control and regulation of limbs’ movement during downhill running (e.g. vastus medialis), appear strongly hyperintense on T2-weighted images after exercise, while others, such as semitendinosus muscles appear to be preserved. Patterns of inflammatory damages were identified as hyperintense hazy lesions in the thigh muscles as shown in Figure 7. In our data, such patterns were mainly observed in vastii (intermedius, lateralis, and/or medialis) muscles but were not associated with any identified symptoms when present, without noticeable bruising at the time of imaging. Post-processing and segmentation of all individual muscle groups will allow precise evaluation of specific swelling. Our data showed more frequent inflammation patterns at the level of the vastus intermedius, a priori regardless of the effects of fatigue, performance or pain.

Several MRI and ultrasound studies have shown the existence of functional and biochemical alterations in the myocardium after prolonged intense exercise. Published echocardiography studies demonstrated systolic and diastolic transient left ventricle (LV) dysfunction with abnormal strains, and changes in LV torsion kinetics with decreased and delayed peak torsion as well as depressed peak untwisting [11]. Le Gerche et al. described cardiac remodeling of the right ventricle (RV) that could be associated with long-standing endurance training, with cumulative exposure to endurance competition further enhancing cardiac remodeling [12]. Late gadolinium enhanced techniques have also highlighted small areas of myocardial fibrosis [12]. Structural, functional and electrical changes of the athlete’s heart, probably linked to the disproportionate hemodynamic stress on the RV during endurance activity, appears to lead to exercise-induced heart phenotype, which in turn requires specific reading during diagnosis in order not to dramatize findings that
would be the evident sign of abnormalities in 'normal' subjects. Moreover, some arrhythmias appeared to be more prevalent amongst our endurance athletes.

Additional knowledge will be acquired from the extensive collection of blood biomarkers that have been obtained before, half-way, at the end of the race, and after three days of recovery. Indeed, while it has been shown that muscular and myocardial biomarkers are increased in MUM [2], little is known about their kinetics related to the distance, even if over 200 km the biomarkers increased more in the second half than in the first one [13]. Together with biomarkers of the inflammation and oxidative stress, the response of emerging biomarkers of cardiac stress and remodeling (Galectin-3, ST2, GDF15) will help to better understand myocardial damage that is likely to occur with such major stress for the body.

Conclusion

This study aimed to characterize a new model of human tissue stress with clinical and biological inflammatory responses close to severe conditions such as those met in intensive care units. From an imaging perspective, it is a unique opportunity for MRI researchers to validate MR-derived organ specific quantitative biomarkers with an accelerated kinetics where each subject is its own control. It will also provide new insights into the physiological mechanisms involved during ultra-endurance exercise, and its impact on the human body.

The preliminary results confirm previous work conducted in flat ultra-marathons, underlying potential risks from intense endurance activities that can lead to sports injuries. Peripheral muscles and articulations are probably on the frontline of damage, with noble organs such as the brain and myocardium which appear to suffer in a minor extend from the intense and/or extreme activities. There is definitely a social cache to excess performance in trail. Moreover, the world of sport places an ever-increasing demand on the athletic community without addressing the appropriateness of such burdens on either professional athletes or recreational athletes who run longer and harder races than ever before.

This article does not aim at negating the obvious fact that physical activity can reduce cardiovascular risk and mortality, and that it is essential for well-being in our sedentary and permanently connected cybernetic society. The optimal dose of physical activity and its benefits in terms of cardiovascular or all-cause mortality is still an open debate, and a recent study has shown in a cohort of 55,137 adults followed over 15 years, that running 5-10 min/day and at
slow speed <6 miles/h is associated with marked reduced mortality, without any further benefit from increased distance, frequency, amount or speed [14]. The upper limit of the dose-response of vigorous-intensity activities is unclear and needs to be individually clarified. Various studies have suggested that excessive endurance sports may induce adverse cardiovascular effects such as arrhythmias and myocardial damage [15, 16]. From a broader perspective, MRI can definitely help in the early recognition of exercise-induced tissue damage, and this study, testing innovating quantitative imaging methods in conditions close of those met with fragile patients – hence difficult to include in clinical trials – will accelerate the transfer and the validation of the newly developed organ-protection therapies.

We therefore also hope that it will provide our athletes with the benefits of the organ-protection therapies that are at the development or evaluation stages, so that they can pursue athletic glory in greater safety.

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