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TESI DI LAUREA

SEGMENTAL QUANTITATIVE T1 AND T2 MAPPING BY CARDIAC MAGNETIC RESONANCE IN COMPETITIVE ATHLETES: COMPARISON WITH HEALTHY SUBJECTS

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INDICE

ABSTRACT

Background: Cardiovascular Magnetic Resonance (CMR) is the primary imaging modality for the non-invasive myocardial tissue characterisation, and it is considered as the gold standard test for quantifying cardiac function, myocardial volumes, and mass. Up to now, most of the CMR studies in athletes were based on qualitative or semiquantitative techniques for detecting oedema and/or macroscopic fibrosis by T2-weighted or late gadolinium enhancement (LGE) sequences. Modern-day mapping techniques, allowing for precise, quantitative, and segmental characterization of the myocardial are significantly changing the clinical management in the patients with cardiac involvement. Thus, parametric imaging is aiming to close the gaps in diagnostic accuracy in trained subjects, as there are still various uncertainties in the differential diagnosis of the athlete's heart with other cardiac diseases.

Objectives: The aims of this study are: the comparison between T1 and T2 mapping values determined in an athletes' population consecutively referred to our Institute for pathological suspects and the reference values calculated on 50 healthy volunteers in the same center; the comparison between parametric versus non-parametric techniques and the assessment of the correlation between CMR findings and clinical/instrumental characteristics in the above-mentioned study population.

Materials and methods: We studied 50 athletes consecutively underwent CMR in our Institute for pathological suspects. T1 and T2 mapping values of the 50 athletes were compared to reference values calculated on 50 healthy volunteers in our centre. ECV values were compared with literature references. The correlation between parametric sequences (MOLLI and T2p-SSFP for T1 and T2 mapping, respectively) and non-parametric imaging (LGE, TIRM, steady state free precession (SSFP) cine sequences) findings was studied. We compared CMR findings with other instrumental data (ECG, ECG-Holter, ECG stress test), and we evaluated the correlation between Sars-CoV-2 infection versus parametric and non-parametric

CMR findings. Furthermore, we assessed clinical, instrumental and CMR data stratified according to age (paediatrics versus adults).

Results: Patients included were 43 (86%) males and 7 (14%) females, mean age was 26 ± 15 years (range 12-63). T1, T2 mapping and Extra Cellular Volume (ECV) values in our athlete's cohort were predominantly normal. Regarding correlations between parametric and non-parametric findings, apparently parametric imaging does not give an advantage in trained subjects. ECV global values were pathological in all the subjects with positive LGE findings (p=0.015). T1 global had normal values in 98% (n=41) of patients with normal kinesis (p<0.001). LGE was present in 31 (79%) of the subjects with exercise induced ventricular arrythmias (p=0.026), while T2 ratio was pathological in 13 of them (81%, p=0.028). When at least one between ECG, ECG-Holter or EST was abnormal, ≥ 2 T2 mapping pathological segments were present in 55% of the patients (n=22, p=0.048), while T2 ratio was pathological in 13 of them (93%, p=0.028). Moreover, ECV was pathological in all patients who experienced COVID-19 prior to CMR examination. We did not find significant differences in the clinical, instrumental and CMR data stratified according to age group (pediatric versus adult athletes).

Conclusion: This preliminary study shows that, besides morphological and functional alterations which can be found in the athlete's heart, statistically significant correlation was found between segmental T2 mapping abnormal values and ECG, Holter or EST alterations. ECV pathological values shows a correlation with the presence of macroscopic fibrosis. Our results require further evaluation in a larger population and prospective data are raccomended.

RIASSUNTO

Background: La risonanza magnetica cardiaca (RMC) è la principale modalità di caratterizzazione tissutale del miocardio ed è considerata il gold standard per la valutazione di funzione cardiaca, volume e massa del miocardio. Ad oggi, la maggior parte degli studi di cardio-risonanza negli atleti si sono basati sulle tecniche qualitative e semiquantitative per rilevare edema e/o fibrosi macroscopica con sequenze T2 pesate o late gadolinium enhancement (LGE). Le tecniche di mapping moderne, consentendo una caratterizzazione precisa, quantitativa e segmentale del miocardico, stanno significativamente cambiando il management clinico nei pazienti con coinvolgimento cardiaco. Pertanto, l'imaging parametrico sta puntando a riempire le lacune nella precisione diagnostica nei soggetti sportivi, essendoci ancora diverse incertezze nella diagnosi differenziale tra il cuore d'atleta e altre patologie cardiache.

Obiettivi: Gli scopi di questo studio sono: la comparazione tra i valori di T1 e T2 mapping definiti in una popolazione di atleti consecutivamente indirizzati al nostro Istituto per sospetti patologici e i valori di riferimento calcolati su 50 volontari sani nello stesso centro; la comparazione tra tecniche parametriche e non-parametriche e la valutazione della correlazione reperti di CRM e caratteristiche cliniche/strumentali nella sopracitata popolazione di studio.

Materiali e metodi: Abbiamo studiato 50 pazienti che hanno svolto RMC consecutivamente nel nostro centro. I valori di T1 e T2 mapping dei 50 atleti sono stati confrontati ai valori di riferimento calcolati su 50 volontari sani nel nostro centro. I valori di ECV sono stati confrontati con riferimenti in letteratura. È stata studiata la correlazione tra i reperti delle sequenze parametriche (MOLLI e T2p-SSFP per il T1 e T2 mapping, rispettivamente) e dell'imaging non parametrico (LGE, TIRM, steady state free precession (SSFP)). Sono stati inoltre confrontati i reperti di RMC con i risultati di altre analisi strumentali (ECG, ECG-Holter, test da sforzo); è stata altresì valutata la correlazione tra l'infezione da Sars-CoV-2 rispetto ai reperti di RMC. Inoltre, abbiamo valutato i dati clinici, strumentali e di CRM stratificati in base all'età (pediatrici vs adulti).

Risultati: I pazienti inclusi erano 43 (86%) maschi e 7 femmine (14%), l'età media era 26 ± 15 anni (intervallo 12-63). I valori di T1, T2 mapping e volume extra cellulare (ECV) nella nostra coorte di atleti sono risultati prevalentemente normali. Riguardo la correlazione tra i reperti parametrici e non parametrici, apparentemente l'imaging parametrico sembra non dare un vantaggio nei soggetti sportivi. I valori di ECV erano patologici in tutti i soggetti con LGE positivo ($p=0.015$). Il T1 global aveva valori normali nel 98% ($n=41$) dei pazienti con cinesi normale ($p<0.001$). Il LGE era presente in 31 (79%) dei pazienti con aritmie indotte dall'esercizio fisico ($p=0.026$), mentre il T2 ratio era patologico in 13 di loro (81%, $p=0.028$). Quando almeno uno tra ECG, ECG-Holter o test da sforzo era anormale, erano presenti ≥ 2 segmenti patologici al T2 mapping nel 55% dei pazienti ($n=22$, $p=0.048$), mentre il T2 ratio era patologico in 13 di loro (93%, $p=0.028$). Inoltre, in tutti i pazienti che hanno avuto infezione da Sars-CoV-2 prima dell'esecuzione di RMC, l'ECV è risultato essere patologico. Non abbiamo trovato significative differenze nei dati clinici, strumentali e di CRM stratificati per gruppi di età (atleti pediatrici vs adulti)

Conclusione: Questo studio preliminare mostra che, al di là delle alterazioni morfologiche e funzionali che possono essere riscontrate nel cuore dell'atleta, correlazioni statisticamente significative sono state trovate tra i valori anormali di T2 mapping segmentale e alterazioni dell'ECG, Holter o test da sforzo. I valori patologici dell'ECV mostrano una correlazione con la presenza di fibrosi macroscopica. I nostri risultati richiedono ulteriori rivalutazioni su una popolazione più grande e dati prospettici sono raccomandati.

INTRODUCTION

Cardiovascular Magnetic Resonance (CMR) is the primary imaging modality for non-invasive myocardial tissue characterisation, and it is considered as the gold standard test for quantifying cardiac function, myocardial volumes, and mass. [Aquaro et al. JMRI 2016 (1)]. The possibility of evaluating myocardial tissue by exploiting the magnetic properties of the myocardial structures has had a major impact on clinical cardiological management. Late gadolinium enhancement (LGE) techniques with post-contrast T1-weighted sequences have been used to evaluate focal processes such as fibrosis and have been extensively used to assess ischemic and non-ischemic heart diseases. In a similar way, T2-weighted sequences enabled evaluation of oedema and inflammation. However, both techniques are limited by their qualitative or semi-quantitative nature, as they both rely on the relative difference in the relaxation properties of the diseased and healthy myocardium. [Seraphim et al. 2020 (2)]

In the recent years, parametric mapping has permitted the evaluation of quantitative changes in myocardium, based on T1, T2 and extracellular volume (ECV) parameters. [Seraphim et al. 2020 (2)] This capability introduces a new frontier in cardiology, enabling to quantify properties of both regional and global myocardium comparing them with normal reference values acquired under the same scanning conditions [Meloni et al., 2021, 2022 (3,4)]. Previously, diffuse myocardial disease has always been difficult to measure or even appreciate without invasive procedures. This advance is important, because focal and diffuse changes often directly reflect pathophysiologic processes of various diseases from their preclinical phase up to the end stage and it improves diagnosis, measures of disease severity and prognosis. [Moon et al. 2013 (5)]

Initially, much of the research published about parametric imaging was focused on progress in acquisition methodology. This allowed to achieve numerous fast and robust mapping techniques, some of which are commercially available on modern CMR systems. There is now growing evidence on the clinical value of CMR myocardial mapping from large scale clinical outcomes trials. Mapping techniques

have an important potential for making diagnosis, risk-stratifying, and monitoring therapy. Thus, it can be considered as a natural extension of comprehensive CMR protocols for the assessment of myocardial disease. [Messroghli et al., 2017 (6)]

The main limitation for spreading the T1 and T2 mapping techniques in the routine clinical and research arena is due to its high reliance on the single scanner, on the type of sequence used and on imaging acquisition modality. This is the reason why normal values are not always coherent in different centers. Moreover, seems that these parameters can be partially influenced by age and sex, suggesting the use of normal reference range values relative to different age groups and sex.

NON-PARAMETRIC IMAGING IN CARDIAC MAGNETIC RESONANCE

Late Gadolinium Enhancement

Contrast agents such as gadolinium shorten T1 relaxation time within the tissue and increase the signal intensity of regions with high gadolinium concentrations. Gadolinium is a rare earth element that has seven unpaired electrons. Because of its paramagnetic properties, it facilitates water visualization in the intravascular or in the extravascular space. For this reason, it is used to selectively identify areas with reduced or increased uptake of contrast agent. [ACCF/AHA Expert Consensus Document 2011 (7)].

Regional differences of gadolinium concentration immediately after intravenous injection can be used to assess myocardial perfusion. Following the first pass of the contrast agent, a significant fraction enters the interstitial space. [ACCF/AHA Expert Consensus Document 2011 (7)].

Late gadolinium enhancement is evaluated, around 8-20 minutes after intravenous administration of gadolinium chelate contrast material (0.1– 0.2 mmol/kg), by a cardiac-gated T1-weighted pulse sequence. [ACCF/AHA Expert Consensus Document 2011 (7)].

Fibrotic or necrotic myocardium have a higher concentration of contrast agent compared to normal myocardium due to their larger volume of distribution available. [ACCF/AHA Expert Consensus Document 2011 (7)]. The reason why this happens is based on two phenomena. First, gadolinium chelates are extracellular

contrast agents that cannot cross cell membranes. [Rehwald et al., 2002 (8)] Second, in normal myocardium myocytes are densely packed and thus myocyte intracellular space forms the majority of the volume. [Kim et al. 1999 (9)]. Therefore, in presence of normal myocardium the overall number of gadolinium molecules will be low. Conversely, in acute myocardial damage, the myocyte's membrane is ruptured so a larger amount of contrast agent can infiltrate in the intercellular space. In chronic myocardial damage, myocytes are replaced with collagenous scars, thus again the interstitial space is expanded increasing gadolinium concentration. [Rehwald et al., 2002 (8)]. This mechanism is not specific for myocardial infarction and can occur in various disorders, such as inflammatory or infectious diseases of the myocardium, cardiomyopathy, cardiac neoplasms, and congenital or genetic cardiac pathologic conditions. If images are acquired too early, for example less than 5 minutes after the initial contrast material injection, contrast difference between pathological and normal myocardium can be reduced because insufficient contrast material has been washed out of the normal myocardium, leading to an overestimation of the ischemic region. On the other hand, imaging too late, for example after more than 30 minutes, may result in excessive washout of the contrast agent from the infarcted tissue and poor signal-to noise ratio [Vogel-Claussen et al. 2006 (10)].

Typically, areas of scar or fibrosis related to myocardial infarction show high LGE signal intensity which are subendocardial or transmural and related to coronary artery distribution. [Vogel-Claussen et al. 2006 (10)] Unlike the latter, in non-ischemic myocardial diseases LGE generally does not correspond to any particular coronary artery distribution and is often midwall rather than subendocardial or transmural [Mahrholdt et al., 2005 (11)] (Figure 1).

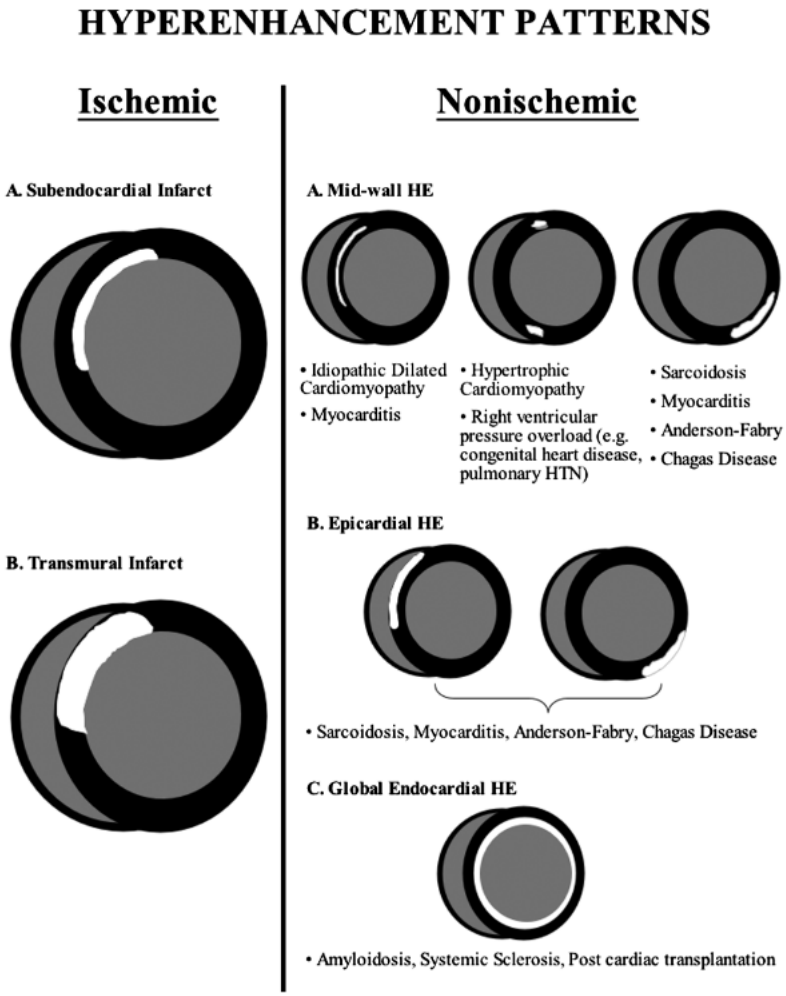


Figure 1: LGE hyperenhancement patterns [Mahrholdt et al., 2005 (11) *]*

An important limitation to this LGE technique is that it can detect only myocardial enhancement in relation to normal myocardium and has limited ability to detect diffuse myocardial changes. This occurs because there is no normal myocardium acting as a comparator, therefore signal will be globally nulled becoming indistinguishable from normal tissue. [Sado et al., 2011 (12)] Figure 2 shows an example of this kind of problem.

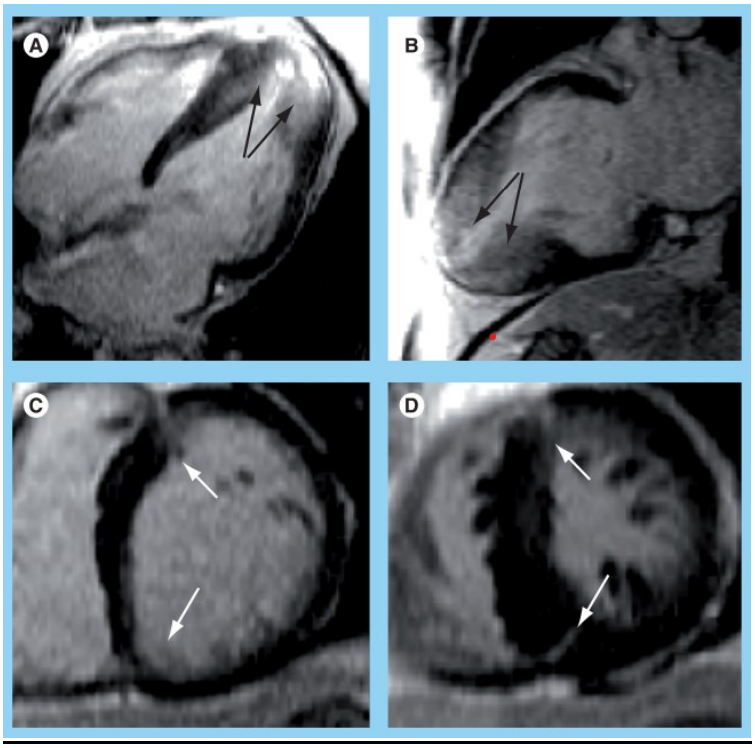


Figure 2: A patient with apical hypertrophic cardiomyopathy showing the limits of the late gadolinium enhancement (LGE) technique. In the long axis views (A and B), there is increasing myocardial signal (highlighted by the arrows) towards the apex in the hypertrophied myocardium likely to reflect diffuse fibrosis. Apparently, this is not present in the basal short axis (C), there is just some focal right ventricular insertion point LGE (arrows). The apical short axis (D) continues to show the right ventricular insertion enhancement (arrows) but not the diffuse process. [Sado et al., 2011 (10)]

T2 Turbo Inversion Recovery Magnitude

T2-weighted CMR has an exceptional role in identifying and quantifying myocardial oedema in vivo. In fact, the long T2 relaxation times of water's protons are used to generate contrast, allowing to detect high signal intensity when myocardial tissue contains oedema [Eitel e Friedrich, 2011(13)].

Ischemia with or without reperfusion causes alterations in these fluid balance mechanisms leading to the development of cell swelling, increased interstitial water accumulation or both. This situation occurs not only in irreversible damage, as in myocardial infarction, but also in severe transient myocardial ischemia. Elevated T2 signal can also be found in myocarditis, Takotsubo cardiomyopathy and cardiac transplant rejection. As aforementioned for LGE, the global, patchy, or subepicardial regional distribution patterns of oedema in these conditions are

different from ischemia, which predominantly affects the subendocardium or is regionally transmural in a coronary artery territory. [Eitel e Friedrich, 2011(13)].
Standard T2-weighted protocols usually employs turbo spin-echo (TSE) sequences with or without fat saturation pulses, mainly combined with dark-blood preparation [Simonetti et al., 1996 (14)]. Nowadays, the most used sequence is short-TI triple-inversion recovery prepared fast spin echo sequences (STIR). The inversion pulses for fat and blood suppression provide excellent contrast between regional oedema and normal myocardium due to the dual suppression of the fat and flowing blood signal. [Simonetti et al., 2001 (15)].The problem with this technique is that many elements can cause reduced signal-to-noise-ratio and artifacts. In fact, in some cases, signal losses can cause an intensity variation indistinguishable from the increase in T2 due to oedema, or it may cause normal myocardium to appear to have increased T2, resulting in a false-positive diagnosis. Furthermore, an incomplete dark-blood preparation sometimes leaves a bright rim blood artifact adjacent to the endocardium called "slow flow artefact", making it difficult to differentiate subendocardial oedema from intracavitary blood [Abdel-Aty et al., 2007 (16)]. Lastly, another limitation is its qualitative or semi-quantitative nature since the interpretation of the image depends on regional differences in myocardial signal intensity, especially when comparing oedema with scars. [Eitel e Friedrich, 2011 (10)]

PARAMETRIC IMAGING IN CARDIAC MAGNETIC RESONANCE

T1 mapping

T1 mapping measures the longitudinal or spin-lattice relaxation time, which is determined by how rapidly protons re-equilibrate their spins after being excited by a radiofrequency pulse. It requires the acquisition of multiple images to derive the T1 recovery curve, allowing to build a pixelwise illustration of an absolute T1 relaxation time through the generation also of a color-encoded map to simplify visual interpretation. (Figure 3)

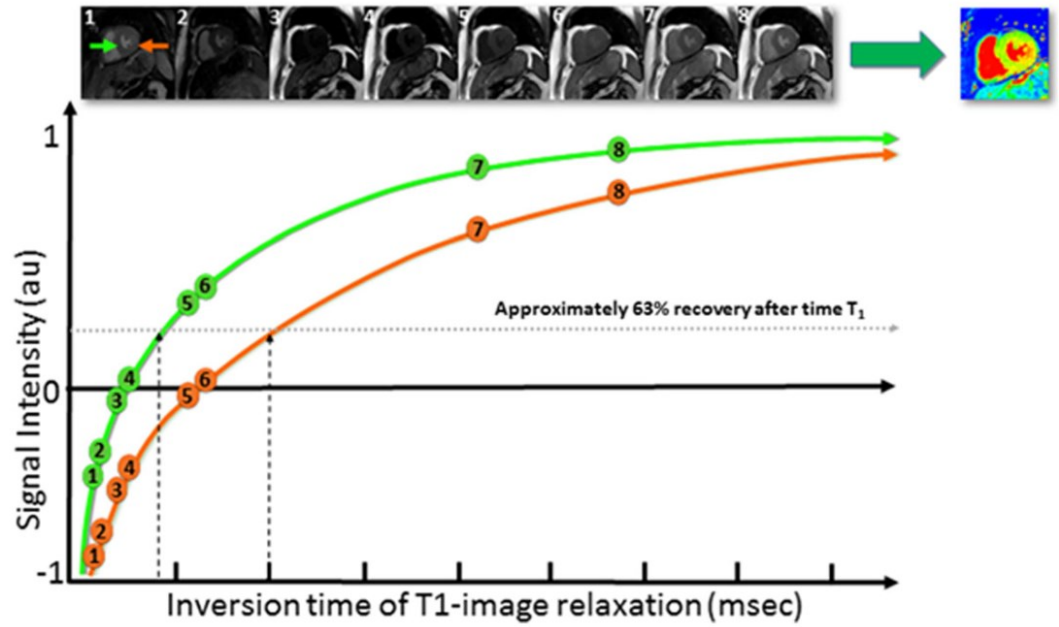


Figure 3: T1 map generation. [Haaf et al., 2016 (17)]

The use of this parameter is based on the principle that changes in longitudinal relaxation time (T1) reflect changes in the water content as well as the local molecular environment. Its values are established by a composite signal of myocytes and ECV. [Haaf et al. (17)]

The most important determinants of an increase in T1 are:

- amyloid deposition;
- increase of interstitial space (e.g., fibrosis in ischemic and non-ischemic cardiomyopathy);
- oedema, which is an increase of tissue water that can be detected for example in acute infarction or inflammation [Haaf et al. (17)].

On the other hand, low native T1 values can be determined by lipid overload, e.g., in Anderson-Fabry disease, lipomatous metaplasia in chronic myocardial infarction and iron overload. [Meloni et al. 2021 (18), Haaf et al. (17)] (Figure 4, Table I)

T1 mapping can also be measured after administration of standard gadolinium-based contrast agents. These substances are distributed throughout the extracellular space and T1 relaxation times of myocardium reduce in proportion to the local concentration of gadolinium. Areas of scar and fibrosis will therefore produce shorter T1 relaxation times. [Haaf et al. (17)]

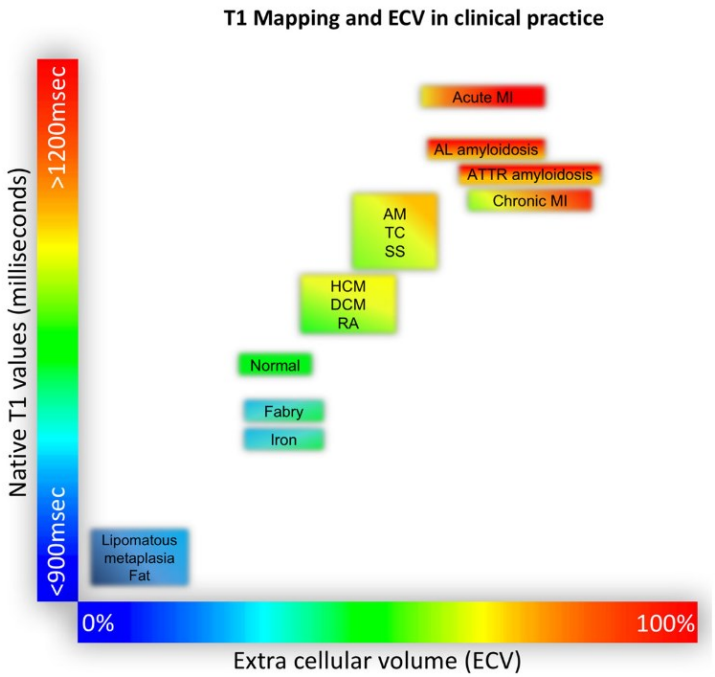


Figure 4: Alterations of T1 and ECV in different myocardial diseases [Messroghli et al., 2017 (6)]

The main concern in T1 quantification in myocardium is the severe time constraint due to cardiac and respiratory motion. [Messroghli et al. 2004 (19)]. Various techniques for the quantification of myocardial T1 have been described. The first method used was the Look Locker (LL) Sequence that acquired data using a continuous train of radiofrequency pulses after the inversion magnetisation pulse [Look and Locker 1970 (20)]. The important limitation about the Look Locker sequence is that data acquisition was performed continuously during the cardiac cycle without considering cardiac motion, acquiring at least 20 images, without using gating to a certain phase to reduce cardiac motion during a single breath-hold. [Hamlin et al. 2014 (21)]. Therefore, it can be difficult to create a pixel-based T1 map from an LL sequence because of the variability of heart rate (HR) [Nacif et al. 2011 (22)] and also because values can only be derived manually for every frame of each region of interest (ROI), meaning they could face inaccuracy caused by misregistration effects [Messroghli et al. 2004 (19)].

The Modified Look-Locker Inversion recovery (MOLLI) sequence is an evolution of the LL sequence and has become the most popular T1 mapping method. It acquires inversion recovery weighted images at different inversion times using single-slice, single-shot readouts throughout one breath-hold within a specific phase of the

cardiac cycle, following which the images are sorted into a single data set according to consecutive inversion times [Messroghli et al. 2004 (19)]. Figure 4 presents an example of a MOLLI sequence with a 5(3)3 protocol. [Kellman et al. 2012 (23)]. This protocol includes 2 inversion pulses, then 5 images after the first inversion and 3 after the second inversion, with 3 RR intervals for T1 recovery. Images are then sorted according to inversion time, following which, three-parameter model fitting is performed, in order to obtain a pixel-wise T1 map. [Kim et al. 2017 (24)]. (Figure 5)

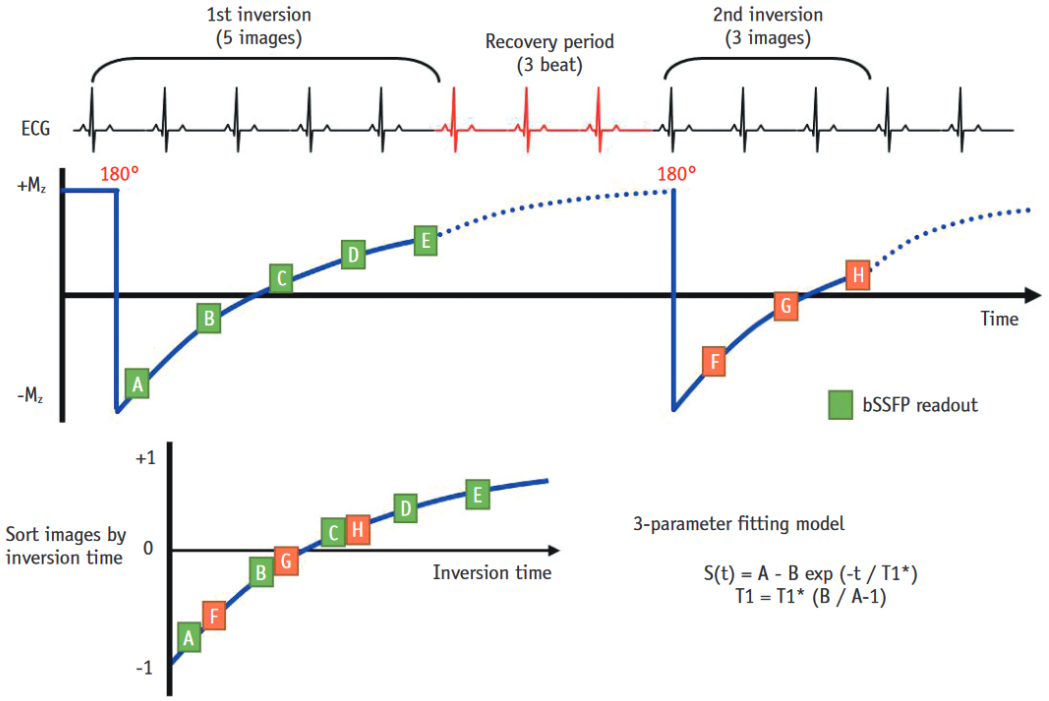


Figure 5: Modified Look–Locker inversion recovery (MOLLI) with 5(3)3 protocol. ECG = electrocardiogram, RR = the time interval between 2 consecutive R waves in the electrocardiogram, SSFP = steady-state free precession. [Kim et al. 2017 (24)]

Other versions of MOLLI have been developed with the aim to reduce breath-hold durations and sensitivity to heart rate [Haaf et al. 2016 (17)]. In particular, the Shortened MOLLI (ShMOLLI) scheme uses sequential inversion recovery impulses within a single breath hold of only 9 heart beats [Piechnik et al. 2010 (25)]. This technique is very similar to MOLLI, but it does not require the full recovery of longitudinal magnetization because of the conditional data analysis algorithm that can distinguish between short and long T1 values using curve-fitting errors,

requiring a shorter scan time. The price to pay for its shortening in scan and breath-hold time, is that also precision is reduced. [Kim et al. 2017 (24)]

One more pulse sequence used in clinical practice is saturation recovery single-shot acquisition (SASHA) that consists in 10 single-shot balanced steady-state free precession (bSSFP) images acquired over consecutive heartbeats. The first image is initially acquired without any saturation preparation and the remaining images are acquired after a saturation pulse with a different saturation delay over the RR interval [Chow et al. 2014 (26)].

Lastly a different technique is saturation pulse prepared heart-rate-independent inversion recovery (SAPPHIRE) [Weingärtner et al. 2014 (27)].

As mentioned earlier, different acquisition techniques can alter the range of normal T1 and are considered methodological confounders. In fact, MOLLI and ShMOLLI generally underestimate T1 [Messroghli et al. (6)]. T1 mapping must always be obtained with the same acquisition scheme at the same field strength and using the same post-processing methods. [Haaf et al. 2016 (17)].

The main method for motion correction is breath-holding: if it is not done correctly, it can negatively affect the quality of the maps. Despite this they can be counterbalanced through manual or automatic motion correction. [Haaf et al. 2016 (17)]. For example, it can be used respiratory motion compensation methods [Xue et al. (28)] and phase sensitive inversion recovery reconstruction [Xue et al (29)]. However, uncorrected respiratory motion is still a problem particularly if it cannot be recognized and in areas of thin myocardium [Kellman et al. 2013 (30)].

Extracellular Volume fraction

ECV fraction is a marker of myocardial tissue remodelling: it is a measurement of the free water between myocardial and red blood cells. Its assessment requires measurement of myocardial and blood T1 before and after administration of contrast agents as well as the patient's haematocrit value (because it represents the cellular fraction of blood). [Haaf et al. (17)]

An increased ECV is most often due to amyloid and excessive collagen deposition, thus it is a more robust measure of myocardial fibrosis; low ECV values occur in thrombus and fat metaplasia. [Haaf et al. (17)]

T2 mapping

T2 relaxation is the time constant representing the decay of transverse magnetization (spin-spin relaxation) and its main biological determinant is the amount and macromolecular state of water. T2 mapping directly quantifies local myocardial inflammation and oedema: in their presence its value increases. As for T1 mapping, a series of T2-wheighted images is acquired to obtain the T2 decay curve and to create a pixelwise illustration. [Seraphim et al. 2020 (2)] (Figure 6)

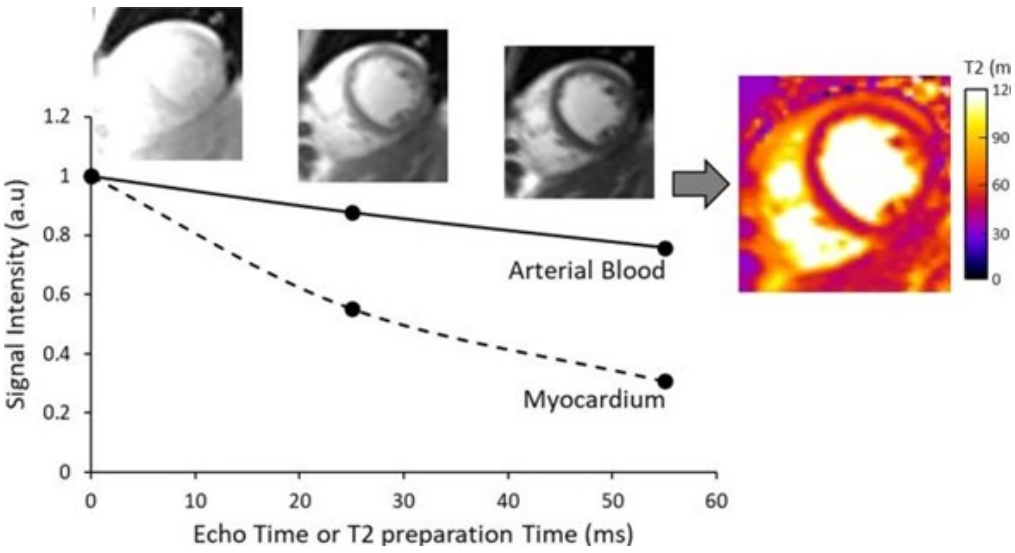


Figure 6: T2 map generation. [O'Brien A.T. et al. 2022 (31)]

This technique has been extensively studied in the diagnosis and risk stratification of patients with myocarditis. T2 mapping is also being explored in other inflammatory diseases including acute cardiac allograft rejection, sarcoidosis, sclerodermia, systemic lupus erythematosus, and acute infarction, with the potential of reducing the need for invasive cardiac biopsy in some scenarios. Elevated T2 mapping values compared with healthy controls have also been demonstrated in subsets of dilated cardiomyopathy and aortic stenosis,

potentially enabling disease substratification. [Seraphim et al. 2020 (2)] (Figure 7, Table I)

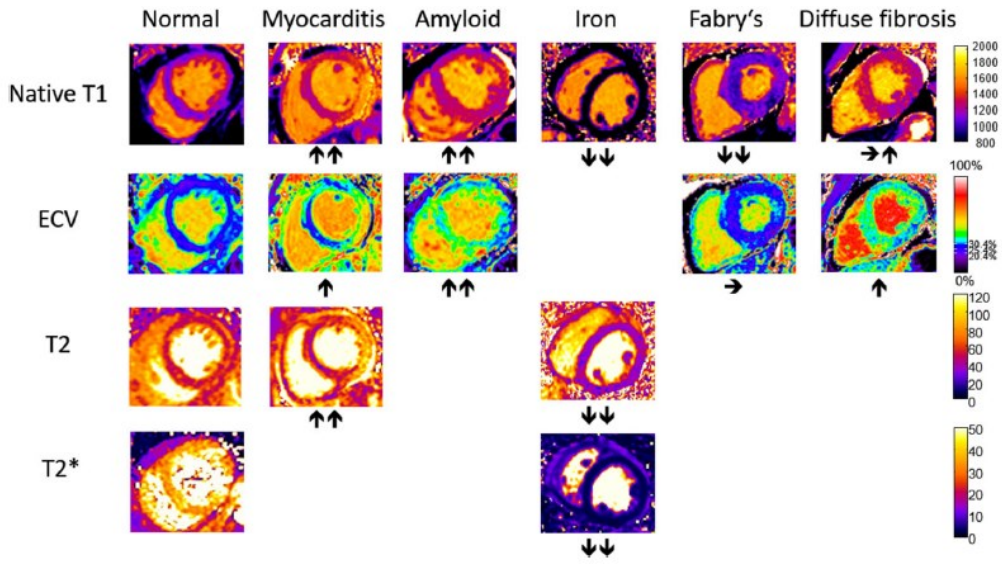


Figure 7: Typical appearance of T1, T2, T2, and ECV maps in healthy subjects and in patients with myocardial disease. [Messroghli et al., 2017 (6)]*

Table I: Typical alterations of T1, T2, T2 relaxation times and ECV according to pathology. [Messroghli et al., 2017 (6)]*

Measure	Decrease	Mild increase	Moderate or severe increase
Native T1	Anderson-Fabry, iron overload, fat, hemorrhage (athlete's heart)	diffuse fibrosis, scar, subacute inflammation	amyloid, acute inflammation, acute ischemia, necrosis
ECV	athlete's heart	diffuse fibrosis	amyloid, necrosis, scar
T2	iron, hemorrhage	subacute inflammation	acute inflammation, acute ischemia, necrosis

Two types of sequences can be used to obtain T2 mapping: dark-blood turbo spin-echo and bright-blood T2-preparation pulse-based sequences [Kim et al. 2017 (24)]. Turbo spin echo has some limitations that can influence negatively its performance; for example, it can cause through-plane motion artifact, with consequent myocardial signal loss, and the appearance of ghosting artifacts from blood flow, which may produce bright subendocardial rims [Giri et al. 2009 (32)].

On the other hand, the T2-preparation pulse-based sequences are less inclined to these artifacts [Giri et al. 2009 (32)]. They are based firstly on a preparation module made up of non-selective 90° and 180° pulses to create spin-spin relaxation between two 90° pulses. After that, the imaging sequence, consisting of either a balanced steady state free precession or a gradient echo sequence, is run immediately after the preparation. [Kim et al. 2017 (24)]. Images are acquired with different T2 preparation times (e.g. 0, 25, and 50 ms) and same trigger delay time, to ensure the same cardiac cycle phase during breath-hold [Giri et al. 2009 (32)]. Finally the T2 map is generated by a two or three-parameter fit model [Akçakaya et al. (33)] (Figure 8)

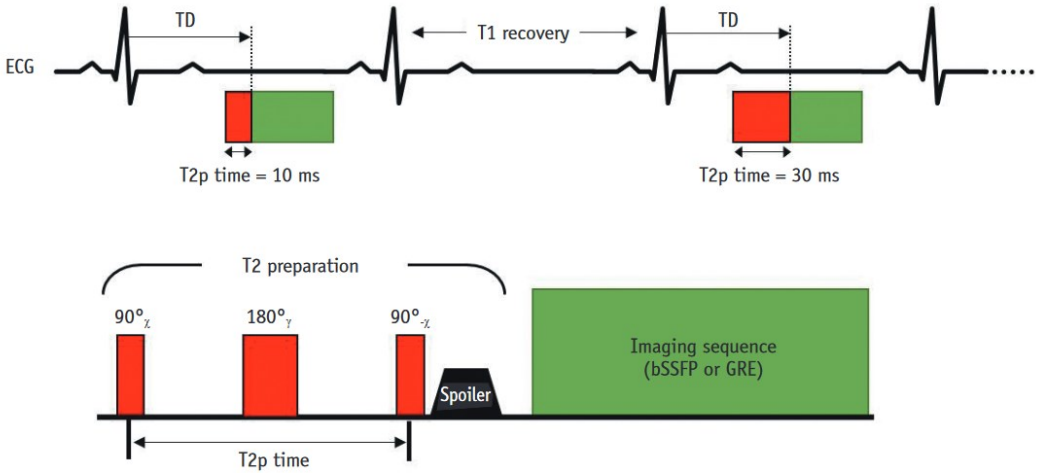


Figure 8: T2 mapping scheme with T2 preparation modules. ECG = electrocardiogram, GRE = gradient echo, SSFP = steady-state free precession [Kim et al. 2017 (24)]

Normal values

Myocardial tissue in healthy subjects exhibits a very uniform composition and thus possesses very regular magnetic properties. For this reason, T1 and T2 values from normal myocardium are highly reproducible and show relatively narrow ranges when acquired under the same conditions. Clinical recommendations published in 2017 by Messroghli et al. (6) emphasize the importance that measurements have to be made under the "same conditions", otherwise it becomes very difficult to determine if abnormal outcomes are due to a pathologic states or simply to a different way the measurement was performed. The main confounders can be

divided in two groups. The first one includes biological confounders, such as the magnetic field strength and body temperature: values are different if acquired in 1,5 T and in 3 T and T1 values increase almost by 1% for every 1°C increment in body temperature, while on the other hand T2 reduces in the same conditions. The second group is composed by methodological confounders: the acquisition and processing require many technical steps and each one of them has different types of error to the measurement. For example, inversion recovery Look-Locker based acquisition schemes for T1 mapping introduce a significant negative falsifying to T1 values if compared to saturation recovery sequences.

As a result, it is suggested to use a local reference range, established for the specific setup of the site, and compared to published reported ranges. This local reference range of values is calculated through the analysis of healthy volunteers, whose inclusion criteria should be normal electrocardiogram, no cardiovascular diseases, no cardiovascular symptoms or risk factors, no systemic diseases, normal renal function, and no contraindications to CMR.

Besides the aforementioned confounders, T1 and T2 values can also be influenced by gender and age. For example, Liu et al. (34) pointed out that in 1231 participants aged 54 to 93 years, women's native T1 was stable throughout different age groups, while on the other hand men had lower native T1 at 54 to 63 years that increased in higher age groups and reached that of women in the group of >84 years. Regarding T2 mapping, Bonner et al. 2015 (35) studied a large population of volunteers demonstrating that T2 values were increased in females subjects compared to males. Moreover, age was correlated with increasing T2 values. [Bonner et al. 2015 (35)]

However other studies posted in literature point out that age is not always associated with alterations in normal values as it was showed by Meloni et al. in 101 healthy volunteers (3) using a General Electric (GE) scanner. Despite this, they concluded that myocardial T1 values differ among myocardial regions, are influenced by sex, heart rate, and wall thickness, and vary according to the cardiac cycle in healthy adults. In fact, values were significantly lower in males than in females, significantly correlated with heart rate, inversely correlated with wall thickness, and significantly lower in the systolic phase [Meloni et al. 2021 (3)].

On the other hand, Meloni et al. (4) found the aging associated with increased segmental and global T2 values and no correlation to heart rate in 100 healthy volunteers using a GE scanner; females showed higher values than males and a significant inverse correlation was detected between global values and mean wall thickness.

The fact that age and gender can have such and influence in the definition of normal T1 and T2 values makes it mandatory to define specific gender and age-related segmental reference values in order to allow a better discrimination between healthy and diseased myocardium.

In our centre, the Radiology Institute of Padua University Hospital, the reference range of values regarding the machine in dotation (Siemens Magnetom Avanto Fit 1.5-T) has been calculated on 50 healthy volunteers. A stratified approach was adopted for recruitment, ensuring the presence of 5 participants for both sexes in each age decile: 20-29, 30–39, 40–49, 50–59, and 60–69 years. T1 and T2 mapping were generated using MOLLI sequences, and T2p-steady state free precession sequences, respectively.

CMR, CLINICAL APPLICATIONS IN SPORTS MEDICINE

Pre-participation cardiovascular evaluation for athletes

Sudden cardiac death in athletes is a relatively uncommon but devastating event. These deaths are highly visible in the public health debate because of significant media attention. Sports cardiologists from around the world have worked to identify risk factors and to develop pre-participation screening tools. Corrado et al. 2006 (36) published one of the first large scale studies of sudden cardiac death in athletes in the Veneto region of Italy. Over the final period of the study (2003 to 2004), the incidence of sudden cardiac death was 0.4 per 100,000 person years, whereas in the initial period (1979 to 1980), it was 3.6 per 100,000 person years with an average of approximately 2 deaths per year over the entire 26-year study period. [Corrado et al. 2006 (36)]

Italy has a long story in safeguard of athletes, in fact according to the 1982 Italian law, pre-participation protocol is mandatory and includes a constant-load ECG

stress test (EST), in addition to personal history evaluation, physical examination and resting ECG [“Decree of the Italian Ministry of Health, 18 February 1982. (37)]. The eligibility for competition is given in case of negative findings for cardiovascular diseases, otherwise further non-invasive examinations are required, such as echocardiography, 24h Holter, imaging stress tests, CMR or coronary computed tomography (CT), until invasive examinations as endomyocardial biopsy, electrophysiological studies or coronary angiography. [Biffi et al 2013 (38)]

In terms of medical history, in the young most conditions at risk of sudden death are usually genetically determined diseases with an autosomal dominant pattern. The family history is considered positive when close relatives had experienced a premature heart attack or sudden death or in the presence of a family history of hereditary diseases. The personal history is considered positive in the case of exertional chest pain or discomfort, syncope or near-syncope, irregular heartbeat, or palpitations and in the presence of shortness of breath or fatigue out of proportion to the degree of exercise. [Biffi et al 2013 (38)]

Positive findings during the physical examination include reduced and delayed femoral artery pulses, mid-systolic or end-systolic clicks, a second heart sound single or widely split and fixed with respiration, marked heart murmurs, irregular heart rhythm and brachial blood pressure more than 140/90 mmHg. [Biffi et al 2013 (38)]

However, most of the cardiovascular alterations observed in athletes may be suspected based on an abnormal ECG. The international criteria for ECG interpretation in athletes divides abnormalities in 3 groups according to their prevalence, their relation to exercise training, their association with an increased cardiovascular risk, and need for further clinical investigations to evaluate the presence of underlying cardiovascular disease. [Sharma et al., 2018 (39)]
The first group of ECG findings includes sinus bradycardia, first degree AV block, and early repolarization resulting from physiologic adaptation of the cardiac autonomic nervous system to training, such as increased vagal tone or reduced sympathetic activity. [Sharma et al., 2018 (39)] Another common finding is voltage criteria for left ventricular hypertrophy that reflects the physiological remodelling,

consisting of increased left ventricular wall thickness and chamber size. [Pelliccia et al., 2018 (40)]. These elements do not imply an increased cardiovascular risk, as they can be considered physiological adaptations to regular practice, hence in absence of symptoms with a negative family history they do not require further evaluation and are classified as “normal” [Sharma et al., 2018 (39)] .

It is important to clearly separate this situation from training unrelated ECG patterns, which are found less frequently, but can be an expression of cardiovascular disorders, cardiomyopathies, and cardiac ion channel diseases, with potential risk of sudden cardiac death during exercise. Examples of these abnormal findings are ST-segment depression and T-wave inversion, pathologic Q waves, major intraventricular conduction defects, ventricular pre-excitation, long or short QT interval, and ventricular arrhythmias [Sharma et al., 2018 (39)]. Borderline findings were previously categorised as normal but they actually may represent normal variants or the result of physiological cardiac remodelling in athletes and do not usually portray pathological cardiac disease [Sharma et al., 2018 (39)] (Figure 9)

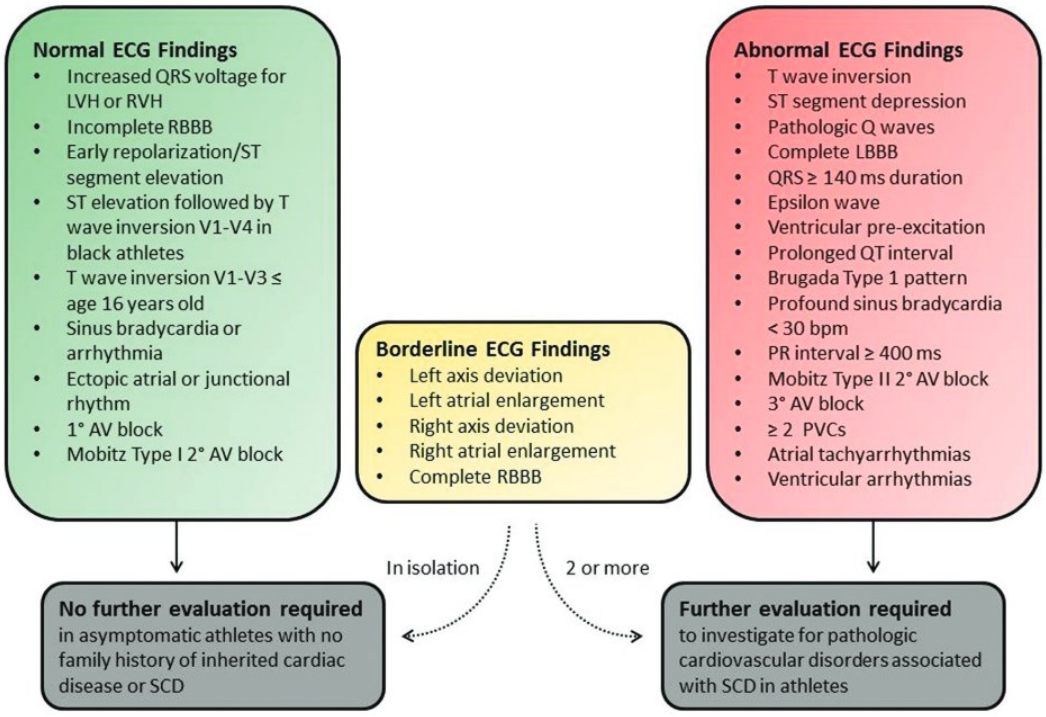


Figure 9: International consensus standards for ECG interpretation in athletes. AV = atrioventricular; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PVC = premature ventricular contraction; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; SCD = sudden cardiac death. [Sharma et al., 2018 (39)]

ECG should always be examined in relation with the athlete's gender, age and race, family history of cardiovascular disease, clinical symptoms, physical examination, and intensity of physical exercise [Sharma et al., 2018 (39)].

EST is performed by many sports medicine centres using a bicycle or treadmill and under continuous ECG monitoring. The main purpose of this exam is to reveal myocardial ischaemia and detect coronary artery disease. Moreover, it is useful the blood pressure behaviour, to evaluate symptoms occurring during physical activity, and to assess the physical performance and its progression in relation to exercise training and competitive sport participation. [Mont et al., 2017 (41)]. Another benefit is its ability to evaluate the appearance of arrhythmias. Zorzi et al. in 2020 (42) proved that, in young athletes, the use of exercise testing for the evaluation of ventricular arrythmias resulted in an increase of the diagnostic power of pre-participation evaluation (PPE) at the expense of an increase in false positive results. [Zorzi et al. 2020 (42)]

Prolonged ECG recordings are second line evaluations, they can provide data over extended and variable periods of time, allowing assessment of ECG during normal day life. Currently, useful tools are 24 h or 7-day ECG Holter or implantable devices lasting for more than 2 years. The most common indications for ECG monitoring are unexplained syncope and palpitations, although it could also be used to explore brady-arrhythmias or to quantify premature ventricular contraction density after initial PPE. Another application is QT assessment in patients with suspected long QT syndrome. [Mont et al., 2017 (41)].

The diagnostic benefit is highly dependent on the frequency of symptoms and the duration of the ECG recording. Certain times, for example in PVB quantification, 24 h recording might be enough to obtain the necessary information. At the same time infrequent signs or symptoms are rarely reproduced during a 24 or 48 h recording and show a very low sensitivity, while longer recording periods can detect them more successfully. [Mont et al., 2017 (41)]

Trans thoracic echocardiography (TTE) is a useful tool for the evaluation of athletes who are labelled by the initial PPE as potential carriers of cardiac disease. (Table II). It is frequently used because it is widely available, portable and of relatively low cost, and it can be a useful tool to detect cardiomyopathies, aortic aneurysm, and bicuspid aortic valve. However, if compared to CMR, TTE has important limitations regarding image quality and the analysis of the morphology and function of all cardiac chambers while still not allowing the assessment of acute oedema and myocardial fibrosis.

Despite current recommendations, it is increasingly being used as a first line examination in PPE in various populations, including professional and amateur athletes. Contemporary studies in healthy children and young athletes have confirmed that the addition of echocardiography as a first-line screening tool to the 12-lead ECG does not increase the diagnostic potential of cardiomyopathies. In addition, elite athletes may express a cavity dilatation and left ventricular (LV) hypertrophy that overlaps with mild or incomplete phenotypes of cardiomyopathies, raising concerns that echocardiography may increase false positive results in PPE. In conclusion, the value of echocardiography as a first-line screening tool remains to be proven, mainly because of the absence of evidence for incremental diagnostic value compared to ECG alone. [Mont et al., 2017 (41)]

CMR represents a valuable imaging method in the study of athletes and has an important role in the evaluation of cardiac disease especially when the sports clinician meets symptoms such as syncope, chest pain or uncommon ECG findings. Table II shows some clinical indications to perform CMR in athletes. The main diagnoses relevant for a CMR study are: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC), left ventricular non-compaction (LVNC), bicuspid aortic valve, aortic root diseases, myocarditis, pericarditis, and ischaemic heart disease. [Pelliccia et al., 2018 (40)].

It has the distinct advantage of being able to provide high-quality images in all subjects and giving details of regions of the heart which are difficult to image with echocardiography. In fact, CMR is not limited by the echocardiographic windows, which is a clear advantage when attempting to visualize the heart through a

muscular athletic body. [Fogel, 2008 (43)]. In particular, CMR enables greater visualization of the LV apex and RV, and it can identify pathology in athletes when the ECG and echocardiography appear to be normal. [Mont et al., 2017 (41)] Moreover, ventricular function, flow, and velocity can be measured accurately without assumptions as opposed to echocardiography, where generally geometric assumptions are made for the ventricle and physiologic and geometric assumptions are made to turn velocity into flow. [Fogel, 2008 (43)]

In sports medicine, CMR can be used for many aims, for example:

- Assessment of symptomatic athletes. A subject that has a syncopal episode or has chest pain can undergo CMR to assess for hypertrophic cardiomyopathy, anomalous coronary origins, or to aid in the diagnosis of arrhythmogenic right ventricular dysplasia, to name a few possibilities in the differential diagnosis. [Fogel, 2008 (43)]
- Assessment of the non-athlete to play sports. If there is a suspicion of cardiovascular disease in the patient or a family history that raises the spectre of possible danger to the individual in playing sports, CMR can be used to screen the individual prior to allowing activities after the usual mandatory PPE. [Fogel, 2008 (43)]
- Assessment of patients with cardiac disease to play sports. Patients with aortic insufficiency, aortic stenosis, and so on can undergo CMR to follow the anatomic makeup of the lesion and to quantitate hemodynamic in order to determine whether it is safe to play sports [Fogel, 2008 (43)]. A further example is return-to-play cardiac testing program during Sars-CoV-2 disease pandemic given the unknown incidence of adverse cardiac sequelae after infection in athletes.

Table II: Clinical indications to perform cardiovascular imaging studies in athletes. [Pelliccia et al. 2018 (40)]

Clinical history:	**Imaging tests of choice**	**Heart disease**	**Additional testing**
SCD in the family	Echocardiography	Cardiomyopathies	Clinical and genetic family screening in selected cases
Known cardiomyopathy in the family	CMR	Mitral valve prolapse	
Palpitations	Echocardiography	Cardiomyopathies	Consider 24-h and/or long-term ambulatory ECG monitoring and/or electrophysiological study in selected cases
Syncope	CMR	Coronary artery disease/ anomalies	CT according to clinical suspicion Consider stress echo to rule out LV outflow obstruction
Chest pain	Echocardiography	Coronary artery disease/ anomalies	Consider the risk profile, age and radiation exposure
	CMR CT Nuclear imaging		Consider exercise stress imaging
Physical examination	**Imaging tests of choice**	**Heart disease**	**Additional testing**
Cardiac murmurs Abnormal cardiac sound	Echocardiography	Valvular heart disease Congenital heart defects	Additional tests on the basis of echocardiographic findings and clinical suspicion (e.g. CMR)
Marfanoid habitus	Echocardiography CT CMR	Marfan disease	Clinical and genetic family screening Accurate evaluation of thoracic aorta
12-leads electrocardiogram	**Imaging tests of choice**	**Heart disease**	**Additional testing**
T-wave inversion	Echocardiogram CMR	Cardiomyopathies Myocarditis	Clinical and genetic family screening Annual follow-up with imaging tests in athletes with normal findings at initial evaluation
ST-segment depression	Echocardiogram CMR	Cardiomyopathies Myocarditis Coronary artery disease Valve disease	Consider exercise stress imaging Coronary CT or nuclear imaging in athletes with clinical suspicion of coronary artery disease
Pathologic Q-waves	Echocardiogram CMR	Cardiomyopathies Myocarditis Coronary artery disease	Consider exercise stress imaging Coronary CT or nuclear imaging in athletes with clinical suspicion of coronary artery disease
Complete LBBB	Echocardiogram CMR CT Nuclear imaging	Cardiomyopathies Myocarditis Cardiac sarcoidosis Valve disease Coronary artery disease/ anomalies	Comprehensive cardiac evaluation for exclusion of heart disease Consider exercise stress imaging
Bifascicular block (RBBB and left anterior hemiblock)	Echocardiogram	Cardiomyopathies Myocarditis Cardiac sarcoidosis Coronary artery disease	Additional tests on the basis of echocardiographic findings and clinical suspicion
Non-specific intraventricular conduction delay	Echocardiogram	Cardiomyopathies Coronary artery disease/ anomalies	Additional tests on the basis of echocardiographic findings and clinical suspicion
Minor non-voltage criteria for LV or RV hypertrophy (atrial enlargement and QRS axis deviation)	Echocardiogram	Cardiomyopathies Valve disease Congenital heart disease Pulmonary hypertension	Additional tests on the basis of echocardiographic findings and clinical suspicion
Abnormal exercise testing (repolarization abnormalities/ symptoms/arrhythmias)	Echocardiography	Coronary artery disease/ anomalies	Consider the cardiovascular risk profile and age
	CMR		Consider also exercise stress imaging
	CT Nuclear imaging	Cardiomyopathies Myocarditis	Low-radiation examinations advised in young individuals

Athlete's heart

The main concern in Sports Medicine is that athletic training is associated with morphologic and functional cardiac adaptations which are part of what is known as the athlete's heart (AH). A vast amount of literature has been collected over the years, allowing an improvement in the understanding of the characteristics of this para-physiologic cardiac remodelling. [Pelliccia et al. 2018 (40)] In such a case,

CMR is particularly convenient to investigate changes of cardiac structure and function.

In general, athletes have an increased cardiac preload and afterload followed by symmetrical expansion of all cardiac chambers. [Luijkx et al., 2012 (44)]. Their LV wall thickness is usually increased of 10-20% and both left, and right ventricular cavity size are 10-15% higher compared with individuals of similar age and size. They also display an elevate cardiac filling in diastole, augmented stroke volume, and an increased oxidative capacity and capillary conductance within the skeletal muscle which results in high-peak oxygen consumption during exercise [Sharma et al., 2015 (45)]

The athlete's heart most of the time is associated with normal ECG findings and they do not imply an increased cardiovascular risk in these subjects if they are asymptomatic and with a negative family history. [Pelliccia et al., 2018 (40)]

The alterations in the athlete's heart are attributable to the subject's characteristics (BSA, sex, age, ethnicity) and the type of sport, its training characteristics, intensity, and years of activity, with a "dose-effect" relation. Figure 10 shows the impact of different clinical variables on LV end-diastolic cavity dimensions in a large population of male and female elite athletes. [Maron e Pelliccia, 2006 (46)].

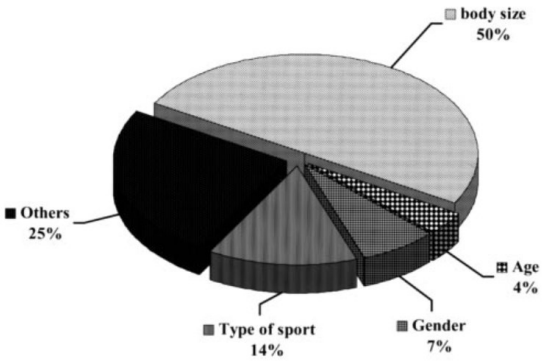


Figure 10: Impact of different clinical variables on LV end-diastolic cavity dimensions in a large population of male and female elite athletes. [Maron e Pelliccia, 2006 (46)]

Professional athletes usually train intensively more than 10-15 hours per week. Such high levels of exercise require an increase in cardiac output for prolonged

periods that causes electrical, structural, and functional cardiac modifications [Pelliccia et al. 2018 (40)]. Morganroth et al. in 1975 (47) have been the first to describe differences in cardiac adaptations in relation to the type of sport: they observed a concentric LV hypertrophy in “endurance” sports and an eccentric hypertrophy in “strength” disciplines (47). (Figure 11)

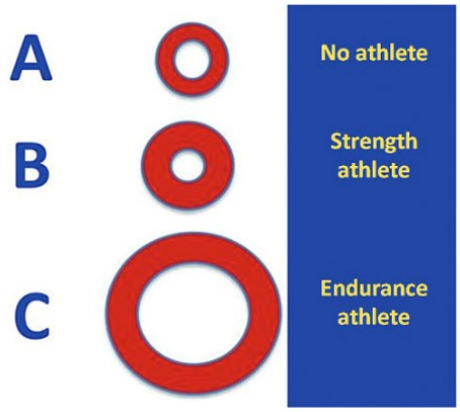


Figure 11: Morganroth hypothesis. [Galderisi et al., 2015 (48)]

However, this model was not suitable for many other sports because each of them has a varying degree of both isometric and isotonic component. For this reason, other classifications based on the main physiologic characteristics of the exercise have been suggested. In Italy the main guidelines in disciplines classifications have been drawn up by COCIS (Comitato Organizzativo Cardiologico per l’Idoneità allo Sport) [COCIS 2017 (49)] (Figure 12):

- Sports in which the most important elements are technical abilities or the athlete’s skills are classified as group A. Golf, archery, horse riding etc. are some examples. These disciplines trigger the autonomic nervous system, causing an increase of heart rate and blood pressure for certain periods of time separated by long or short resting pauses. The hemodynamic overload is low or absent, so the heart doesn’t usually undergo morphological adaptations. [COCIS 2017 (49)]
- Strength disciplines with static muscular work characterised by short bursts of intensive anaerobic effort, such as body-building, short distance running or swimming, artistic gymnastics, climbing, synchronized

swimming etc. are group B [COCIS 2017 (49)]. Myocardial mass increases due to an expansion in wall thickness, whereas ventricular volumes are only slightly higher. [Pelliccia et al. in 1993 (50)]

- Group C gathers most of the sports, especially those that require the use of a ball like football, rugby, tennis, basketball, handball, but also dance sport, martial arts, boxing, ice hockey, fencing etc. These disciplines have combined elements of aerobic and anaerobic metabolisms. High intensity training alternated with recovery periods causes a higher preload alternated with an increased afterload. The heart turns out to have larger endocavitary dimensions followed by an increase in LV wall thickness, whose amount is still lower than endurance sports. [COCIS 2017 (49)]
- Group D includes sports disciplines with isotonic and dynamic muscular activity and aerobic commitment. Some examples are swimming, long distance running, triathlon, roller skating etc. Athletes in this category usually face an increase of cardiac output due to a raise of preload, which consequently increases all the heart's endocavitary dimensions, followed by thickening of the LV wall. [COCIS 2017 (49)]
- Endurance disciplines that massively stress both aerobic and lactacid anaerobic metabolism, and increase peripheral resistances and afterload are classified as group E [COCIS 2017 (49)]. Cycling, rowing, canoeing, biathlon, speed ice skating, mountain run etc. are part of this category and they cause a greater increase in wall thickness, as demonstrated by Pelliccia et al. in 1991 (51).

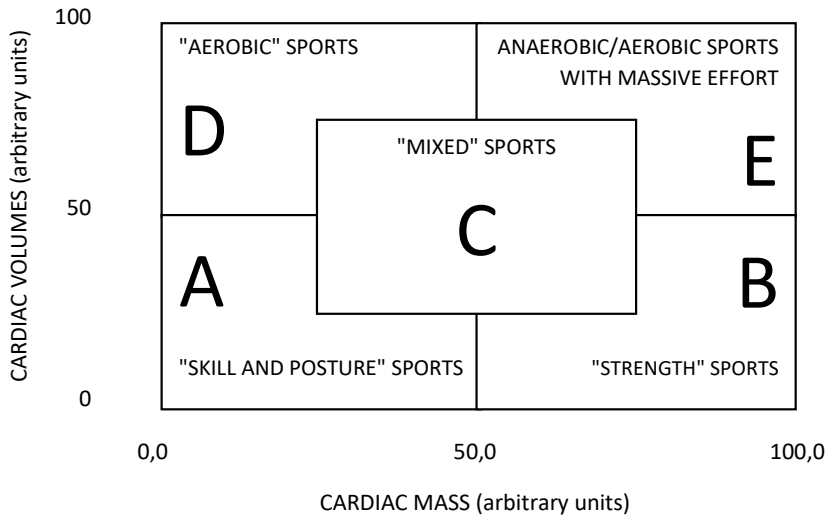


Figure 12: COCIS Classification 2017. Simplified diagram representing the 5 groups in which sports are divided based on cardiac volume and mass adaptations. (49)

Caselli et al. in 2011 (52) pointed out that regardless of the type of exercise, the ratio between LV mass and end-diastolic volume remains constant. Therefore, most sport disciplines cause a balanced and harmonic remodelling of physiologic LV hypertrophy. [Caselli et al. 2011 (52)]

The haemodynamic overload caused by endurance training is responsible for higher left and right atrial volume and right ventricular size as well. On the other hand, strength training does not seem to change left atrial or right ventricular size substantially. [Pelliccia et al., 2005 (53)' D'Andrea et al., 2010 (54)]. Endurance disciplines are also associated with an increase in aortic root dimensions, while power disciplines have an insignificant impact. [Pelliccia et al., 2010 (55)].

In summary, athletes are always characterized by a balanced increase in the dimension of all cardiac chambers with normal heart function; on the contrary, an unbalanced remodelling suggests a pathological process. Reasons of unbalanced remodelling can be cardiomyopathies, shunts and doping substances (mostly anabolic androgenic hormones, peptide hormones, growth factors, erythropoietin or its derived, and stimulants) [Pelliccia et al., 2018 (40)].

The sizes of these physiological adaptations are lower in adolescent athletes who are generally physically less mature and have trained for shorter periods. [Makan et al., 2005 (56)]. The LV wall thickness is usually within the normal accepted ranges for the sedentary population (8-12 mm). Only 2% of Caucasian athletes

show LV wall thickness higher than 12 mm and such dimensions are typical of male athletes. [Pelliccia et al. in 1991 (51)]. At the same time, LV hypertrophy >12 mm is relatively common in black male athletes. [Basavarajaiah et al., 2008 (57)]

Despite the improving knowledge about physiological cardiac remodelling in highly trained subjects, there are still various uncertainties in the differential diagnosis of the athlete's heart with other cardiac diseases, for example hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC) and left ventricular non-compaction (LVNC) cardiomyopathy. The difficulty is given by the fact that many of the morphological adaptations are shared both by the athlete's heart and some of these conditions. (Figure 13). The implications of an incorrect diagnosis either as athlete's heart or other diseases, may lead to unnecessary exclusion from sport or sudden cardiac death if undertaking exercise. [Pelliccia et al. 2018 (40)]. The published literature has recently started to focus on the use of T1, ECV and T2 mapping aiming to close these gaps in diagnostic accuracy.

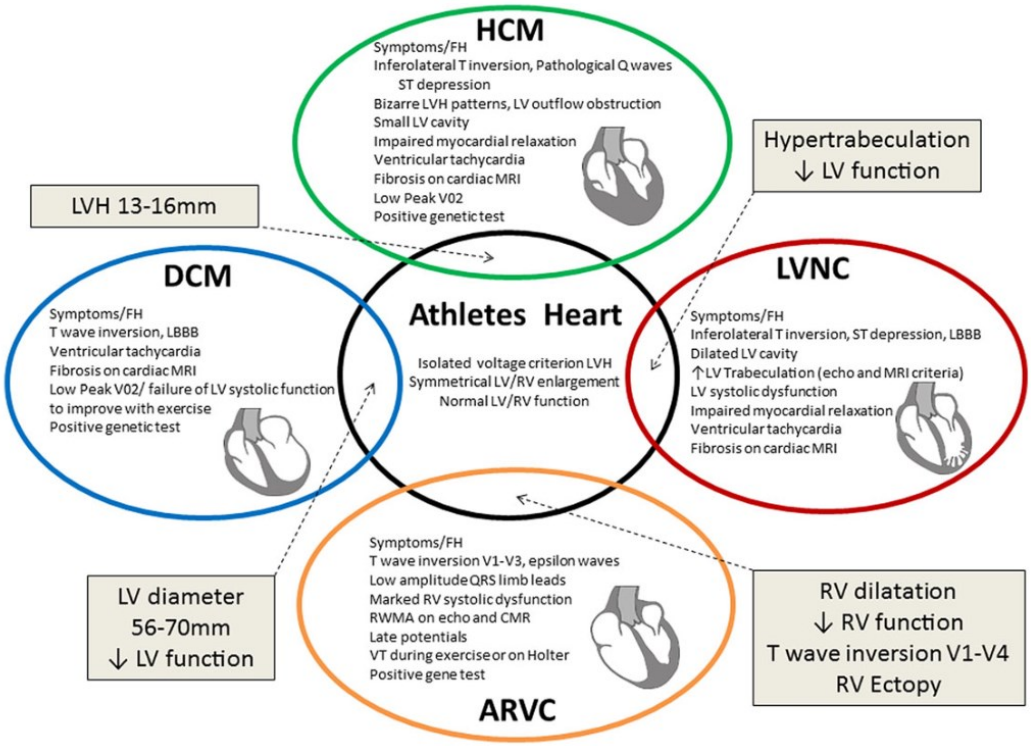


Figure 13: Different features between athlete's heart and cardiomyopathy. Sharma et al., 2015 (45)

CMR imaging in athletes

Left and right ventricular volumes and mass, as well as global and regional contractile function, can be accurately assessed with steady state free precession (SSFP) cine sequence. [Scharf et al. 2010 (58)]. LGE technique is very useful to determine myocardial fibrosis and is usually used to search for myocardial scar and to evaluate cardiomyopathies. [Vogel-Claussen et al. 2006 (10)]. LGE also differentiates between athlete's heart and other diseases, even though small areas of fibrosis have been occasionally reported in endurance athletes without other obvious disease [Breuckmann et al., 2009 (59)]. Myocardial fibrosis can have both ischaemic and non-ischaemic patterns, the latter is ulteriorly made up of different sub patterns which can better distinguish different diseases. As an example, in normal hearts common non-ischaemic LGE patterns involve the mid-wall and the sub-epicardium, highlighting inflammatory disease-related necrosis or scars (myocarditis, sarcoidosis, and collagen vascular diseases). On the other hand, presence of LGE in a dilated left ventricle suggests acute or subacute inflammatory diseases like dilated cardiomyopathy. [Satoh et al., 2014 (60)]

Several studies suggested that prolonged and extensive physical activity might lead to increased prevalence of myocardial fibrosis in athletes. These alterations were shown to be only transient and do not persist long term. Traditionally, the detection of myocardial fibrosis in CMR is done acquiring images 8 to 15 minutes after the administration of a gadolinium-based contrast agent. While this technique can detect the focal macroscopic myocardial fibrosis, it cannot detect the diffuse interstitial fibrosis. Up to now, most of the CMR studies on fibrosis in athletes were based only on LGE detection, but recently there are studies incorporating T1 mapping and ECV calculation, which are better ways to assess interstitial fibrosis. [Malek et al. 2020 (61)]

Most of the studies demonstrate that endurance exercise does not lead to an increase of ECV or is related to only slight increase, with its absolute values remaining within the reference range for the normal population. For instance, Mordi et al. (62) searched for elements in T1 and T2 mapping that could be able to differentiate between patients with LV dilatation due to early dilated cardiomyopathy (DCM) and athletes. DCM is typically characterized by a dilatation

of the left ventricle with an impairment of systolic function in the absence of significant obstructive coronary artery disease and in presence of normal wall thickness. LV dilatation, despite being considered as the distinctive sign of DCM, it can also be found in the athlete's heart. In fact, endurance exercise typically causes LV dilatation with an increase in end-diastolic diameter, volume, and mass, leading to a reduction in left ventricular ejection fraction (LVEF). For these reasons, the use of criteria such as LVEF, could not be enough to discriminate between early DCM and physiological adaptation to exercise. Moreover, the presence of LGE can be found both in DCM and in healthy older marathon runners. They demonstrated that T1, T2 mapping and ECV calculation can be very useful to differentiate between athlete's heart and DCM and they are also able to assess diffuse myocardial fibrosis missed by LGE.

Tahir et al. 2018 (63) likewise investigated the presence of myocardial fibrosis in competitive triathletes detected by LGE in correlation with the performance. They showed that triathletes with presence of LGE had higher ECV in LGE negative areas of myocardium, indicating diffuse myocardial fibrosis in these subjects, while LGE negative athletes had normal ECV. This suggests that fibrosis might not be limited to the macroscopically visible areas of non-ischemic LGE in these individuals. They also found lower native T1 values in male and female triathletes than in controls. [Tahir et al. 2018 (63)]

Another study compared 40 healthy middle-aged endurance athletes with a minimum of 10 years of competitive endurance sport history with 8 recreationally active control subjects. It demonstrated that endurance athletes had a higher ECV fraction as opposed to recreationally active adults, while still being within the normal range. [Banks et al. 2017 (64)]

Another study by [Görmeli et al. 2016 (65)] showed that in athletes who had more than 5 years of sports activity, there was a raise in the interventricular septum thickness and in the T1 mapping values compared to the LV global values, with a significant positive correlation when compared to athletes who had less than 5 years of sports activity. Therefore, the authors suggest that evaluating the interventricular septum with native T1 mapping can provide important hints about

cardiac remodelling, because native T1 values may be affected more significantly than it would in the remaining myocardium.

All these observations were based on asymptomatic athletes; nevertheless, CMR is currently an important second line imaging test in athletes with specified cardiomyopathy. The study by Mordi et al. (62) quoted earlier gave important information about the use of T1 and T2 mapping to differentiate athlete's heart and dilated cardiomyopathy, but as said only athletes with no symptoms were selected.

Differential diagnosis is challenging also between athlete's heart and hypertrophic cardiomyopathy (HCM). It has been demonstrated that HCM has higher values of T1, T2 mapping and ECV compared to athlete's heart. For example, [Gastl et al. 2021 (66)] demonstrated that T2 values were significantly increased in HOCM and HNCM, while AH showed no difference from its respective controls. In segmental analysis, the difference of T2 values was greater for the anterior and anteroseptal basal interventricular septum (segments 1 and 2), especially it was most pronounced in segment 2. There was also a difference in the inferolateral and anterolateral basal segments (segments 5 and 6) between HOCM and AH. (Figure 14) [Gastl et al. 2021 (66)]

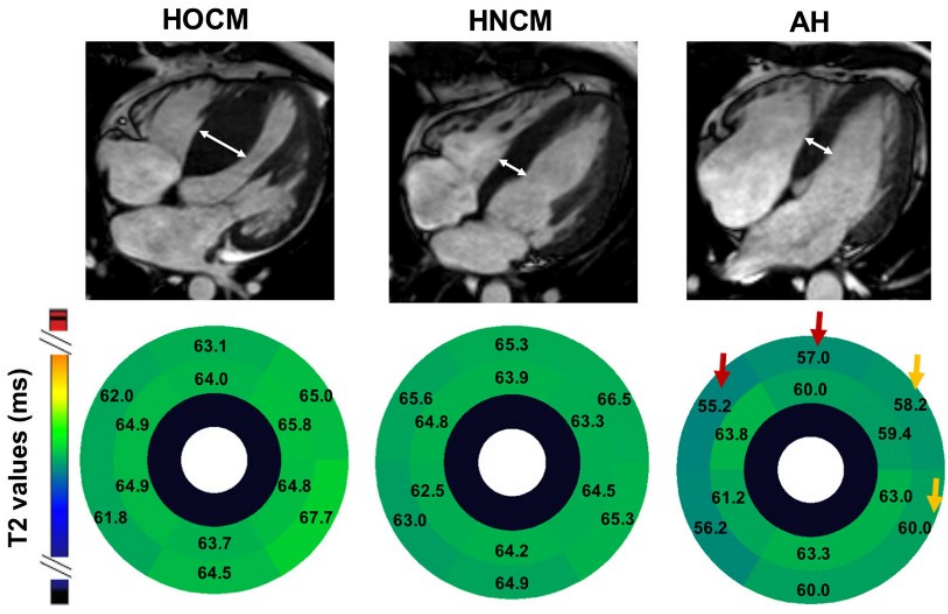


Figure 14: Segmental analysis of T2 values. Red arrows indicate reduced T2 values compared with both entities of LVH, orange arrows to only HOCM. AH: athlete's heart; HOCM: hypertrophic obstructive cardiomyopathy; HNCM: hypertrophic non-obstructive cardiomyopathy

Based on the results they also identified cutoffs values for an better differentiation between HCM and AH. T2 cutoff value of > 61.4 ms (sensitivity 67%, specificity 83%) discriminated AH from HOCM/HNCM. However these limits are hardly reproducible in other centres, given the fact that every site has its specific values. The published literature suggests that T1 mapping can also be used for the evaluation of LVNC because its values are higher compared with normal controls, even in the absence of LGE. [Fogante et al. 2021 (67)]

Depending on what has been presented so far, it could be said that the increased availability and use of CMR and parametric imaging is likely to identify small volume of diffuse fibrosis of uncertain significance in a considerable proportion of athletes. In any case the index of suspicion, regarding potential cardiac disease, should increase if abnormal ECG or the presence of arrhythmias accompanies the detection of fibrosis. Cipriani et al. in 2019 (68) performed CMR in athletes from 15 to 50 years old who suffered of frequent or repetitive premature ventricular beats (PVBs). It showed that pathological myocardial substrates on CMR were observed significantly more often in athletes with exercise induced ventricular arrythmias (EIVA) compared to those with non-EIVA. Moreover, the athletes with the highest probability of CMR abnormalities presented repolarization abnormalities on basal ECG and complex EIVA with a right-bundle-branch-block or polymorphic morphology.

Crescenzi C et al. 2021 (69)(69) tried to determine which type of premature ventricular beat predicted a higher probability of pathological CMR findings in athletes with ventricular arrythmia and negative family history, no previous cardiac arrest or sustained ventricular tachyarrhythmia and unremarkable electrocardiographic or echocardiographic findings. PVBs are not rare in competitive athletes, thus recently criteria for differentiating between common and uncommon PVBs have been proposed, with the aim to restrict CMR prescription to high-risk athletes. Common ones are usually benign, while uncommon PVBs are potentially associated with heart disease. This study confirmed that negative ECG and echocardiography cannot definitely rule out an underlying structural myocardial abnormality in athletes with ventricular

arrythmia. CMR has a higher sensitivity for detecting myocardial abnormalities such as non-ischemic LV scar [Crescenzi et al. 2021 (69)]. As mentioned earlier in the previous studies, T1 mapping and ECV are frequently able to detect diffuse myocardial fibrosis missed by LGE. For this reason, it is possible to hypothesize that different PVBs can correlate with parametric imaging abnormalities.

AIMS OF THE STUDY

CMR represents the gold standard imaging method for tissue characterization and can offer a significant contribution to the assessment of both cardiac structure and function to help in the evaluation of the athlete or patients with heart disease who are interested in playing sports.

Conventional non-parametric CMR techniques require a reference tissue, such as normal myocardium, to detect alterations of myocardial tissue composition. The direct quantification of myocardial tissue properties, using T1, T2 mapping and ECV, eliminates the need for such a reference tissue, which makes parametric mapping the main tool that allows direct assessment of diffuse myocardial disease.

The aims of this study are:

- the comparison between T1 and T2 mapping values determined in an athletes' population consecutively referred to our Institute for pathological suspects and the reference values calculated on healthy volunteers in the same centre.
- the comparison between parametric *versus* non-parametric sequences in the above-mentioned study population.
- the assessment of the correlation between CMR findings and clinical/instrumental characteristics of the above-mentioned study population.

MATERIALS AND METHODS

STUDY POPULATION

We evaluated the first 50 competitive athletes consecutively underwent CMR for pathological suspects in our centre since November 2021.

All subjects were addressed to CMR following the completion of the protocol for cardiovascular evaluation to be eligible to compete in a sport activity as established by Italian law ["Decree of the Italian Ministry of Health, 18 February 1982." (37)]. According to this protocol, cardiovascular evaluation includes personal history, physical examination, resting 12-lead ECG and ECG stress test (EST). The indication for CMR was based on positive findings in basal ECG, EST, echocardiography, or Holter-ECG.

Data regarding sex, age, height, weight, body surface area (BSA), body mass index (BMI), cardiological history and examinations were collected.

A questionnaire about the sport activity containing the following questions was submitted to the patients:

- "What sport do you practise? Which specialty?"
- "For how long have you been practising this sport?"
- "For how many hours per week?"
- "Do you practise another sport contemporaneously? If yes, for how many hours per week?"
- "Have you practised another discipline before? If yes, for how many years?"

Subjects were also asked if they had been infected by Sars-CoV-2 before the exam and when, and if they were affected by other diseases.

All patients were informed about the exam protocol and signed written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

CARDIAC MAGNETIC RESONANCE AND ANALYSIS

CMR was performed on a 1.5-T MRI-system (Siemens Magnetom Avanto Fit) at the Radiology Institute of Padua, University Hospital. All image analyses were performed using cvi42 software (Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada).

Functional and structural assessment was determined by cine steady-state free precession (SSFP) images in standard long-axis geometries (two, three, and four-chamber view) as well as in sequential 8 mm short-axis slices from the atrioventricular ring to the apex to assess biventricular function parameters quantitatively in a standard way [Aquaro JMRI 2016 (1)]. Thirty cardiac phases were acquired per heartbeat. The sequence parameters were as follows: flip angle 55°, matrix 304 x 207 pixels. Cine MR sequences allowed the assessment of the regional myocardial kinetic through the evaluation of the systolic-to-diastolic wall thickness changes. The wall kinetic abnormalities were defined according to international guidelines as hypokinesia (decreased wall motion), akinesia (absent wall motion), and dyskinesia (uncoordinated wall motion).

Calculations involved indexed to body surface area and absolutes values of the left and right ventricular end-diastolic volume (EDV), end-systolic volume (ESV), mass and wall thickness. They also included left and right ventricular stroke volume, cardiac output (CO), and ejection fraction (EF), left and right atrium area, and LV wall thickness. The results for patients older than 19 years old were confronted with normal reference values classified for different age groups and sex reported by Maceira et al. in 2006 (70), (71). As for patients younger than 18 years old, reference values from Robbers-Visser et al. 2009 (72) were employed.

Atrial areas were measured from the 4-chamber view projection in ventricular end-systolic phase. The limit to define left and right atrium areas as increased was considered 15 mm^2/m^2 [Maceira et al. 2010 (73), Maceira et al. 2013 (74)].

T2 inversion recovery magnitude (TIRM) sequences were acquired to evaluate the presence of oedema, if clinically indicated. The sequence parameters were as follows: flip angle 180°, matrix 256 × 256 pixels, slice thickness = 8 mm. The presence of edema was firstly assessed qualitatively by visual analysis, and it was

considered present when visualised in two different views and confirmed by a semi-quantitative analysis (signal intensity more than 2 standard deviations-SD above the mean value of skeletal muscle). Moreover, the TIRM sequences were evaluated semi-quantitative by measuring the T2 ratio between myocardial muscle and skeletal muscle. The T2 ratio calculations were made in 9 different slices: 3 basal, 3 mid-cavity and 3 apical. Cut-off for normal values was 1.9 [Abdel-Aty et al., 2005 (75)].

The basal perfusion was assessed by first-pass perfusion technique using saturation-prepared T1-weighted fast gradient-echo sequence of 3 short-axis views of the left ventricle (basal, mid-cavity and distal), after the intravenously administration of administration of Gadobutrol (Gadovist®; Bayer) at a dose of 0.1 mmoL/kg. The acquisition parameters were; matrix = 160 x 100 pixels; slice thickness = 8 mm.

LGE short-axis, vertical, horizontal, and oblique long-axis images were acquired by a T1-weighted gradient-echo inversion-recovery sequence in the same spatial position used for SSFP images, 8-20 min after Gadobutrol (0.1 mmoL/kg before the perfusion sequences and 0.1 mm/Kg immediately after the perfusion sequences). Inversion times were adjusted to null for the normal myocardium (from 210 ms to 300 ms) with voxel size of 1.6 x 1.6 x 8.0 mm. The presence of LGE was assessed qualitatively using a two-point scale (enhancement absent or present). Enhancement was considered present whenever it was visualized in two different views. Positive LGE findings were assessed as ischemic, non-ischemic or mixed. Ischemic sub-patterns were either transmural or non-transmural, while non-ischemic sub-patterns were mid-wall, subepicardial or junctional.

Native and post-contrast T1 mapping were generated using MOLLI sequences [pre-contrast 5s(3s)3s, post-contrast 4s(1s)3s(1s)2s] with shortened inversion pulse for improved efficiency and reduced T2 dependence. MOLLI post-contrast images were acquired 10 minutes after the intravenous administration of Gadobutrol (Gadovist®; Bayer) at a dose of 0.2 mmoL/kg (0.1 mmoL/kg before the

perfusion sequences and 0.1 mm/Kg immediately after the perfusion sequences). The acquisition parameters were: pixel bandwidth 1085 Hz/pixel; echo time = 1.15 ms; flip angle = 35°; matrix = 256 x 124; slice thickness = 8 mm. Inline motion correction and a non-linear least-square curve fitting were performed with the set of images acquired at different inversion times to generate a pixel-wise coloured T1 map.

For myocardial T1 analysis, epicardial and endocardial contours were drawn on the 3 MOLLI short axis slices using an artificial intelligence algorithm provided by the cvi42 software with manual adjustment if needed. In order to avoid confounders, with blood partial voluming and epicardial being a particular concern, an off-set erosion of 20% was applied on both the endocardial and epicardial borders using a function of the software. These endocardial and epicardial borders were then copied on to MOLLI post- contrast T1 maps with manual adjustment if needed.

For the blood analysis, a ROI was drawn in the LV blood pool of the 3 short axis slices of the pre-contrast MOLLI T1 map and care was taken to avoid papillary muscles. This ROI was then copied on to the post-contrast MOLLI images. ECV was calculated using the mean segmental pixel value from the MOLLI ECV maps and using the formula ECV = (D[1/T1myo]/D[1/T1blood]) * [1-Hct]).

ECV values were obtained using haematocrit of the patient, performed within 6 days before the CMR examination. Based on the literature data from Siemens scans, ECV values comprised in the range 26.8-27.9% were considered normal [Rosmini et al. in 2018 (76)].

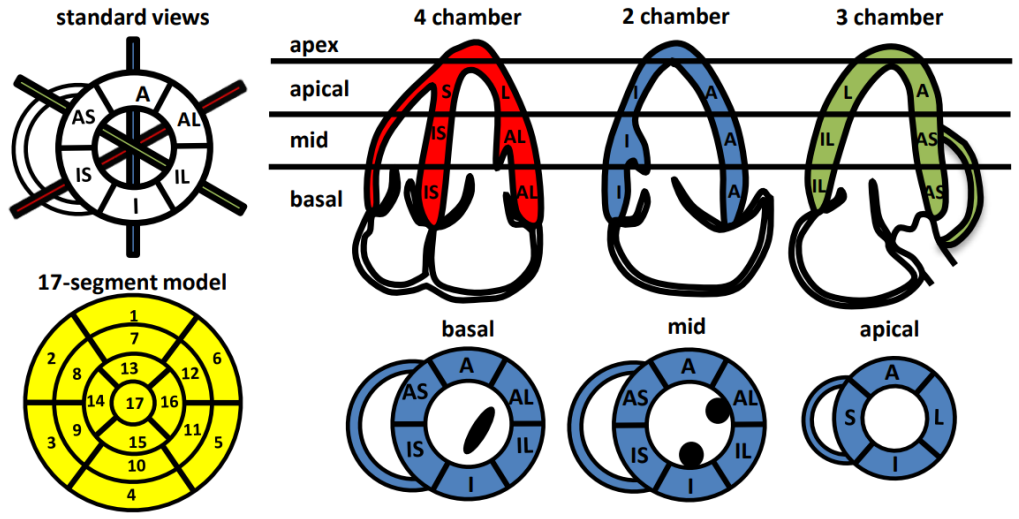
For T2 mapping imaging, three parallel sections (basal, mid-cavity and distal), were acquired using short axis T2p-SSFP end expiatory breath-hold sequences and telediastolic cardiac gating. The technique involved a black blood preparation pulse (double inversion recovery), followed by 3 echo times (TE) at 0 ms, 25 ms and 55 ms. The acquisition parameters were: flip angle (α) = 70°; matrix = 256 x 256; slice thickness = 8 mm. For myocardial T2 analysis, epicardial and endocardial contours were drawn on the 3 short axis slices using an artificial intelligence algorithm provided by the cvi42 software with manual adjustment if needed. In

order to avoid confounders, with blood partial voluming and epicardial being a particular concern, an off-set erosion of 20% was applied on both the endocardial and epicardial borders using a function of the software.

Global T1 and T2 values were obtained by averaging all segmental T1 and T2 values, respectively. Mid-septum T1 and T2 values were obtained by averaging the values in segments 8 and 9.

Applying the segmental approach to image analysis, according to AHA guidelines (77), the myocardium was divided into 17 segments. [AHA 2002 (77)]. Figure 12 shows the location and the recommended names for all the LV myocardial segments [Herzog et al. 2017 (78)].

Segmental approach is also applied to the right ventricle. The free wall is divided in basal, mid-cavity and distal, the outflow wall in anterior and posterior, and finally, the diaphragmatic wall in basal, mid-cavity and distal segments.



1: basal anterior A; 2: basal anteroseptal AS; 3: basal inferoseptal IS; 4: basal inferior I; 5: basal inferolateral IL; 6: basal anterolateral AL; 7: mid-anterior A; 8: mid-anteroseptal AS; 9 mid-inferoseptal IS; 10 mid-inferior I; 11 mid-inferolateral IL; 12 mid-anterolateral AL; 13: apical anterior A; 14: apical septal S; 15: apical inferior I; 16: apical lateral L; 17: apex

Figure 15: Left Ventricular Segmentation Model by American Heart Association (Herzog BA, Greenwood JP, Plein S. Cardiovascular Magnetic Resonance Pocket Guide 2017) (78)

Both native and mapping images have all been evaluated to assess the presence of artifacts (i.e. respiratory, vectorcardiographic or partial volume artifacts). The

possible presence of artifacts excluded the involved myocardial segment from following analysis.

Images and consequently pathological findings have been analysed under direct supervision of a 22-year experienced cardio-radiologist (A.P.).

The total CMR scan duration was between 40 to 60 minutes.

STATISTICAL ANALYSIS

- To determine increased or reduced mapping values, native T1 and T2 global and segmental values were compared to normal reference ranges calculated in our centre through the analysis of the 50 healthy volunteers, whose inclusion criteria were a normal electrocardiogram, no cardiovascular diseases, no cardiovascular symptoms or risk factors, no systemic diseases, normal renal function, no contraindications to CMR, and no Sars-CoV-2 infection within 3 months prior to the CMR.
- To assess the additive value of parametric sequences, T1, T2 mapping and ECV results were compared with corresponding nonparametric sequences evaluations (i.e. LGE and TIRM). In details, regarding pathological findings on mapping results, were considered separately: global values, at least 2 segments with altered value, or altered middle septum.
- CMR findings on both non-parametric and parametric sequences were compared with morphological and functional characteristics (i.e., LVEF, kinesis, atrial and ventricular dilatation), other instrumental findings (i.e., ECG, EST, and Holter examinations), and COVID-relates status.
- LV wall thickness was compared with T1 and T2 mapping values increased or reduced and with COCIS sport classification.
- Analysis of results of population stratified according to age group (i.e., pediatric subjects $\leq$ 18 years-old versus adult subjects > 18 years old) is provided.

Descriptive statistics were reported as median (interquartile range) and mean (standard deviation) for continuous variables and absolute numbers (percentages)

for categorical variables. Wilcoxon test was performed to compare the distribution of continuous variables. Chi-squared test was performed to compare the distribution of categorical variables, while Fisher's exact test was used when any expected cell count was below 5. A two-sided $p < 0.05$ was considered statistically significant. Benjamini-Hochberg (79) correction was performed to account for the multiplicity of testing, controlling for the false discovery rate.

Finally, the performance of T1 and T2, in diagnosing the LGE, was evaluated by calculating the specificity, sensitivity and the Cohen's Kappa.

Analyses were performed with the R software (80).

RESULTS

STUDY POPULATION DEMOGRAPHICS AND CHARACTERISTICS

The population was made up of 43 males (86%) and 7 females (14%), average age was 26 $\pm$ 15 years (range 12-63). Mean BMI was 22.6 $\pm$ 3.3 kg/m^2 and mean BSA was 1.84 m^2 (Table III).

The indication for CMR was based on positive findings in PPE. 2 participants had repolarization alterations in the basal ECG, whereas one of them had both repolarization alterations and right bundle branch block. (Table III)

Among the ECG stress test reports, 31 subjects (62% of total) had premature ventricular contractions, of which 5 were frequent PVBs, couplets, triplets, or runs. 12 (24% of total) had repolarization alterations and 5 had arrythmias suppressed by exercise. Almost all the EST alterations were occasional findings, most of the patients in fact referred to be asymptomatic, except 6 of them: 3 mentioned cardiopalm and palpitations during exercise or resting, 1 had a lypothimia after exercise and 2 experienced oppressive chest pain.

Holter ECG has shown repetitive PVBs in 12 subjects (24%).

24 patients also underwent echocardiography prior the CMR exam. 2 patients presented increased wall thickness, one reduced ejection fraction, one septal hypokinesia, one LV dilatation and one RV dilatation.

2 patients had indication to CMR because of suspected hypertrophic cardiomyopathy based on ECG (deep negative T waves), and 2 patients because of the clinical suspicion of myocarditis, of which one of them was hypothesized to be related to Sars-Cov-2.

18 patients (36%) had been infected by Sars-CoV-2, 12 (24%) of them were infected less than 3 months before CMR evaluation and 5 (10%) more than 3 months, whereas for one subject we do not have any information regarding the time of infection. The remaining 32 subjects (64%) have never been infected.

4 patients were taking medications at the time of the examination. 3 of them were taking beta-blockers because they were diagnosed with ventricular arrythmias,

and one was taking both beta-blockers and ACE inhibitors because he was diagnosed with myocarditis 6 months prior the evaluation. Besides, 3 other patients had been previously medicated for ventricular arrythmias and one of them underwent transcatheter ablation twice with no clinical efficacy.

Furthermore, one subject suffered of type 1 diabetes and 3 subjects of dyslipidemia. 3 subjects had a suspected hypertrophic cardiomyopathy, and one had a suspected post-covid myocarditis. 2 patients had already been diagnosed with respectively myocarditis and pericarditis based also a previous CMR and the exam was performed for follow up. One patient had X-fragile syndrome

Table IIIa: Clinical characteristics of the competitive athletes

Characteristic			N = 50
Sex	*Females*	7	14%
	Males	43	86%
Weight (kg)	Median (IQR)	71	(64, 80)
	Mean (SD)	70	(14)
Height (cm)	Median (IQR)	178	(170, 182)
	Mean (SD)	175	(10)
BSA (m²)	Median (IQR)	1.88	(1.70, 2.00)
	Mean (SD)	1.84	(0.24)
BMI (kg/m²)	Median (IQR)	23	(20.0, 24.0)
	Mean (SD)	22.6	(3.3)
Age at CMR (years)	Median (IQR)	18	(16, 38)
	Mean (SD)	26	(15)
Heart rate (bpm)	Median (IQR)	69	(60, 83)
	Mean (SD)	73	(18)
Sars-CoV-2	*Never infected*	32	64%
	Infected <3 months before CMR	12	24%
	Infected >3 months before CMR	5	10%
	No information about the time of infection	1	2%
Symptoms	*None*	44	88%
	Basal and post-exercise cardiopalm	1	2%
	Cardiopalm during excercise	1	2%
	Oppressive chest pain	2	4%
	Lypothimia after exercise	1	2%
	Palpitations	1	2%

Table IIIb: ECG and EST findings in the competitive athletes

Characteristic			N = 50
Basal ECG findings	*None*	47	94%
	RBBB and Repolarization alterations	1	2%
	Repolarization alterations	2	4%
PVB during exercise (EST)	*No*	12	24%
	Yes	31	62%
	NA	7	14%
Frequent PVBs, couplets, triplets, or runs during exercise (EST)	*No*	30	60%
	Yes	5	10%
	NA	15	30%
Repolarization alteration during exercise (EST)	*No*	27	54%
	Yes	12	24%
	NA	11	22%
Arrythmias suppressed by exercise (EST)	*No*	30	60%
	Yes	5	10%
	NA	15	30%
Pathological Holter ECG showing repetitive PVCs	*No*	17	34%
	Yes	12	24%
	NA	21	42%

Through the questionnaire it had been possible to obtain information about the sports discipline of 42 subjects (84%); the other 8 subjects (16%) did not provide complete answers. The most practised sport in our population was football (n=15, 30% of the total), while all the other disciplines were equally distributed among the other participants. The average years of activity were 12 while the mean hours per week were 7. Based on the COCIS 2017 Classification, only 1 subject practiced a group A sport, 7 group B, 25 group C, 4 group D and 5 group E. (Figure 16)

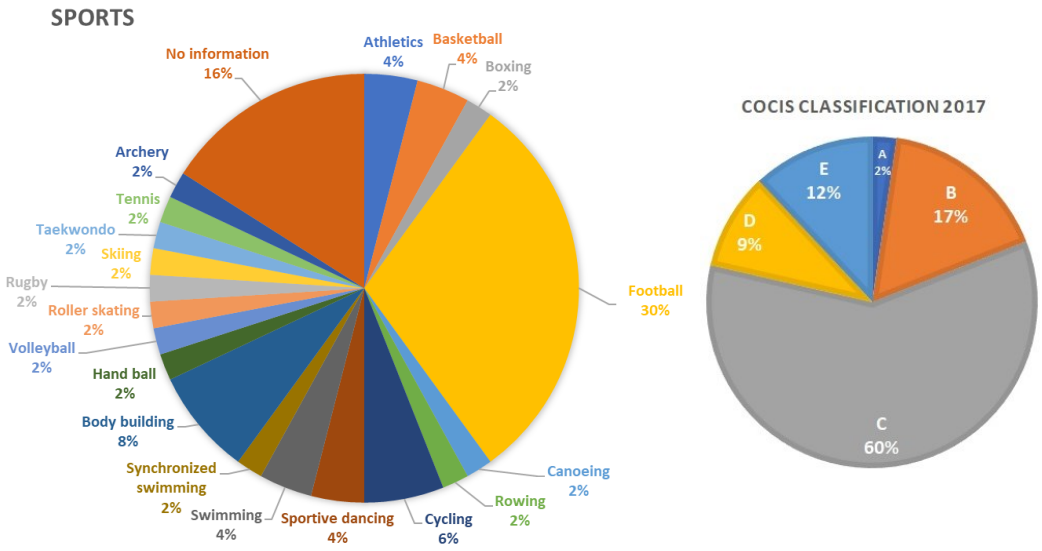


Figure 16: On the left a pie chart that represents the type of sports practised by the population. On the right the percentage of each group according to the COCIS Classification 2017.

CMR CHARACTERISTICS

All patients underwent gadolinium-based contrast agent administration. Each of them completed the examination successfully. The TIRM sequences were acquired in only 20 patients based on the clinical indications.

7 patients (14% of total) did not show pathological CMR findings. 2 patients showed CMR data attributable for a cardiomyopathy with a hypertrophic phenotype (one apical non-obstructive and the other one obstructive). Furthermore, 2 subjects had pathological findings compatible for biventricular arrhythmogenic cardiomyopathy (kinetic alterations with RV dilatation and/or reduced EF, and signal alterations suggestive for fibro-fatty infiltration).

Table IV shows the reports of cine steady-state free precession (SSFP) imaging.

Based on these evaluations 29 subjects (58% of total) had normal ventricular dimensions and preserved global systolic function. Out of the 29 subjects with normal ventricular dimension and systolic function, 19 athletes (66%) had positive non ischemic LGE findings, 2 had both LGE and kinetic alterations and one both LGE and increased wall thickness.

11 patients (22% of total) had a normal global systolic function and balanced ventricular dilatation. Among them, 4 did not have any other alteration, 4 had positive non ischemic LGE findings, one had both LGE and kinetic alterations and 2 had both LGE and increased wall thickness.

One subject had biventricular reduction of the EF and balanced ventricular dilatation. In addition, he had positive non ischemic LGE findings and kinetic alterations. Another one had a reduced LV function and balanced ventricular dilatation, in addition to having kinetic alterations.

Only one patient had reduced dimensions in both ventricles and a normal global systolic function, he also had non ischemic LGE findings and a severe increased of wall thickness (> 15 mm), being was diagnosed with obstructive HCM.

4 people in total (8% of total) showed a LV dilatation, in 2 of them global systolic function was normal, while the other 2 showed a reduced LV global systolic function. Among the 2 with normal global systolic function, one did not have any other alteration, while the other one presented kinetic alterations. As for the 2 patients with reduced LV function, one of them had positive non ischemic LGE findings and the other both LGE and kinetic alterations.

Finally, 3 patients (6% of total) had a right ventricular dilatation: 2 of them had normal global systolic function, in addition to having non ischemic LGE findings, and one of them had a reduced global systolic function with both LGE and kinetic alterations on both ventricles. (Table V)

LV ejection fraction values were higher or lower than the normal reference limit in 32 patients (64% of total).

Right atrium areas resulted increased in 6 patients and one of them had both left and right atrium areas increased.

Table IVa: CMR morphological and function parameters. LVEDV = Left ventricular end-diastolic volume; LVESV = Left ventricular end-systolic volume; LVSV = Left ventricular stroke volume; LVEF = Left ventricular ejection fraction; RVEDV = Right ventricular end-diastolic volume; RVESV = Right ventricular end-systolic volume; RVSV = Right ventricular stroke volume; RVEF = Right ventricular ejection fraction;

LVEDV Indexed (mL/m²)	Median (IQR)	96 (88, 105)
	Mean (SD)	96 (13)
LVESV Indexed (mL/m²)	Median (IQR)	39 (35, 45)
	Mean (SD)	41 (10)
LVSV Indexed (mL/m²)	Median (IQR)	52 (48, 58)
	Mean (SD)	55 (11)
LVEF (%)	Median (IQR)	55 (53, 61)
	Mean (SD)	57 (6)
LV Mass Indexed (g/m²)	Median (IQR)	58 (52, 64)
	Mean (SD)	59 (13)
Cardiac Output (L/min)	Median (IQR)	6.40 (5.80, 7.75)
	Mean (SD)	6.84 (1.88)
Cardiac Index (L/min/m²)	Median (IQR)	3.50 (3.18, 4.10)
	Mean (SD)	3.69 (0.82)
RVEDV Indexed (mL/m²)	Median (IQR)	100 (90, 110)
	Mean (SD)	102 (22)
RVESV Indexed (mL/m²)	Median (IQR)	43 (38, 50)
	Mean (SD)	44 (10)
RVSV Indexed (mL/m²)	Median (IQR)	54 (49, 62)
	Mean (SD)	55 (11)
RVEF (%)	Median (IQR)	55.5 (51.2, 60.8)
	Mean (SD)	56.2 (6.0)

Table IVb: CMR morphological and function parameters. LA = Left atrium; RA = Right atrium.

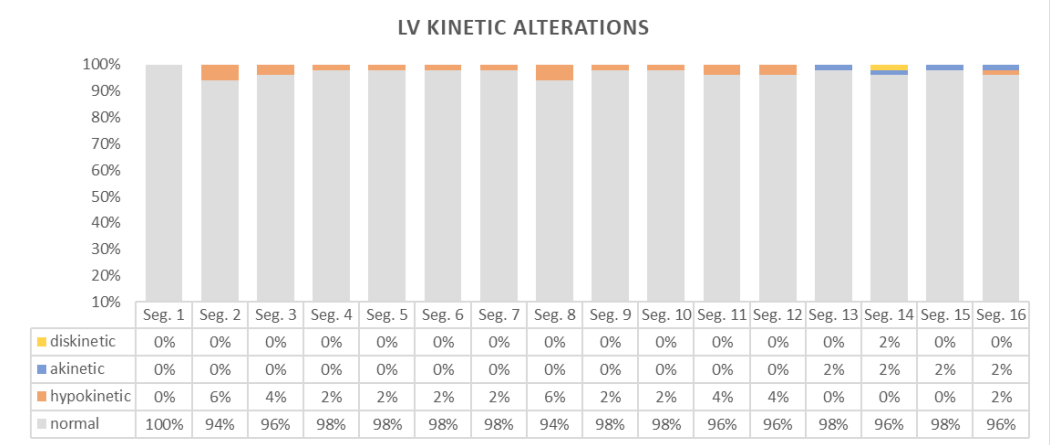
LA Area Indexed (mm^2/m^2) (N=49)	Median (IQR)	11.00 (9.50, 13.00)
	Mean (SD)	11.20 (2.20)
RA Area Indexed (mm^2/m^2) (N=49)	Median (IQR)	11.00 (9.60, 13.00)
	Mean (SD)	11.44 (2.80)
LV wall thickness (mm)	< 12	46 (92%)
	> 12	4 (8.0%)

Table V: Ventricular dimension and global systolic function by CMR

		Biventricular systolic function		*Left systolic function*	
		Normal	*Reduced*	*Reduced*	*Total*
Ventricular dimension	*Normal*	29	-	-	*29 (58%)*
	Balanced dilatation	11	1	1	*13 (26%)*
	Reduced	1	-	-	*1 (2%)*
	LV dilatation	2	-	2	*4 (8%)*
	RV dilatation	2	1	-	*3 (6%)*
	Total	*45 (90%)*	*2 (4%)*	*3 (6%)*	*50*

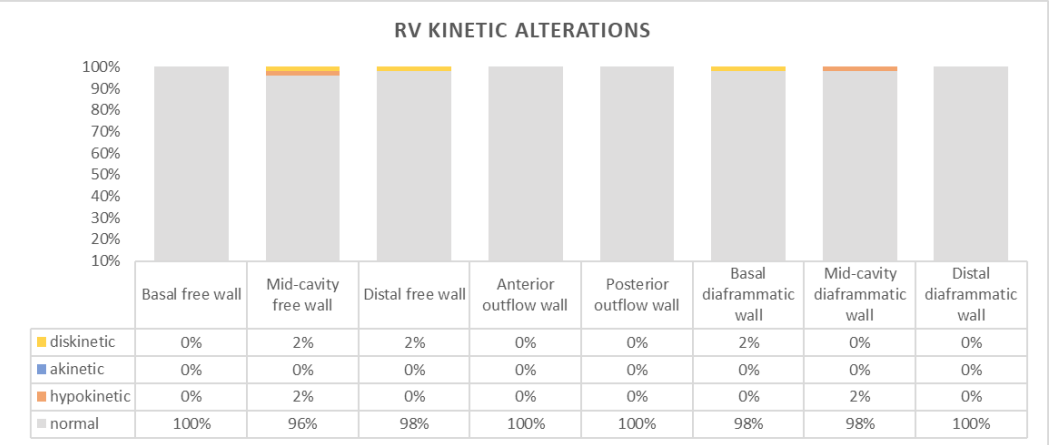
Increased wall thickness was reported in 4 patients, 3 of them practiced football (group C, COCIS) and one rowing (group E, COCIS). 2 patients showed CMR data compatible for a cardiomyopathy with a hypertrophic phenotype (wall thickness > 15 mm); the remaining 2 did not have noteworthy increasing of their values.

LV kinetic alterations have been assessed in 6 (12%) subjects, 5 of them showed hypokinetic segments, and the other one had dyskinetic segments. Among them, both right and left ventricular kinetics alterations have been found twice. One patient presented both hypokinetic and akinetic segments in the LV while in the RV had dyskinetic segments. Only one subject had akinetic segments in the RV alone. (Figures 17, 18)



	Seg. 1	Seg. 2	Seg. 3	Seg. 4	Seg. 5	Seg. 6	Seg. 7	Seg. 8	Seg. 9	Seg. 10	Seg. 11	Seg. 12	Seg. 13	Seg. 14	Seg. 15	Seg. 16
diskinetic	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	0%	0%
akinetic	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	2%	2%	2%
hypokinetic	0%	6%	4%	2%	2%	2%	2%	6%	2%	2%	4%	4%	0%	0%	0%	2%
normal	100%	94%	96%	98%	98%	98%	98%	94%	98%	98%	96%	96%	98%	96%	98%	96%

Figure 17: Distribution of LV kinetic alterations.



	Basal free wall	Mid-cavity free wall	Distal free wall	Anterior outflow wall	Posterior outflow wall	Basal diaframmatic wall	Mid-cavity diaframmatic wall	Distal diaframmatic wall
diskinetic	0%	2%	2%	0%	0%	2%	0%	0%
akinetic	0%	0%	0%	0%	0%	0%	0%	0%
hypokinetic	0%	2%	0%	0%	0%	0%	2%	0%
normal	100%	96%	98%	100%	100%	98%	98%	100%

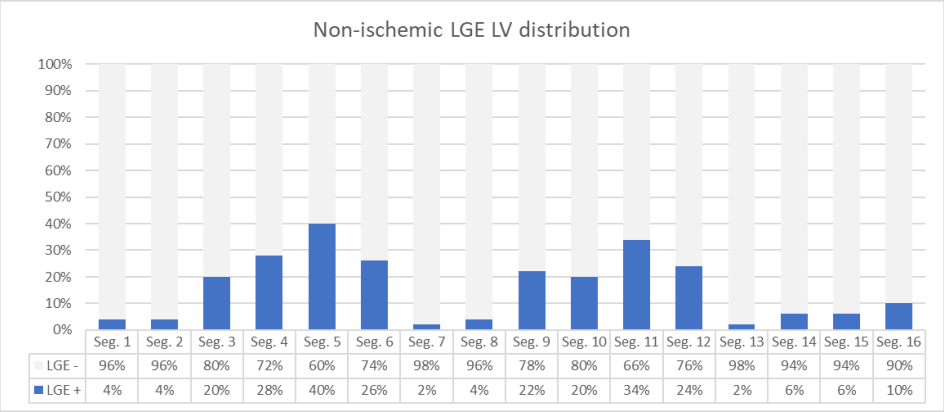
Figure 18: Distribution of RV kinetic alterations.

Among the 20 subjects who underwent TIRM imaging, no signs of oedema were detected by a qualitative analysis; 16 of them (84%) showed a pathological mean T2 ratio value (cut-off >1.9).

Based on SSFP and TIRM images pericardial effusion was reported in 7 participants (35%).

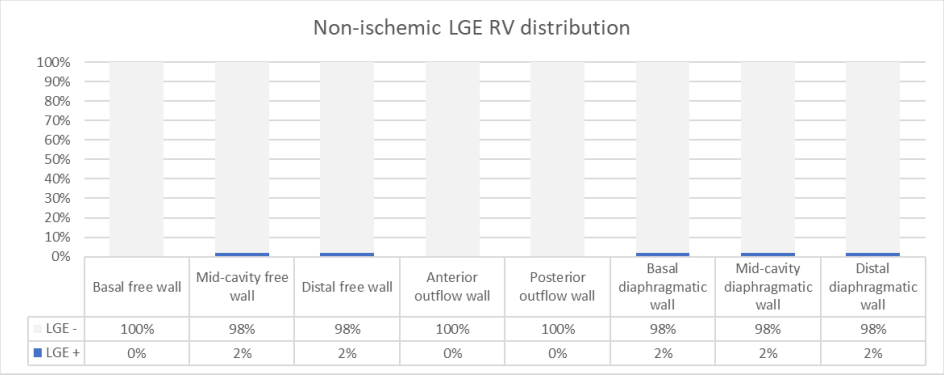
Only one patient has been found with hypoperfusion in the basal and mid-lateral wall of the LV.

36 patients presented non-ischemic LGE findings on the LV, 2 of them also had non-ischemic LGE areas on the right ventricle. 19 of these LGE+ patients (38% of the total) had a mid-wall pattern, 3 of them had subepicardial pattern, three of them junctional, 5 of them both junctional and mid-wall, and 6 of them both subepicardial and mid-wall. (Figures 19, 20).



	Seg. 1	Seg. 2	Seg. 3	Seg. 4	Seg. 5	Seg. 6	Seg. 7	Seg. 8	Seg. 9	Seg. 10	Seg. 11	Seg. 12	Seg. 13	Seg. 14	Seg. 15	Seg. 16
LGE -	96%	96%	80%	72%	60%	74%	98%	96%	78%	80%	66%	76%	98%	94%	94%	90%
LGE +	4%	4%	20%	28%	40%	26%	2%	4%	22%	20%	34%	24%	2%	6%	6%	10%

Figure 19: Distribution of non-ischemic-LGE findings in LV segments.



	Basal free wall	Mid-cavity free wall	Distal free wall	Anterior outflow wall	Posterior outflow wall	Basal diaphragmatic wall	Mid-cavity diaphragmatic wall	Distal diaphragmatic wall
LGE -	100%	98%	98%	100%	100%	98%	98%	98%
LGE +	0%	2%	2%	0%	0%	2%	2%	2%

Figure 20: Distribution of non-ischemic-LGE findings in RV segments.

COMPARISON OF T1 AND T2 MAPPING VALUES BETWEEN ATHLETES AND HEALTHY SUBJECTS

Compared to normal reference values based on age and gender, global T1 mapping values turned out to be pathological in 4 patients (8% of total), while global T2 mapping values in 13 patients (26% of total). (Figure 21, Table VII)
ECV global values have been measured in 29 patients, the mean value was 31 ± 8% and in 26 subjects (90%) exceed the normal reference range (Table VI, VII).

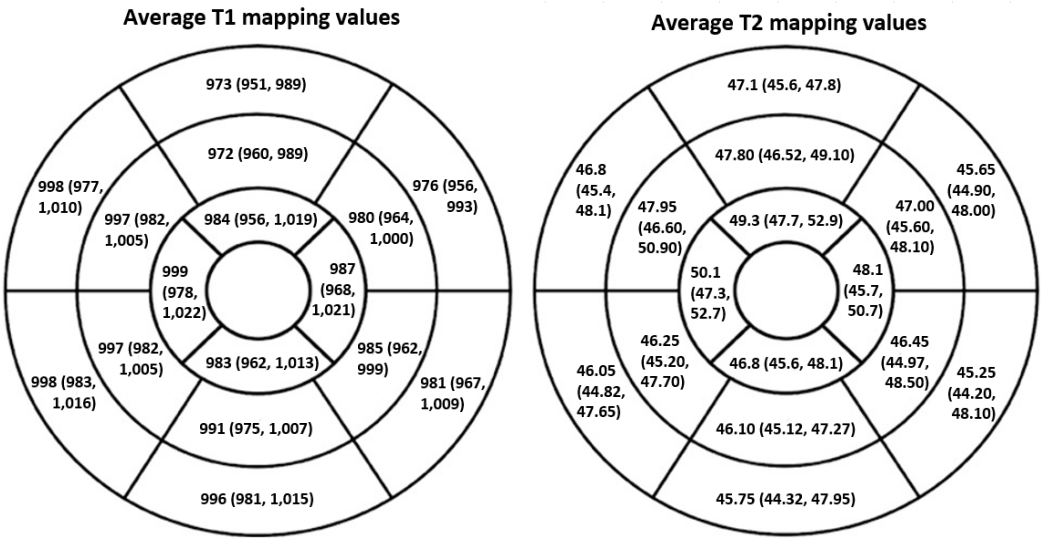


Figure 21: Median segmental T1 (left) and T2 (right) mapping values in the study population of athletes (in brackets the interquartil1e range).

Table VI: Average global T1, T2 mapping and ECV values in the study population of athletes.

		T1 mapping (N = 50)	T2 mapping (N = 50)	ECV
Global	Median (IQR)	988 (972, 1.008)	47 (46, 49)	28 (25, 35)
	Mean (SD)	991 (26)	48 (2.58)	31 (8)

Table VII: Segmental analysis of T1 and T2 values compared to reference limits based on age and sex.

		Values compared to reference limits based on age and sex	
		T1 mapping (N = 50)	**T2 mapping (N = 50)**
Basal anterior	Pathological	4 (8.0%)	7 (14%)
	Normal	46 (92%)	43 (86%)
Basal anteroseptal	Pathological	5 (10%)	9 (18%)
	Normal	45 (90%)	41 (82%)
Basal inferoseptal	Pathological	1 (2.0%)	2 (4.0%)
	Normal	49 (98%)	48 (96%)
Basal inferior	Pathological	6 (12%)	6 (12%)
	Normal	44 (88%)	44 (88%)
Basal inferolateral	Pathological	3 (6.0%)	6 (12%)
	Normal	47 (94%)	44 (88%)
Basal anterolateral	Pathological	9 (18%)	7 (14%)
	Normal	41 (82%)	43 (86%)
Mid-anterior	Pathological	5 (10%)	7 (14%)
	Normal	45 (90%)	43 (86%)
Mid-anteroseptal	Pathological	4 (8.0%)	12 (24%)
	Normal	46 (92%)	38 (76%)
Mid-inferoseptal	Pathological	2 (4.0%)	6 (12%)
	Normal	48 (96%)	44 (88%)
Mid-inferior	Pathological	5 (10%)	5 (10%)
	Normal	45 (90%)	45 (90%)
Mid-inferolateral	Pathological	7 (14%)	8 (16%)
	Normal	43 (86%)	42 (84%)
Mid-anterolateral	Pathological	5 (10%)	5 (10%)
	Normal	45 (90%)	45 (90%)
Apical anterior	Pathological	3 (6.0%)	10 (20%)
	Normal	47 (94%)	40 (80%)
Apical septal	Pathological	8 (16%)	11 (22%)
	Normal	42 (84%)	39 (78%)
Apical inferior	Pathological	6 (12%)	8 (16%)
	Normal	44 (88%)	42 (84%)
Apical lateral	Pathological	5 (10%)	18 (36%)
	Normal	45 (90%)	32 (64%)
Global	Pathological	4 (8.0%)	13 (26%)
	Normal	46 (92%)	37 (74%)

18 (36%) subjects had more than 2 pathological T1 mapping segments, and 24 (48%) presented more than 2 pathological T2 segments.

T1 mapping values in mid-septum were pathological in 39 patients (78% of total), 27 (54% of total) were above normal range and 12 (24% of total) were under. As for T2 mapping 17 subjects (34% of total) had abnormal values, 6 of them (12% of total) were higher than the reference limit and 11 (22% of total) were lower.

CMR PARAMETRIC MAPPING SEQUENCES COMPARED TO CMR NON-PARAMETRIC SEQUENCES IN ATHLETES FOR TISSUE CHARACTERIZATION

Among the 36 athletes with positive non-ischemic LGE findings, 12 (33%) athletes had $\geq$ 2 segments with pathological T1 values; among the 14 athletes with a negative LGE, 6 (43%) patients had $\geq$ 2 segments with pathological T1 values ($p = 0.529$) (Fig 22, A).

Among the 36 athletes with positive non-ischemic LGE findings, 3 (8%) athletes had pathological global T1 values; among the 14 athletes with a negative LGE, 1 (7%) athlete had pathological global T1 values ($p = 0.889$) (Fig 22, B).

Among the 36 athletes with positive non-ischemic LGE findings, 29 (81%) athletes had pathological T1 values in the mid-ventricular septum; among the 14 athletes with a negative LGE, 10 (71%) athletes had pathological T1 values in the mid-ventricular septum ($p = 0.484$) (Fig 22, C).

Among the 36 athletes with positive non-ischemic LGE findings, 13 (36%) athletes had pathological T2 values in the mid-ventricular septum; among the 14 athletes with a negative LGE, 4 (29%) athletes had pathological T2 values in the mid-ventricular septum ($p = 0.613$) (Fig 22, D).

Finally, ECV global values were pathological in all the subjects a positive LGE in which it was evaluated ($n=21$, $p=0.015$). 5 (62%) of the athletes with a negative LGE had abnormal ECV and 3 were normal (Figure 22, E). Table VIII shows the accuracy measurements of the mapping parameters versus the LGE.

Figure 23 represent data acquired from a 40-year-old male athlete with both T1, T2 mapping and LGE pathological findings.

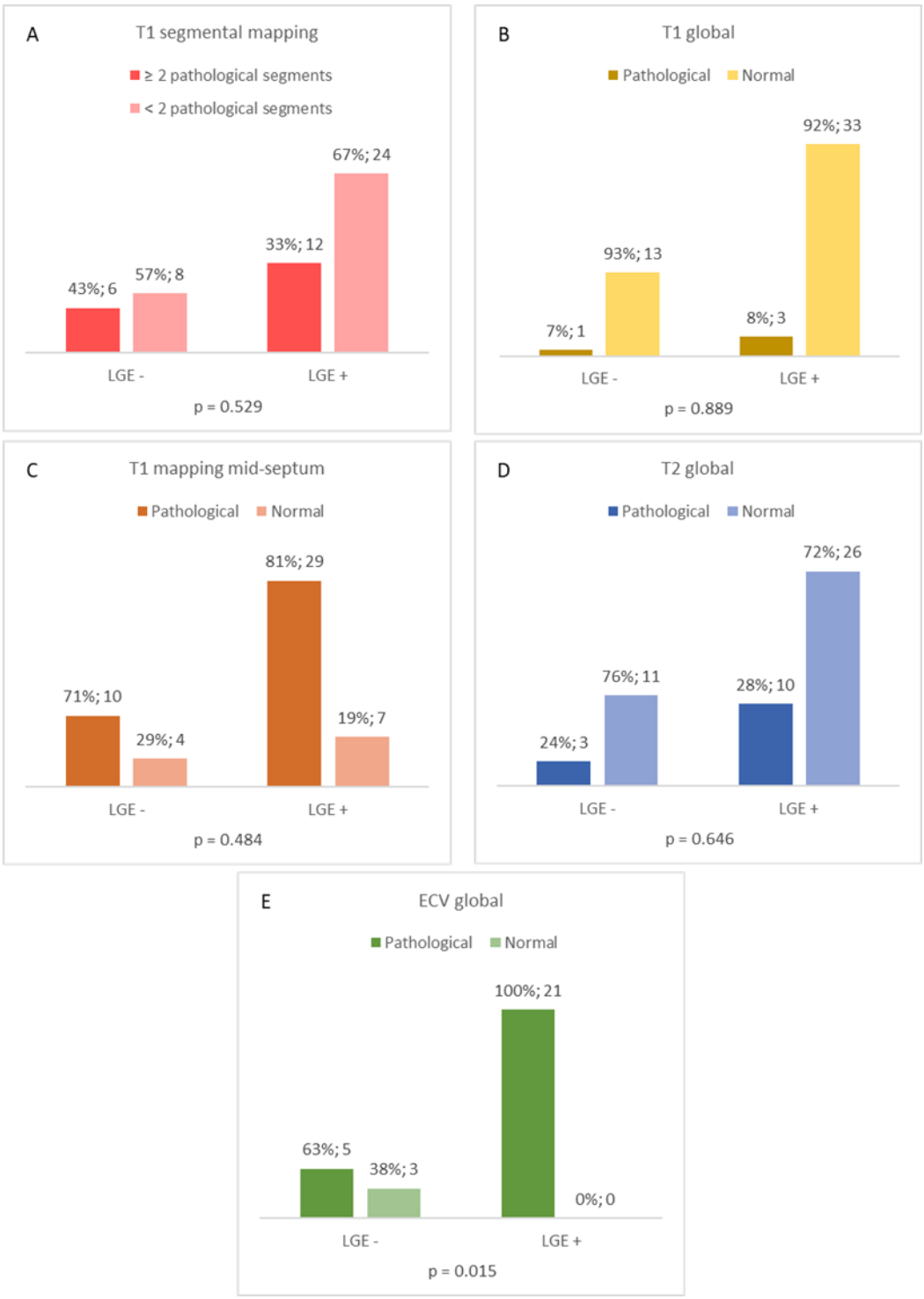


Figure 22: Bar charts that represent the correlation between non-ischemic LGE findings and T1 mapping (segmental (A), global (B) in the mid-septum (C), T2 mapping global (D), ECV global (E).

Table VIII: Accuracy measurements of the mapping parameters versus the LGE.

	Sensibility	Specificity	Cohen Kappa
≥ 2 segments with pathological T1 vs LGE	0.33	0.57	-0.07
Global T1 vs LGE	0.083	0.93	0.01
Global T2 vs LGE	0.278	0.786	0.04
T1 in the mid ventricular septum vs LGE	0.36	0.71	0.05
ECV vs LGE	1.00	0.375	0.46

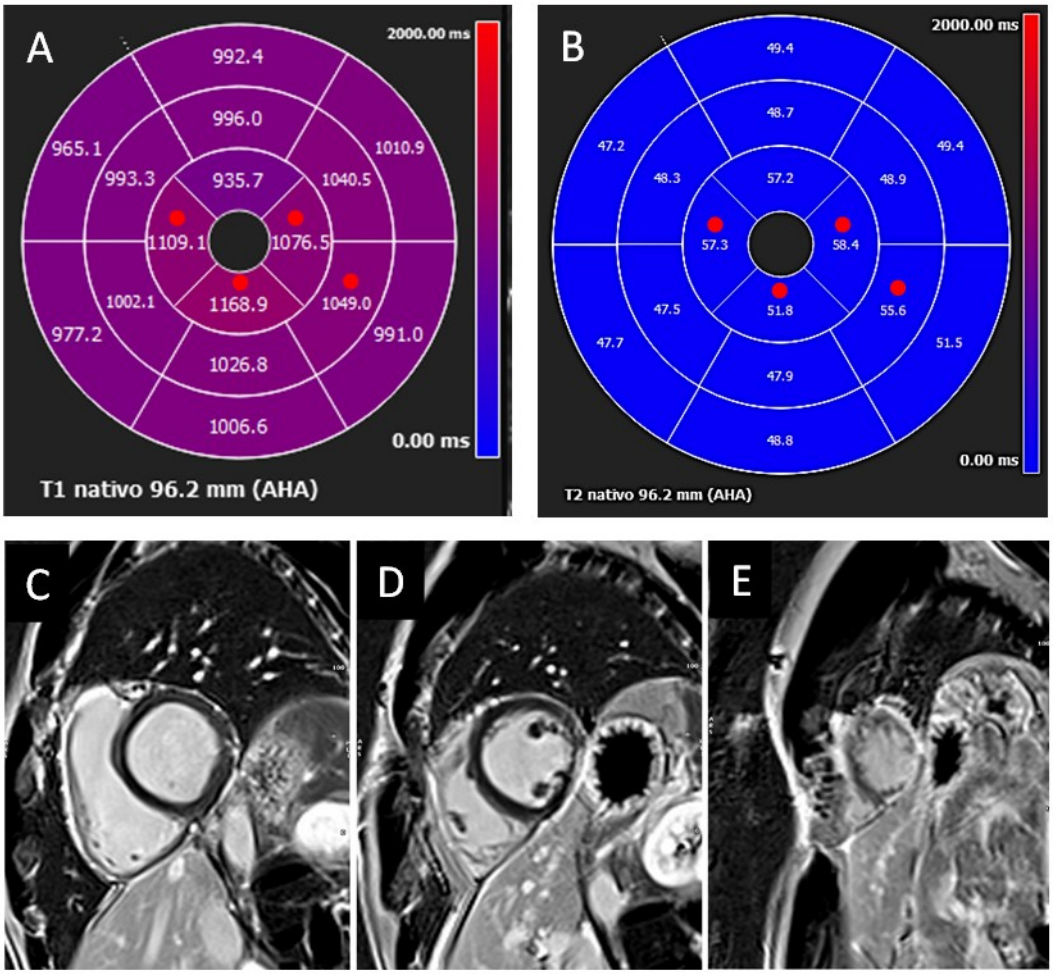


Figure 23: A 40-year-old male athlete that shows higher T1 (A) and T2 (B) values compared to age and gender reference limits in the segments 11, 14, 15, 16 (red points). T1 and T2 global values were also increased (1026 ms and 52 ms, respectively). Non ischemic LGE was detected in the segments 1, 3, 4, 5, 6 in the basal section (C); 9, 10, 11, 12 in the mid -cavity section (D); 16 in the apical section (E).

Of the 20 athletes that underwent TIRM T2 sequences evaluated by T2 ratio analysis, 8 (50%) had ≥ 2 segments with abnormal T2 mapping values and pathological T2 ratio, 5 (31%) had abnormal T2 global values and pathological T2 ratio, 9 (100%) had pathological global ECV values and pathological T2 ratio (p = NS) (Figure 24).

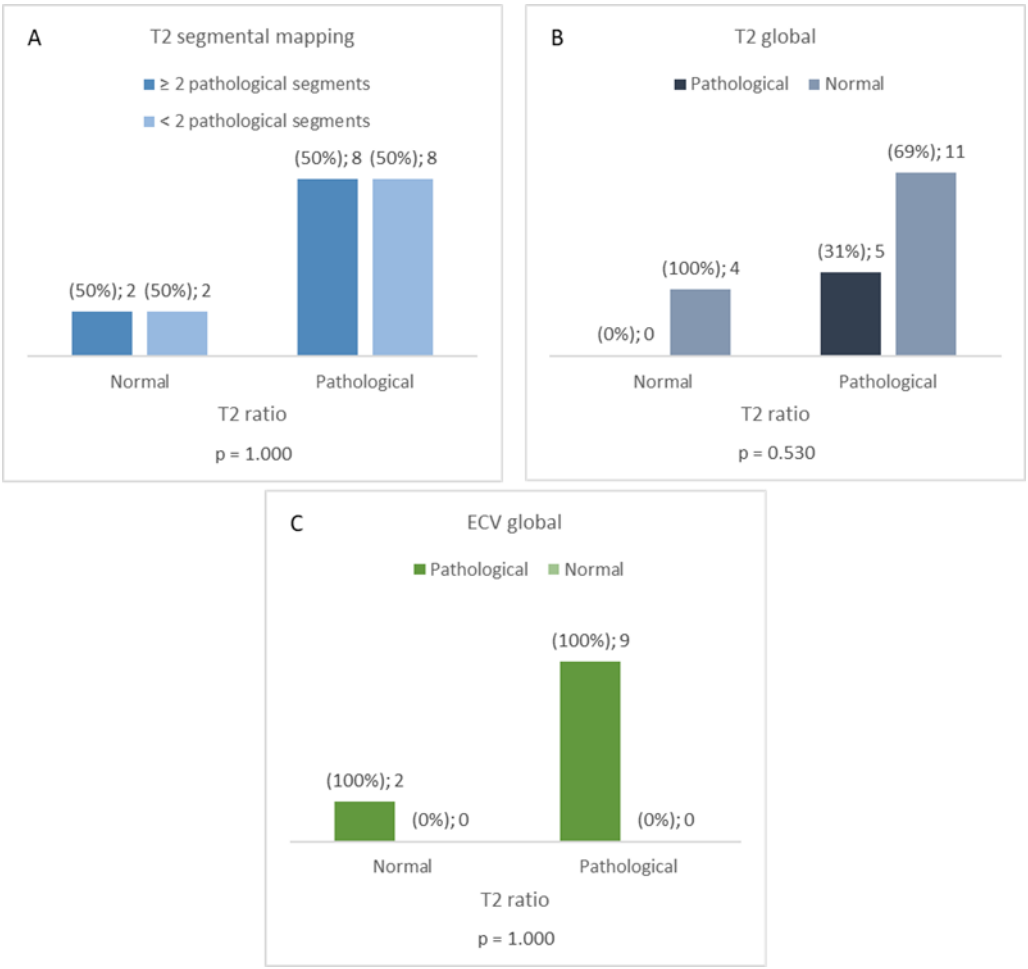


Figure 24: Bar charts that represent the correlation between non-ischemic LGE findings and T2 mapping segmental (A), global (B), ECV global (C).

Figure 25 represents data acquired from a 19-year-old female with T1, T2 mapping, LGE and T2 ratio pathological findings.

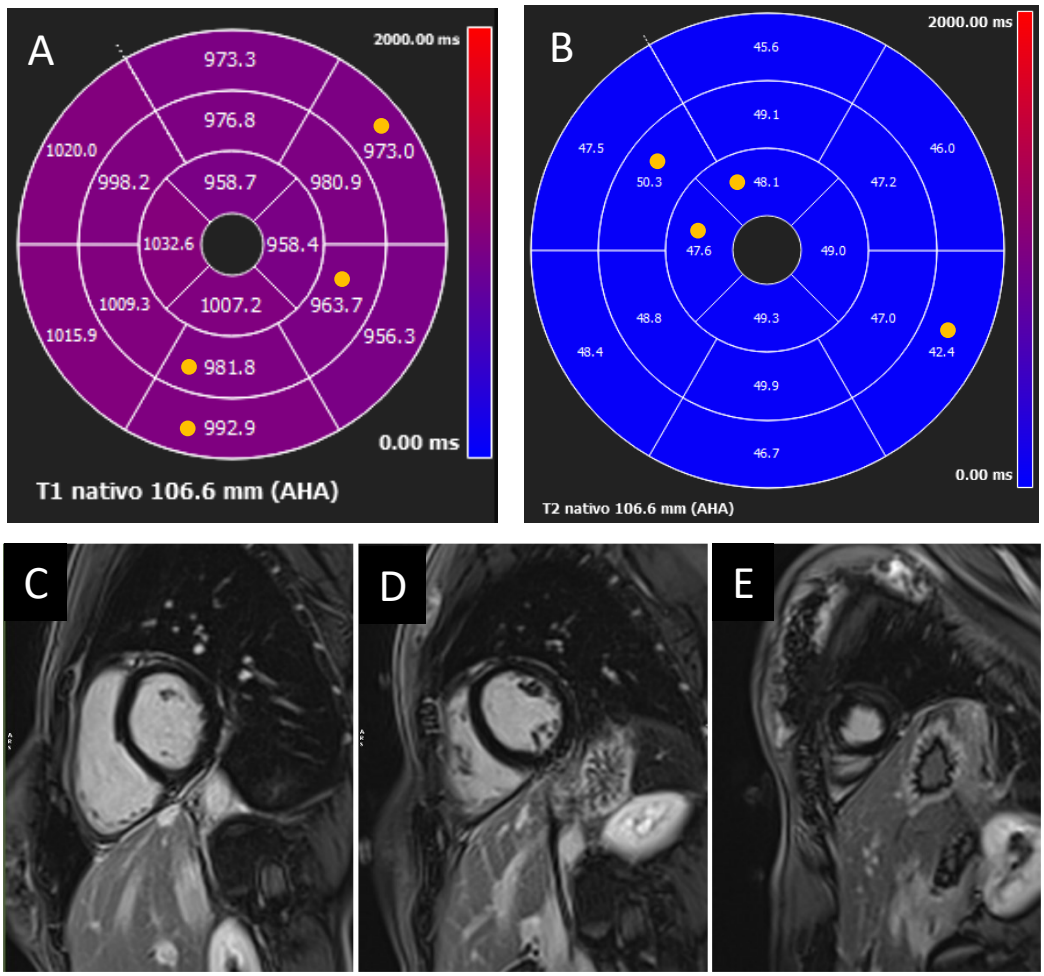


Figure 25: A 19-year-old female athlete that shows lower T1 values (A) compared to age and gender reference limits in the segments 4, 6, 10, 11 and lower T2 values in segments 5, 8, 13, 14 (yellow points). T1 and T2 global values were also reduced (986 ms and 47 ms, respectively). Non ischemic LGE was detected in the segment 3 in the basal section (C); 16 in the apical section (E).

Only 14% of patients had normal conventional non-parametric imaging (no LGE) and normal parametric CMR (T1, T2 mapping and/or ECV. Pathological T1 and/or T2 mapping and/or ECV was present in 14% of athletes with normal conventional non-parametric imaging (Figure 26).

50 athletes	
Conventional non-parametric CMR	
Positive	36 (72%)
Normal	14 (28%)
Non-conventional parametric CMR	
Pathological	34 (68%)
Normal	16 (32%)

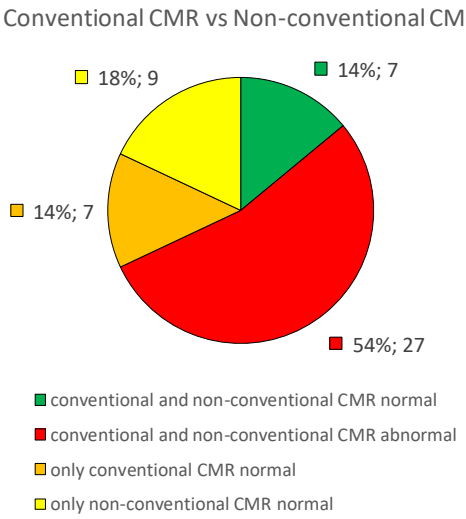


Figure 26: Pie chart that represent the correlation between conventional non parametric CMR and non conventrional parametric CMR.

CMR TISSUE CHARACTERIZATION *VERSUS* CMR MORPHOLOGICAL/FUNCTIONAL VALUES IN ATHLETES

We did not find significant correlation between myocardial tissue characterization by parametric (T1 and T2 mapping, ECV) or non-parametric (LGE or TIRM) CMR and morphological/functional values (ventricular dilatation, atrial dilation, systolic dysfunction, wall thickness) (see table IX, X, XI, XII).

Figures 27 shows the correlation between ventricular kinetic alterations (left and/or right) versus parametric and non-parametric imaging evaluations for tissue characterization (T1 and T2 mapping, ECV). We did not find significant correlations, with the exception of the global T1 mapping (p=<0.001) where the patients without kinetic alteration showed normal values in the 98% of the cases (n=41).

Table IX: Ventricular dilatation compared to parametric and non-parametric imaging.

Characteristic		Left and/or Right Ventricular Dilatation			
		N	No (N = 30)	Yes (N = 20)	
T1 mapping pathological segments	**< 2** **≥ 2**	**50**	18 (60%) 12 (40%)	14 (70%) 6 (30%)	p=0.470
T1 mapping global value	**Normal** **Pathological**	**50**	28 (93%) 2 (6.7%)	18 (90%) 2 (10%)	p=0.670
T2 mapping pathological segments	**< 2** **≥ 2**	**50**	14 (47%) 16 (53%)	12 (60%) 8 (40%)	p=0.355
T2 mapping global value	**Normal** **Pathological**	**50**	20 (67%) 10 (33%)	17 (85%) 3 (15%)	p=0.148
ECV	**Normal** **Pathological**	**29**	1 (6.7%) 14 (93%)	2 (14%) 12 (86%)	p=0.501
LGE	**Negative** **Positive**	**50**	7 (23%) 23 (77%)	7 (35%) 13 (65%)	p=0.368
Pathological TIRM by qualitative analysis	**No**	**20**	13 (100%)	7 (100%)	
T2 ratio	**Normal** **Pathological**	**20**	2 (15%) 11 (85%)	2 (29%) 5 (71%)	p=0.482

Table X: Atrial dilatation compared to parametric and non-parametric sequence for tissue characterization.

Characteristic		Left and/or Right Atrial Dilatation			
		N	No (N = 44)	Yes (N = 6)	
T1 mapping pathological segments	**< 2** **≥ 2**	**50**	29 (66%) 15 (34%)	3 (50%) 3 (50%)	p=0.446
T1 mapping global value	**Normal** **Pathological**	**50**	41 (93%) 3 (6.8%)	5 (83%) 1 (17%)	p=0.404
T2 mapping pathological segments	**< 2** **≥ 2**	**50**	23 (52%) 21 (48%)	3 (50%) 3 (50%)	p=0.917
T2 mapping global value	**Normal** **Pathological**	**50**	33 (75%) 11 (25%)	4 (67%) 2 (33%)	p=0.662
ECV	**Normal** **Pathological**	**29**	3 (12%) 21 (88%)	0 (0%) 5 (100%)	p=0.404
LGE	**Negative** **Positive**	**50**	12 (27%) 32 (73%)	2 (33%) 4 (67%)	p=0.756
Pathological TIRM by qualitative analysis	**No**	**20**	20 (100%)	0 (NA%)	
T2 ratio (TIRM)	**Normal** **Pathological**	**20**	4 (20%) 16 (80%)	0 (NA%) 0 (NA%)	p=1.000

Table XI: LVEF pathological values (increased or reduced) compared to parametric and non-parametric sequence for tissue characterization

Characteristic		N	LVEF Normal (N = 18)	LVEF Pathological (N = 32)	
T1 mapping pathological segments	**< 2** **≥ 2**	**50**	13 (72%) 5 (28%)	19 (59%) 13 (41%)	p=0.364
T1 mapping global value	**Normal** **Pathological**	**50**	18 (100%) 0 (0%)	28 (88%) 4 (12%)	p=0.118
T2 mapping pathological segments	**< 2** **≥ 2**	**50**	10 (56%) 8 (44%)	16 (50%) 16 (50%)	p=0.706
T2 mapping global value	**Normal** **Pathological**	**50**	15 (83%) 3 (17%)	22 (69%) 10 (31%)	p=0.259
ECV	**Normal** **Pathological**	**29**	2 (25%) 6 (75%)	1 (4.8%) 20 (95%)	p=0.110
LGE	**Negative** **Positive**	**50**	7 (39%) 11 (61%)	7 (22%) 25 (78%)	p=0.198
Pathological TIRM by qualitative analysis	**No**	**20**	6 (100%)	14 (100%)	
T2 ratio (TIRM)	**Normal** **Pathological**	**20**	2 (33%) 4 (67%)	2 (14%) 12 (86%)	p=0.329

Table XII: Comparison between patients with increased wall thickness and parametric imaging.

Characteristic		N	Increased wall thickness No (N = 47)	Increased wall thickness Yes (N = 3)	
T1 mapping ≥ 2 segments with values:	**Under upper limit** **Above upper limit**	**50**	38 (81%) 9 (19%)	3 (100%) 0 (0%)	p=0.403
T1 mapping ≥ 2 segments with values:	**Above lower limit** **Under lower limit**	**50**	41 (87%) 6 (13%)	1 (33%) 2 (67%)	p=0.014
T1 mapping global value	**Normal** **Pathological**	**50**	43 (91%) 4 (8.5%)	3 (100%) 0 (0%)	p=0.598
T2 mapping ≥ 2 segments with values:	**Under upper limit** **Above upper limit**	**50**	30 (64%) 17 (36%)	3 (100%) 0 (0%)	p=0.200
T2 mapping ≥ 2 segments with values:	**Above lower limit** **Under lower limit**	**50**	41 (87%) 6 (13%)	2 (67%) 1 (33%)	p=0.320
T2 mapping global value	**Normal** **Pathological**	**50**	35 (74%) 12 (26%)	2 (67%) 1 (33%)	p=0.765

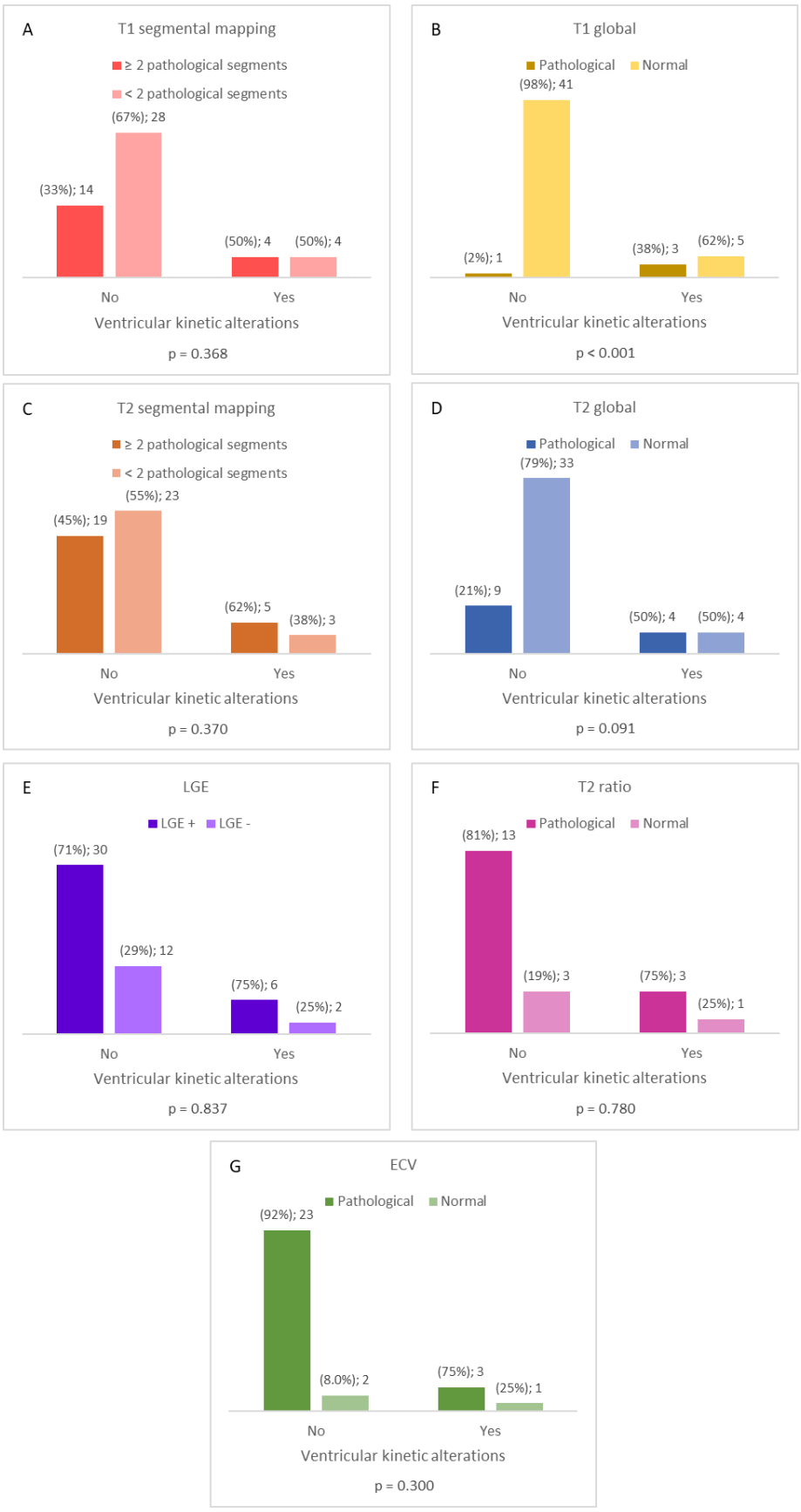


Figure 27: Bar charts that represent the correlation between athletes with ventricular kinetic alterations and T1 segmental (A), T1 global (B), T2 segmental (C), T2 global (D), LGE (E), T2 ratio (F), ECV (G).

CORRELATION BETWEEN CMR FINDINGS AND CLINICAL OR INSTRUMENTAL CHARACTERISTICS OF THE ATHLETES

Figures 28 and 29 show the correlation between subjects infected by Sars-CoV-2 versus parametric and non-parametric data. All the 5 athletes that were infected by the virus more than 3 months prior the CMR presented a positive non-ischemic LGE. Athletes that were infected by the virus less than 3 months prior the CMR presented non-ischemic LGE in 10 (83%). High percentages were obtained also for T2 ratio and ECV. In fact, ECV was pathological in all the patients who experienced COVID-19 prior to CMR examination. T1 and T2 mapping, both segmental and global, were predominantly normal.

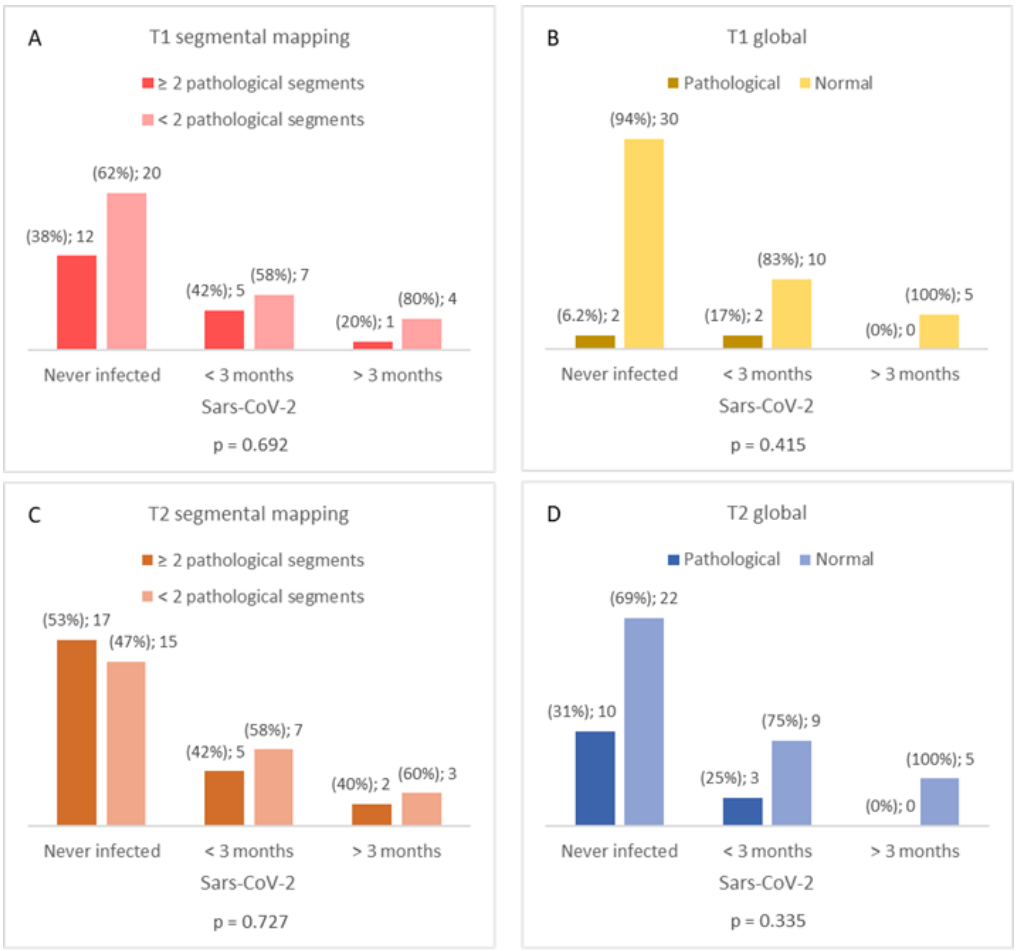


Figure 28: Bar charts that represent the correlation between participants infected by Sars-CoV-2 (> or < than 3 months prior CMR examination) and T1 mapping segmental (A), global (B), T2 mapping segmental (C), global (D).

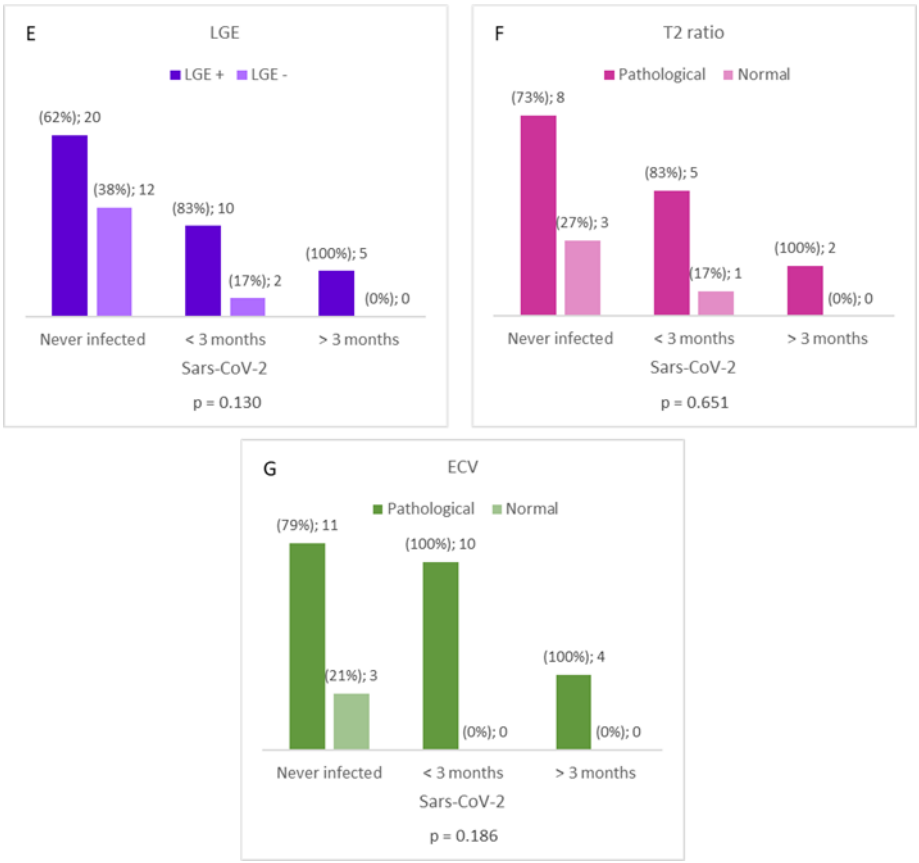


Figure 29: Bar charts that represent the correlation between participants infected by Sars-CoV-2 (> or < than 3 months prior CMR examination) and LGE (E), T2 ratio (F), ECV (G).

39 (78%) participants presented exercise induced ventricular arrythmias (EIVA) assessed through EST. LGE was present in 31 (79%) of the subjects with EIVA (p=0.026), while T2 ratio was pathological in 13 of them (81%, p=0.028) (Figures 30, 31).

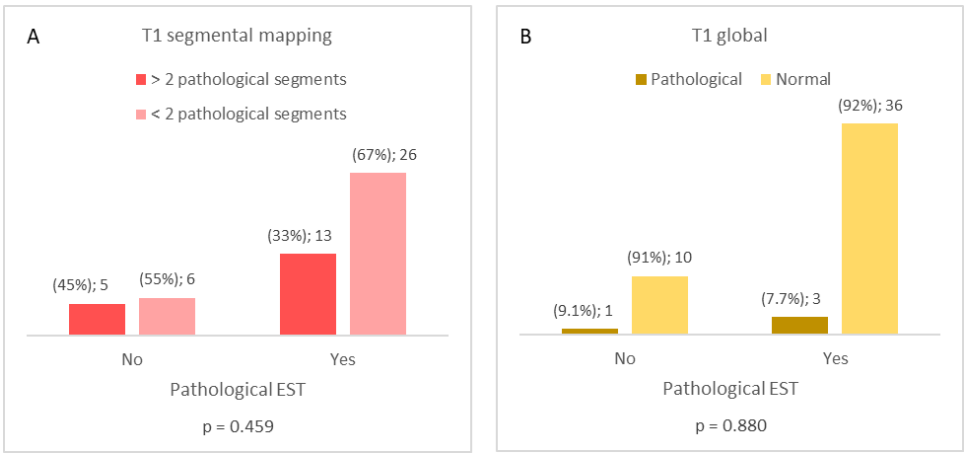


Figure 30: Bar charts that represent the correlation between athletes with pathological findings in EST (presence of PVB and/or repolarization alterations) and segmental T1 mapping (A) and global T1 (B).

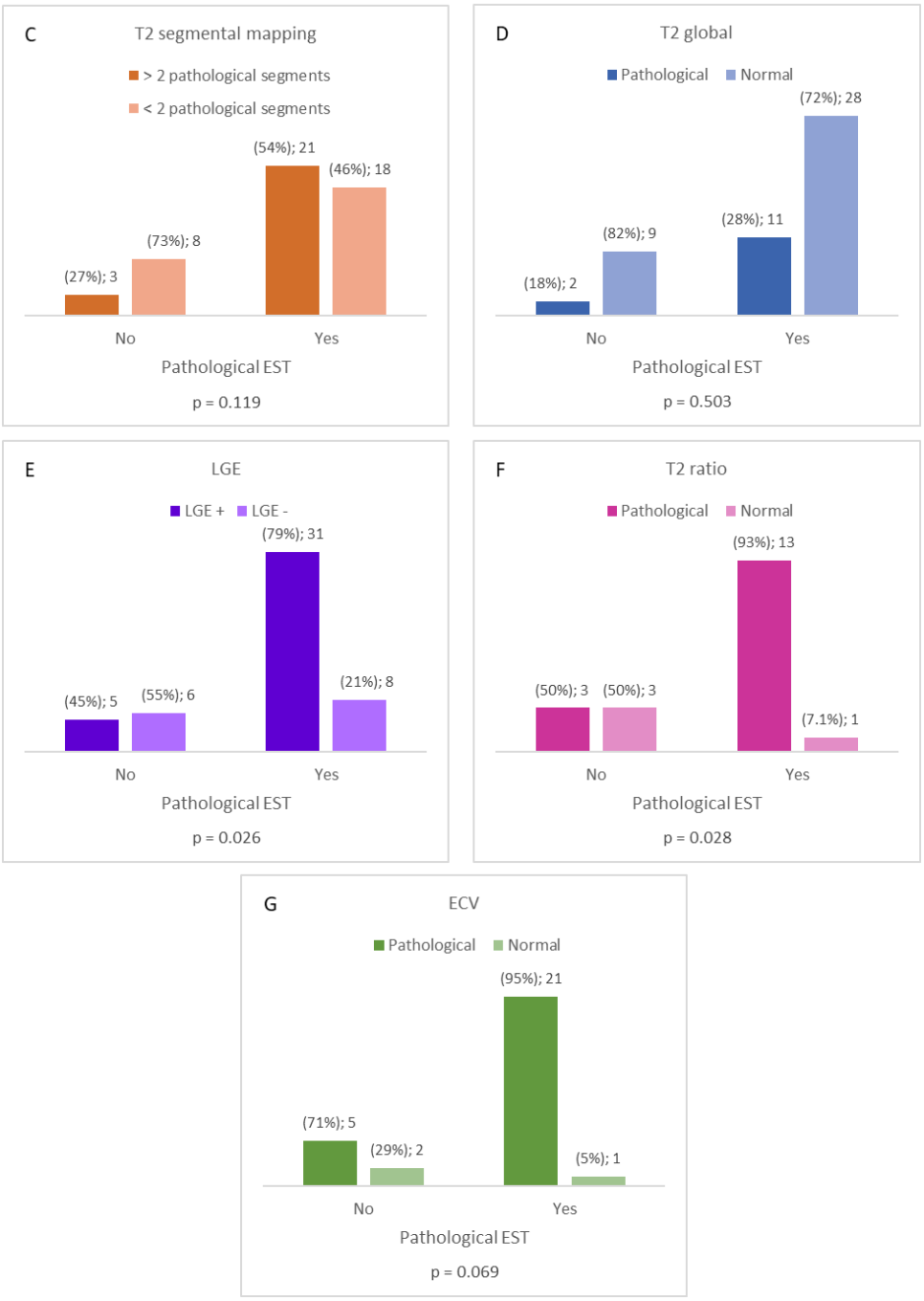


Figure 31: Bar charts that represent the correlation between athletes with pathological findings in EST (presence of PVB and/or repolarization alterations) andl segmental T2 mapping (C), global T2 (D), ECV (G), LGE (E), T2 ratio (F).

Table XIII and XIV include the results of the comparison between basal ECG and ECG-Holter respectively, and parametric and non-parametric imaging; while Figure 32 shows patients with at least one pathological exam between basal ECG, EST, ECG-Holter compared to parametric and non-parametric imaging. Once again 78% (31 subjects) with pathological outcomes presented non-ischemic LGE. More

than two T2 mapping pathological segments were present in 55% of the times (n=22, p=0.048), while T2 ratio was pathological 13 times (93%, p=0.028).

Table XIII: Pathological basal ECG compared to parametric and non-parametric imaging.

Characteristic		Basal ECG			
		N	Normal (N = 47)	Pathological (N = 3)	
T1 mapping pathological segments	**< 2** **≥ 2**	**50**	30 (64%) 17 (36%)	2 (67%) 1 (33%)	p=0.921
T1 mapping global	**Normal** **Pathological**	**50**	43 (91%) 4 (8.5%)	3 (100%) 0 (0%)	p=0.598
T2 mapping pathological segments	**< 2** **≥ 2**	**50**	24 (51%) 23 (49%)	2 (67%) 1 (33%)	p=0.600
T2 mapping global	**Normal** **Pathological**	**50**	35 (74%) 12 (26%)	2 (67%) 1 (33%)	p=0.765
ECV	**Normal** **Pathological**	**29**	3 (11%) 25 (89%)	0 (0%) 1 (100%)	p=0.730
LGE	**Negative** **Positive**	**50**	13 (28%) 34 (72%)	1 (33%) 2 (67%)	p=0.832
Pathological TIRM by qualitative analysis	**No**	**20**	18 (100%)	2 (100%)	
T2 ratio	**Normal** **Pathological**	**20**	4 (22%) 14 (78%)	0 (0%) 2 (100%)	p=0.456

Table XIV: Pathological ECG-Holter compared to parametric and non-parametric imaging.

Characteristic		ECG-Holter			
		N	Normal (N = 17)	Pathological (N= 12)	
T1 mapping pathological segments	**< 2** **≥ 2**	**29**	8 (47%) 9 (53%)	8 (67%) 4 (33%)	p=0.296
T1 mapping global	**Normal** **Pathological**	**29**	16 (94%) 1 (5.9%)	10 (83%) 2 (17%)	p=0.348
T2 mapping pathological segments	**< 2** **≥ 2**	**29**	9 (53%) 8 (47%)	4 (33%) 8 (67%)	p=0.296
T2 mapping global	**Normal** **Pathological**	**29**	13 (76%) 4 (24%)	6 (50%) 6 (50%)	p=0.140
ECV	**Normal** **Pathological**	**14**	2 (22%) 7 (78%)	0 (0%) 5 (100%)	p=0.255
LGE	**Negative** **Positive**	**29**	7 (41%) 10 (59%)	2 (17%) 10 (83%)	p=0.160
Pathological TIRM by qualitative analysis	**No**	**12**	8 (100%)	4 (100%)	
T2 ratio	**Normal** **Pathological**	**12**	2 (25%) 6 (75%)	0 (0%) 4 (100%)	p=0.273

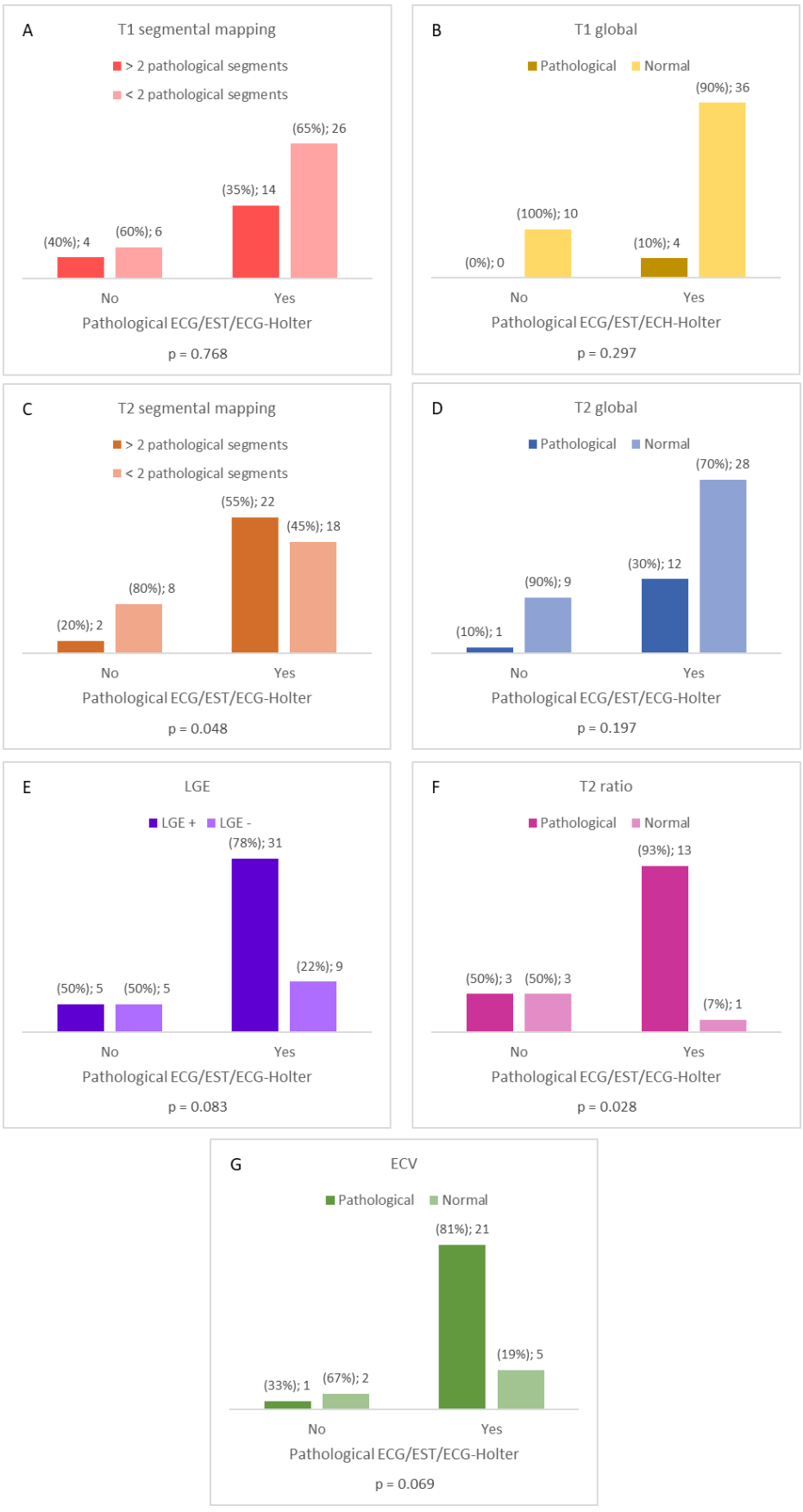


Figure 32: Bar charts that represent the correlation between participants with pathological findings in either ECG and/or EST and/or ECG-Holter and T1 mapping segmental (A), global (B), T2 mapping segmental (C), global (D), LGE (E), T2 ratio (F), ECV (G).

We did not find significant differences in the clinical, instrumental and CMR data stratified according to age group (pediatric athletes ≤ 18 years-old versus adult athletes > 18 years old) (see Tables XV and XVI)

Table XV: Clinical and instrumental data stratified according to age groups.

Characteristic		**N**	**≤ 18 years**	**(N = 25)**	**> 18 years**	**(N = 25)**	**q-value**
Sex	*Female*	50	3	(12%)	4	(16%)	>0.9
	Male		22	(88%)	21	(84%)	
Years of activity	Median (IQR)	33	5	(1, 10)	16	(7, 26)	0.2
	Mean (SD)		6	(4)	18	(13)	
Symptoms	*None*	50	23	(92%)	21	(84%)	>0.9
	Oppressive chest pain		2	(8%)	0	(0%)	
	Lypothimia after exercise		0	(0%)	1	(4%)	
	Palpitations at rest and/or during and after excercise		0	(0%)	3	(12%)	
Diabetes mellitus type 1	*No*	50	25	(100%)	24	(96%)	>0.9
	Yes		0	(0%)	1	(4.0%)	
Sars-CoV-2	*Never infected*	50	13	(52%)	19	(79%)	0.8
	Infected <3 months before CMR		8	(32%)	4	(16%)	
	Infected >3 months before CMR		3	(12%)	2	(8.3%)	
	No information		1	(4%)	0	(0%)	
ECG	*Normal*	50	25	(100%)	22	(88%)	0.8
	Pathological		0	(0%)	3	(12%)	
EST	*Normal*	50	6	(24%)	5	(20%)	>0.9
	Pathological		19	(76%)	20	(80%)	
Holter	*Normal*	29	8	(57%)	9	(60%)	>0.9
	Pathological		6	(43%)	6	(40%)	
Pathological ECG and/or EST and/or ECG-Holter	*No*	50	5	(20%)	5	(20%)	>0.9
	Yes		20	(80%)	20	(80%)	

Table XVI: CMR data stratified according to age groups.

Characteristic		**N**	**≤ 18 years**	**(N = 25)**	**> 18 years**	**(N = 25)**	**q-value**
≥ 2 T1 pathological segments	*No*	50	15	(60%)	17	(68%)	>0.9
	Yes		10	(40%)	8	(32%)	
T1 mapping global	*Normal*	50	24	(96%)	22	(88%)	>0.9
	Pathological		1	(4.0%)	3	(12%)	
ECV global	*Normal*	29	1	(6.7%)	2	(14%)	>0.9
	Pathological		14	(93%)	12	(86%)	
≥ 2 T2 pathological segments	*Normal*	50	16	(64%)	10	(40%)	0.6
	Pathological		9	(36%)	15	(60%)	
T2 mapping global	*Normal*	50	22	(88%)	15	(60%)	0.3
	Pathological		3	(12%)	10	(40%)	
T2 ratio	*Normal*	20	2	(18%)	2	(22%)	>0.9
	Pathological		9	(82%)	7	(78%)	
LVEF	*Normal*	50	8	(32%)	10	(40%)	>0.9
	Pathological		17	(68%)	15	(60%)	
Atrial dilation (> 15 mm)	*No*	50	25	(100%)	19	(76%)	0.3
	Yes		0	(0%)	6	(24%)	
Ventricular dilation	*No*	50	19	(76%)	11	(44%)	0.3
	Yes		6	(24%)	14	(56%)	
Kinetic alterations	*No*	50	23	(92%)	19	(76%)	0.8
	Yes		2	(8.0%)	6	(24%)	
LGE	*Negative*	50	7	(28%)	7	(28%)	>0.9
	Positive		18	(72%)	18	(72%)	
Hypoperfusion	*No*	50	25	(100%)	24	(96%)	>0.9
	Yes		0	(0%)	1	(4.0%)	

DISCUSSION

COMPARISON OF T1 AND T2 MAPPING VALUES BETWEEN OUR POPULATION OF ATHLETES AND REFERENCE VALUES

Parametric T1, T2 mapping and ECV provide a direct, quantitative myocardial characterization without the need for contrast agents for T1 and T2 images or reference regions of interest to detect changes within the myocardium. The application of a segmental approach allows a full sampling of the LV and precise localization of potential alterations, improving the sensitivity in detecting early pathological findings.

Our study shows that, in the given population of highly trained subjects, pathological segments by mapping have not been found frequently and there was not segments significantly more frequently abnormal compared to the others. Conversely, by LGE the distribution of pathological segments was significantly different being the infero-lateral wall more frequently involved. T1 mapping segmental values, when evaluated in each segment alone were 90% of the times in average within the normal range limit, compared to age group and sex, and the same result has been assessed for T1 global values (n=42, 92%). Higher percentages are obtained when considered if the patient has 2 or more pathological segments, rising to 36% (n=18). As for T2 mapping 48% (n=24) of the participants had ≥ 2 segments with abnormal values, while the global values were altered in 26% of them (n=13).

On the other hand, ECV global values were pathological in 90% (n=26) of the athletes in which it was evaluated (n=29). Eleven of them were lower than the normal reference range and 15 were higher.

The fact that T1 and T2 mapping values have been found predominantly normal is in accordance with Mordi et al. 2016 (62) study, in which they examined 58 men in total: 21 with a history of aerobic exercise, 16 with mild DCM and 21 age-matched healthy controls. The results proved that athletes shared the same values in T1, T2 and ECV as the healthy controls, while DCM patients had significantly higher numbers. Midwall LGE presence was found in 4 subjects in the DCM groups

(25%) and, contrarily to our study, only 2 athletes (10%) had small amounts of LGE at the right ventricular insertion points. Therefore, they pointed out that T1, T2 mapping and ECV calculation could be very useful to differentiate between athlete's heart and DCM and they were also able to assess diffuse myocardial fibrosis missed by LGE. The authors suggest that the reason why T1, T2 and ECV values can be find normal in athletes could be because the pathological processes that contribute to the development of irreversible myocardial injury in DCM in these subjects do not occur, despite the ventricular remodelling caused by exercise. An important limitation in this study is that they only examined males, excluding females. [Mordi et al. 2016 (62)]

The same considerations can not be made for ECV values, in fact our study differs from many others published literature. Like the one mentioned above, they demonstrated that endurance exercise does not lead to a variation of ECV or at least it causes a slight raise while still being within the normal range. For example Banks' et al. study (2017) (64) compared 40 healthy middle-aged endurance athletes with a minimum of 10 years of competitive endurance sport history with recreationally active control subjects. It demonstrated that endurance athletes had a higher ECV fraction as opposed to recreationally active adults, while still being within the normal range. [Banks et al. 2017 (64)]. Although, alterations in ECV values can still support the hypothesis of a physiological cardiac adaption of the heart to exercise.

In our study T1 and T2 values were also measured only in mid-septum (segments 8 and 9) and resulted pathological respectively in 39 (78%) and 17 subjects (34%). The percentages of altered T1, unlike T2, are clearly higher if compared to the rest of the left ventricular segments. The added bonus of evaluating mid-septum values was studied by Görmeli et al. 2016 (65) study, even though the main difference is that they used a 3T machinery and we used a 1.5T. In this study they wanted to show the correlation between athletes' cardiac modifications and myocardial fibrosis, comparing 41 healthy non-athletic control subjects and 46 athletes. Athletes were then divided in two groups depending on whether they had been training for more or less than 5 years. This cut-off was set based on a study which suggested that less of 5 years of training would not lead to any specific

risk for cardiac disease in young athletes [Maron et al. 1986 (81)]. Unlike our study, the native T1 values resulted to be increased in athletes compared to non-athletic controls. Furthermore, native T1 values were significantly higher in athletes who had more than 5 years of sports activity, rather than athletes of less than 5 years. However, it revealed that in athletes who had more than 5 years of sports activity, there was a raise in in the interventricular septum thickness and in the T1 mapping values compared to the left ventricular global values, with a significant positive correlation when compared to athletes who had less than 5 years of sports activity. Therefore, the authors suggest that evaluating the interventricular septum with native T1 mapping can provide important hints about cardiac remodelling, because native T1 values may be affected more significantly than it would in the remaining myocardium.

EVALUATION OF THE ADDITIONAL VALUE OF PARAMETRIC SEQUENCES COMPARED TO NON-PARAMETRIC TECHNIQUES IN TRAINED SUBJECTS

The high percentages of LGE findings (n=36, 72%) in our population are in line with what Breuckmann et al. pointed out in 2009 (59) in a population of one hundred and 2 healthy marathon runners. Among their population, 5 had an ischemic pattern of LGE, and 7 had a non-ischemic pattern of LGE. The prevalence of LGE in runners was higher than that in age matched control subjects suggested that the amount of exercise conducted by the marathon runners may have had a role in the development of LGE. Regardless of the underlying mechanism and the cardiac structural alteration, such as replacement scarring or interstitial fibrosis, LGE may represent the substrate responsible for ventricular tachyarrhythmias.

In our study, however, when LGE is compared to parametric imaging, it seems to have a superior diagnostic performance over segmental and global T1 mapping. Among the athletes with positive non-ischemic LGE most of them had normal T1 values both in singular segments and in global. On the contrary, if we considered only the mid-septum T1 mapping values were altered in 81% of LGE+ patients (p=0.484), showing that T1 values in septum can maybe provide important hints about cardiac remodelling.

Moreover, ECV global values are altered in all the LGE+ patients in which it had been measured (n=21, p=0.015). These results reflect what Tahir et al. (63) investigated in their study in 2018. They studied the presence of myocardial fibrosis in competitive triathletes detected by late gadolinium-enhancement (LGE) in correlation with the performance. They also measured T1 mapping, T1 post-contrast and ECV to study diffuse myocardial fibrosis, which is not detected by LGE. They excluded areas of focal LGE from T1 and ECV measurements in order to evaluate these parameters unbiased from the presence of LGE. 83 competitive triathletes and 36 control subjects with a similar distribution of age and sex were enrolled. The results showed that triathletes with presence of LGE had higher ECV values in LGE negative areas of myocardium, indicating diffuse myocardial fibrosis in these subjects, while LGE negative athletes had normal ECV. This suggests that fibrosis might not be limited to the macroscopically visible areas of non-ischemic LGE in these individuals. They also found lower native T1 values in male and female triathletes than in controls. The reason for this finding is currently unclear to the authors, but it may be related to reduced free water content in the presence of LV hypertrophy. [Tahir et al. 2018 (63)]
Increased ECV, can be considered a validated surrogate marker of diffuse fibrosis. [Miller et al., 2013 (82)].

Global T2 ratio resulted pathological in 16 out of 20 patients. When compared with T2 mapping it resulted that 8 of these subjects (50%) had ≥ 2 pathological T2 mapping segments, while 8 (50%) were normal (p=1.000). Global values were altered in 5 (31%) patients and 11 (69%) were normal (p=0.530). ECV global values were abnormal in all the 9 patients in which it was evaluated (p=1.000).

Abergel et al., 2004 (83) demonstrated that in a large homogeneous cohort of highly trained elite cyclists numerous myocardial adaptations occur, such as an increase in end-diastolic diameter, volume, and mass, leading to a reduction in LVEF. This has important clinical implications, particularly in the differentiation between the normal cardiac adaptations to exercise and athletes, in whom the changes in myocardial structure and function are the early signs of DCM. For these

reasons, the use of criteria such as LVEF, could not be enough to discriminate between early DCM and physiological adaptation to exercise.
In our study LVEF was either higher or lower than normal values in 32 patients (64%). Once again, the only parameter which correlated almost completely with LVEF pathological values was global ECV, in fact it was abnormal in 95% of patients (n=20, p=0.110)). Only one patient had altered LVEF and normal ECV. LGE was positive in 78% (n=25, p=0.198) patients with positive LVEF while 22% of them were LGE-. T1 global mapping was positive in only 12% (n=4, p=0.118) of the patients with LVEF+, while 88% (n=25) had normal values. More than two T1 mapping pathological segments were present in 41% (n=13, p=0.364) of LVEF+ patients. This suggests that probably segmental T1 mapping is not superior to LGE in evaluating myocardial adaptions that can emerge in athletes and consequently cause LVEF alterations. T2 ratio was pathological in 86% (n=12, p=0.329) of LVEF+ patients, while T2 mapping altered global values and ≥ 2 pathological segments were found respectively in 31% (n=10, p=0.259) and 50% (n=16, p=0.706) LVEF+ patients.

A correlation between the absence of kinetic alterations and T1 global mapping has been found, in fact, 98% (n=41) of patients without kinetic alterations had normal T1 values (p=<0.001).

In 6 patients atrial dilatation was found, of those, 5 underwent ECV global evaluation and in all of them it presented pathological values. LGE was positive in 67% of them (n=4, p=0.756); T1 and T2 global in respectively 17% (n=1, p=0.404) and 33% (n=2, p=0.662); ≥ 2 T1 and T2 pathological segments both in 50% (n=3, p=0.446, p=0.917); T2 ratio in none of them.

Ventricular dilatation was detected in 20 subjects (40% of total), only 4 also had increased wall thickness. Pujadas et al. (2018) (84) investigated the presence of diffuse and focal myocardial fibrosis in a series of high-performance veteran endurance athletes. They enrolled 34 veteran healthy male endurance athletes, still being in regular training, with more than 10 years of exercise and a control

group based on 12 non-trained normal individuals. It turned out that cardiac remodelling in endurance athletes is characterised by a balanced increase in left and right ventricular volumes and in left ventricular wall thickness, while the indexed myocardial mass was normal. On the other hand, native T1 values and ECV were normal in all cases, meaning that the remodelling process in high trained individuals does not involve an expansion of the interstitial space, suggesting a physiological adaptive phenomenon. These results are in accordance with the aforementioned Mordi et al. study (62) in which they did not find alterations in ECV in veteran endurance athletes compared with sedentary controls. At the same time, they differ from the outcomes of another study by McDiarmid et al. 2016 (85), which showed that in young athletes the increase in left ventricular mass is due to an increased cellular mass, thus giving as a result a relative decrease in ECV compared with controls. They also observed a lower value of ECV in higher performance athletes versus low performance ones. Even these findings support the hypothesis of a physiological cardiac adaptation. The authors suggest that this discrepancy may be explained by differences in athlete population between Pujadas' study and McDiarmid's: the first one in fact considered a much older population than the other.

The T1 mapping results of the Pujadas' et al. study seem to be in accordance with the ones of our study even though the populations examined are different. The majority of the subjects with ventricular dilatation (n=14, 70%, p=0.470) had normal T1 mapping segments and 90% (n=18, p=0.670) had normal T1 global values. The same was found in T2 mapping, global values were normal in 85% (n=17, p=0.355) of the patients, while 40% (n=8, p=0.148) had pathological segmental values. On the contrary, ECV global values were evaluated only in 14 patients with ventricular dilatation, they resulted pathological in 86% of the patients (n=12, p=0.501) and normal only twice. LGE was positive in 65% (n=13, p=0.368) of patients with ventricular dilatation and T2 ratio in 71% (n=5, p=0.482).

ASSESSMENT OF THE CORRELATION BETWEEN CMR FINDINGS AND CLINICAL CHARACTERISTICS OF PATIENTS.

Cipriani et al. in 2019 (68) performed CMR in athletes from 15 to 50 years old who suffered of frequent or repetitive premature ventricular beats (PVBs). Clinical and CMR findings were compared between athletes with exercise induced ventricular arrhythmias (EIVA) versus non exercise induced ventricular arrhythmias. We included 36 athletes with EIVA with non-EIVA. CMR revealed cardiac abnormalities in 20 (56%) athletes with EIVA and in 5 (21%) with non-EIVA. In particular, left ventricular LGE was identified in 17 (47%) athletes with EIVA and in 3 (13%) with non-EIVA, mostly with a non-ischemic pattern. Predictors of abnormal CMR were T-wave inversion on ECG, complex ventricular arrhythmias on 24-hour ECG-Holter and complex EIVA with a right-bundle-branch-block (RBBB) or polymorphic morphology on exercise testing. The study concluded that pathological myocardial substrates on CMR were observed significantly more often in athletes with EIVA compared to those with non-EIVA. Moreover, the athletes with the highest probability of CMR abnormalities presented repolarization abnormalities on basal ECG and complex EIVA with a right-bundle-branch-block or polymorphic morphology.

In our study, 78% (n=39) of the participants showed EIVAs, in particular, 31% (n=12) had repolarization alterations and 79% (n=31) had PVBs. In contrast with the previous study, it is not possible to determine if one of the two EIVA is more prone to be associated with pathological findings in CMR. In fact, alterations were found in the same percentage of patients with EIVA for each parametric and non-parametric sequence, likewise for non-EIVA. However, LGE and T2 ratio seem to be more useful to detect CMR abnormalities than parametric imaging. LGE was present in 31 (79%) of the subjects with EIVA (p=0.026), while T2 ratio was pathological in 13 of them (81%, p=0.028). This may be due to the fact that ECG alterations occur mainly when myocardial tissue is affected by major tissue alterations which are more visible with techniques such as LGE or TIRM.

24-h ECG-Holter was considered pathological when it presented repetitive PBVs (n=12, 24%). In this case T2 global mapping appears to be more helpful, in fact 50% have altered global T2 values (p=0.140). Moreover, when at least one between

ECG, ECG-Holter or EST was abnormal, ≥ 2 T2 mapping pathological segments were present in 55% of the patients (n=22, p=0.048), while T2 ratio was pathological in 13 of them (93%, p=0.028).

Myocardial injury is not uncommon in Sars-CoV-2 infection and it can be caused by ischemia, inflammation, or myocarditis. [Atri et al., 2020 (86)]. If athletes return to training too early after viral infection or with silent myocarditis they may have serious consequences [Halle et al., 2020 (87)]. In fact, non-Covid-19 myocarditis is responsible fot 4% to 8% of sudden cardiac deaths in athletes (49,50) or may lead to long-term complications such as myocardial scarring, arrhythmias, and myocardial dysfunction [Marijon et al., 2011 (88)]. Across the studies, the prevalence of myocarditis-like findings on CMR for athletes after Sars-CoV-2 infection is highly variable across the studies. Larger multicenter studies showed lower prevalence rates. A potential false-positive CMR finding was LGE+ at the RV insertion point that has been previously reported in association with athletic activity [Domenech-Ximenos et al., 2020 (89)] and is unlikely to be related to COVID-19. In our study, athletes that were infected by the virus were more likely to have non ischemic LGE findings (100% if infected > 3 months, 83% if < 3 months, p=0.130), similar percentages were obtained for TIRM imaging even though the number of patients evaluated were low. These results correlate with the first publication on CMR in athletes, Rajpal et al. 2021 (90), which has been one of the few that found myocardial LGE in 46% of their population of 26 college athletes, with 4 (15%) having myocarditis-like findings on CMR. ECV global values were pathological among all the patients who recovered from the illness (p=<0.001), demonstrating to be once again a validated surrogate marker of diffuse fibrosis. T1 and T2 mapping did not correlate with pathological findings assessed with non-parametric imaging. This is opposed to Pan et al., 2021 (91) which showed that segmental and global T1 and T2 values were higher than healthy controls. Although the main differences between their study and ours is the use of a 3T machinery, and the population numerosity and characteristics.

LIMITATIONS

The main limitation of our study is that the examined population is strongly unbalanced both for age and sex.

The T1 and T2 normal reference ranges in our centre were not calculated for a paediatric population. Hence, in this study, T1 and T2 mapping results of subjects younger than 19 years old were compared to the 20-29 years age group reference values.

Moreover, TIRM evaluations are limited because such sequences were available only in 20 patients.

CONCLUSION

CMR is the primary imaging modality for myocardial tissue characterisation, and it can be considered as the gold standard test for quantifying cardiac function, myocardial volumes, and mass, even though this population consisted of predominantly healthy subjects.

In our knowledge, besides morphological and functional alterations which can be found in the athlete's heart, relevant data does not emerge in mapping techniques. Pathological segmental and global T1 and T2 mapping values can be found in athletes, however they are frequently normal. On the other hand, ECV global values are more likely to be pathological suggesting a better role as a surrogate marker of diffuse fibrosis. Mid-septum T1 values are clearly more frequently pathological.

Few statistically significant correlations between parametric and non-parametric imaging were found, apparently parametric imaging give an additional advantage in in a low percentage of the cases. LGE appears to be superior to mapping sequences in identifying injured patients.

Athletes with altered EST or Holter, seem to benefit more from LGE than from T1 and T2 mapping to identify cardiac abnormalities. Once again ECV is the most useful tool in parametric imaging and correlates very well with LGE findings.

ECV had statistically significant results even when compared to patients infected less or more than 3 months prior CMR examination.

We can conclude that parametric sequences in our study population show additional diagnostic value in a low percentage of the cases.

Our results require further evaluation in a larger population and prospective data are recommended.

BIBLIOGRAPHY

1. Aquaro GD, Camastra G, Monti L, Lombardi M, Pepe A, Castelletti S, Maestrini V, Todiere G, Masci P, di Giovine G, Barison A, Dellegrottaglie S, Perazzolo Marra M, Pontone G, Di Bella G; working group "Applicazioni della Risonanza Magnetica" of the Italian Society of Cardiology. Reference values of cardiac volumes, dimensions, and new functional parameters by MR: A multicenter, multivendor study. Journal of Magnetic Resonance Imaging. 2017;45(4):1055–67.

2. Seraphim A, Knott KD, Augusto J, Bhuva AN, Manisty C, Moon JC. Quantitative cardiac MRI. Journal of Magnetic Resonance Imaging. 2020;51(3):693–711.

3. Meloni A, Martini N, Positano V, D'Angelo G, Barison A, Todiere G, Grigoratos C, Barra V, Pistoia L, Gargani L, Ripoli A, Pepe A. Myocardial T1 Values at 1.5 T: Normal Values for General Electric Scanners and Sex-Related Differences. Magnetic Resonance Imaging. 2021 Nov;54(5):1486–500.

4. Meloni A, Nicola M, Positano V, D'Angelo G, Barison A, Todiere G, Grigoratos C, Keilberg P, Pistoia L, Gargani L, Ripoli A, Pepe A. Myocardial T2 values at 1.5 T by a segmental approach with healthy aging and gender. Eur Radiol. 2022 May;32(5):2962–75.

5. Moon JC, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M, Gatehouse PD, Arai AE, Friedrich MG, Neubauer S, Schulz-Menger J, Schelbert EB. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. J Cardiovasc Magn Reson. 2013 Dec;15(1):92.

6. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017 Dec;19(1):75.

7. ACCF/ACR/AHA/NASCI/SCMR 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Jun 8;55(23):2614–62.

8. Rehwald WG, Fieno DS, Chen EL, Kim RJ, Judd RM. Myocardial Magnetic Resonance Imaging Contrast Agent Concentrations After Reversible and Irreversible Ischemic Injury. Circulation. 2002 Jan 15;105(2):224–9.

9. Kim RJ, Judd RM, Chen EL, Fieno DS, Parrish TB, Lima JAC. Relationship of Elevated ^{23} Na Magnetic Resonance Image Intensity to Infarct Size After Acute Reperfused Myocardial Infarction. Circulation. 1999 Jul 13;100(2):185–92.

10. Vogel-Claussen J, Rochitte CE, Wu KC, Kamel IR, Foo TK, Lima JA, Bluemke DA. Delayed enhancement MR imaging: utility in myocardial assessment. Radiographics. 2006 Jun;26(3):795–810.

11. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. European Heart Journal. 2005 Aug 1;26(15):1461–74.

12. Sado DM, Flett AS, Moon JC. Novel imaging techniques for diffuse myocardial fibrosis. Future Cardiology. 2011 Sep;7(5):643–50.

13. Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. J Cardiovasc Magn Reson. 2011 Feb 18;13(1):13.

14. Simonetti OP, Finn JP, White RD, Laub G, Henry DA. 'Black blood' T2-weighted inversion-recovery MR imaging of the heart. Radiology. 1996 Apr;199(1):49–57.

15. Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM, Finn JP, Judd RM. An improved MR imaging technique for the visualization of myocardial infarction. Radiology. 2001 Jan;218(1):215–23.

16. Abdel-Aty H, Simonetti O, Friedrich MG. T2-weighted cardiovascular magnetic resonance imaging. Journal of Magnetic Resonance Imaging. 2007;26(3):452–9.

17. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. J Cardiovasc Magn Reson. 2016 Nov 30;18:89.

18. Meloni A, Martini N, Positano V, De Luca A, Pistoia L, Sbragi S, Spasiano A, Casini T, Bitti PP, Allò M, Sanna PMG, De Caterina R, Sinagra G, Pepe A. Myocardial iron overload by cardiovascular magnetic resonance native segmental T1 mapping: a sensitive approach that correlates with cardiac complications. J Cardiovasc Magn Reson. 2021 Jun 14;23:70.

19. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. Magnetic Resonance in Medicine. 2004;52(1):141–6.

20. Look DC, Locker DR. Time saving in measurement of NMR and EPR relaxation times. Rev Sci Instrum. 1970;

21. Hamlin SA, Henry TS, Little BP, Lerakis S, Stillman AE. Mapping the Future of Cardiac MR Imaging: Case-based Review of T1 and T2 Mapping Techniques.

RadioGraphics [Internet]. 2014 Oct 13 [cited 2022 Jul 20]; Available from: https://pubs.rsna.org/doi/10.1148/rg.346140030

22. Nacif MS, Turkbey EB, Gai N, Nazarian S, van der Geest RJ, Noureldin RA, Sibley CT, Ugander M, Liu S, Arai AE, Lima JA, Bluemke DA. Myocardial T1 Mapping with MRI: comparison of Look-Locker and MOLLI sequences. J Magn Reson Imaging. 2011 Dec;34(6):1367–73.

23. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. J Cardiovasc Magn Reson. 2012 Sep 10;14(1):63.

24. Kim PK, Hong YJ, Im DJ, Suh YJ, Park CH, Kim JY, Chang S, Lee HJ, Hur J, Kim YJ, Choi BW. Myocardial T1 and T2 Mapping: Techniques and Clinical Applications. Korean J Radiol. 2017;18(1):113.

25. Piechnik SK, Ferreira VM, Dall'Armellina E, Cochlin LE, Greiser A, Neubauer S, Robson MD. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. J Cardiovasc Magn Reson. 2010 Dec;12(1):69.

26. Chow K, Flewitt JA, Green JD, Pagano JJ, Friedrich MG, Thompson RB. Saturation recovery single-shot acquisition (SASHA) for myocardial T1 mapping. Magnetic Resonance in Medicine. 2014;71(6):2082–95.

27. Weingärtner S, Akçakaya M, Basha T, Kissinger KV, Goddu B, Berg S, Manning WJ, Nezafat R. Combined saturation/inversion recovery sequences for improved evaluation of scar and diffuse fibrosis in patients with arrhythmia or heart rate variability. Magnetic Resonance in Medicine. 2014;71(3):1024–34.

28. Xue H, Shah S, Greiser A, Guetter C, Littmann A, Jolly MP, Arai AE, Zuehlsdorff S, Guehring J, Kellman P. Motion Correction for Myocardial T1 Mapping using Image Registration with Synthetic Image Estimation. Magn Reson Med. 2012 Jun;67(6):1644–55.

29. Xue H, Greiser A, Zuehlsdorff S, Jolly MP, Guehring J, Arai AE, Kellman P. Phase-Sensitive Inversion Recovery for Myocardial T1 Mapping with Motion Correction and Parametric Fitting. Magn Reson Med. 2013 May;69(5):1408–20.

30. Kellman P, Arai AE, Xue H. T1 and extracellular volume mapping in the heart: estimation of error maps and the influence of noise on precision. J Cardiovasc Magn Reson. 2013 Jun 21;15(1):56.

31. O'Brien AT, Gil KE, Varghese J, Simonetti OP, Zareba KM. T2 mapping in myocardial disease: a comprehensive review. J Cardiovasc Magn Reson. 2022 Jun 6;24:33.

32. Giri S, Chung YC, Merchant A, Mihai G, Rajagopalan S, Raman SV, Simonetti OP. T2 quantification for improved detection of myocardial edema. J Cardiovasc Magn Reson. 2009 Dec 30;11(1):56.

33. Akçakaya M, Basha TA, Weingärtner S, Roujol S, Berg S, Nezafat R. Improved Quantitative Myocardial T2 Mapping. Magn Reson Med. 2015 Jul;74(1):93–105.

34. Liu CY, Liu YC, Wu C, Armstrong A, Volpe GJ, van der Geest RJ, Liu Y, Hundley WG, Gomes AS, Liu S, Nacif M, Bluemke DA, Lima JAC. Evaluation of Age-Related Interstitial Myocardial Fibrosis With Cardiac Magnetic Resonance Contrast-Enhanced T1 Mapping in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2013 Oct 1;62(14):10.1016/j.jacc.2013.05.078.

35. Bönner F, Janzarik N, Jacoby C, Spieker M, Schnackenburg B, Range F, Butzbach B, Haberkorn S, Westenfeld R, Neizel-Wittke M, Flögel U, Kelm M. Myocardial T2 mapping reveals age- and sex-related differences in volunteers. J Cardiovasc Magn Reson. 2015 Feb 6;17(1):9.

36. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA. 2006 Oct 4;296(13):1593–601.

37. Decree of the Italian Ministry of Health, 18 February 1982. Norme per la tutela sanitaria dell'attività sportiva agonistica (rules concerning the medical protection of athletic activity). Gazzetta Ufficiale 1982; 63.

38. Biffi A, Delise P, Zeppilli P, Giada F, Pelliccia A, Penco M, Casasco M, Colonna P, D'Andrea A, D'Andrea L, Gazale G, Inama G, Spataro A, Villella A, Marino P, Pirelli S, Romano V, Cristiano A, Bettini R, Thiene G, Furlanello F, Corrado D; Italian Society of Sports Cardiology and Italian Sports Medicine Federation. Italian Cardiological Guidelines for Sports Eligibility in Athletes with Heart Disease: Part 1. Journal of Cardiovascular Medicine. 2013 Jul;14(7):477–99.

39. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, La Gerche A, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez MV, Riding NR, Saarel T, Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International recommendations for electrocardiographic interpretation in athletes. European Heart Journal. 2018 Apr 21;39(16):1466–80.

40. Pelliccia A, Caselli S, Sharma S, Basso C, Bax JJ, Corrado D, D'Andrea A, D'Ascenzi F, Di Paolo FM, Edvardsen T, Gati S, Galderisi M, Heidbuchel H, Nchimi A, Nieman K, Papadakis M, Pisicchio C, Schmied C, Popescu BA, Habib G, Grobbee D, Lancellotti P; Internal reviewers for EAPC and EACVI. European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement: recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete's heart. European Heart Journal. 2018 Jun 1;39(21):1949–69.

41. Mont L, Pelliccia A, Sharma S, Biffi A, Borjesson M, Brugada Terradellas J, Carré F, Guasch E, Heidbuchel H, La Gerche A, Lampert R, McKenna W, Papadakis M,

Priori SG, Scanavacca M, Thompson P, Sticherling C, Viskin S, Wilson M, Corrado D; Reviewers, Lip GY, Gorenek B, Blomström Lundqvist C, Merkely B, Hindricks G, Hernández-Madrid A, Lane D, Boriani G, Narasimhan C, Marquez MF, Haines D, Mackall J, Manuel Marques-Vidal P, Corra U, Halle M, Tiberi M, Niebauer J, Piepoli M. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Eur J Prev Cardiolog. 2017 Jan;24(1):41–69.

42. Zorzi A, Vessella T, De Lazzari M, Cipriani A, Menegon V, Sarto G, Spagnol R, Merlo L, Pegoraro C, Marra MP, Corrado D, Sarto P. Screening young athletes for diseases at risk of sudden cardiac death: role of stress testing for ventricular arrhythmias. Eur J Prev Cardiol. 2020 Feb;27(3):311–20.

43. Fogel MA. Cardiac Magnetic Resonance in Sports Medicine: Current Sports Medicine Reports. 2008 Mar;7(2):81–5.

44. Luijkx T, Cramer MJ, Prakken NH, Buckens CF, Mosterd A, Rienks R, Backx FJ, Mali WP, Velthuis BK. Sport category is an important determinant of cardiac adaptation: an MRI study. Br J Sports Med. 2012 Dec;46(16):1119–24.

45. Sharma S, Merghani A, Mont L. Exercise and the heart: the good, the bad, and the ugly. European Heart Journal. 2015 Jun 1;36(23):1445–53.

46. Maron BJ, Pelliccia A. The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation. 2006 Oct 10;114(15):1633–44.

47. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. Ann Intern Med. 1975 Apr;82(4):521–4.

48. Galderisi M, Cardim N, D'Andrea A, Bruder O, Cosyns B, Davin L, Donal E, Edvardsen T, Freitas A, Habib G, Kitsiou A, Plein S, Petersen SE, Popescu BA, Schroeder S, Burgstahler C, Lancellotti P. The multi-modality cardiac imaging approach to the Athlete's heart: an expert consensus of the European Association of Cardiovascular Imaging. European Heart Journal - Cardiovascular Imaging. 2015 Apr 1;16(4):353–353r.

49. Panno VA, Gulizia M, Colivicchi F, Lenarda AD, Casasco M, Zeppilli P, et al. COMPOSIZIONE COMITATO COCIS. 2017.

50. Pelliccia A, Spataro A, Caselli G, Maron BJ. Absence of left ventricular wall thickening in athletes engaged in intense power training. Am J Cardiol. 1993 Nov 1;72(14):1048–54.

51. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. N Engl J Med. 1991 Jan 31;324(5):295–301.

52. Caselli S, Di Paolo FM, Pisicchio C, Di Pietro R, Quattrini FM, Di Giacinto B, Culasso F, Pelliccia A. Three-dimensional echocardiographic characterization of left ventricular remodeling in Olympic athletes. Am J Cardiol. 2011 Jul 1;108(1):141–7.

53. Pelliccia A, Maron BJ, Di Paolo FM, Biffi A, Quattrini FM, Pisicchio C, Roselli A, Caselli S, Culasso F. Prevalence and Clinical Significance of Left Atrial Remodeling in Competitive Athletes. Journal of the American College of Cardiology. 2005 Aug;46(4):690–6.

54. D'Andrea A, Riegler L, Cocchia R, Scarafile R, Salerno G, Gravino R, Golia E, Vriz O, Citro R, Limongelli G, Calabrò P, Di Salvo G, Caso P, Russo MG, Bossone E, Calabrò R. Left atrial volume index in highly trained athletes. Am Heart J. 2010 Jun;159(6):1155–61.

55. Pelliccia A, Di Paolo FM, De Blasiis E, Quattrini FM, Pisicchio C, Guerra E, Culasso F, Maron BJ. Prevalence and clinical significance of aortic root dilation in highly trained competitive athletes. Circulation. 2010 Aug 17;122(7):698–706, 3 p following 706.

56. Makan J, Sharma S, Firoozi S, Whyte G, Jackson PG, McKenna WJ. Physiological upper limits of ventricular cavity size in highly trained adolescent athletes. Heart. 2005 Apr;91(4):495–9.

57. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008 Jun 10;51(23):2256–62.

58. Scharf M, Brem MH, Wilhelm M, Schoepf UJ, Uder M, Lell MM. Atrial and ventricular functional and structural adaptations of the heart in elite triathletes assessed with cardiac MR imaging. Radiology. 2010 Oct;257(1):71–9.

59. Breuckmann F, Möhlenkamp S, Nassenstein K, Lehmann N, Ladd S, Schmermund A, Sievers B, Schlosser T, Jöckel KH, Heusch G, Erbel R, Barkhausen J. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology. 2009 Apr;251(1):50–7.

60. Satoh H, Sano M, Suwa K, Saitoh T, Nobuhara M, Saotome M, Urushida T, Katoh H, Hayashi H. Distribution of late gadolinium enhancement in various types of cardiomyopathies: Significance in differential diagnosis, clinical features and prognosis. World J Cardiol. 2014 Jul 26;6(7):585–601.

61. Małek ŁA, Bucciarelli-Ducci C. Myocardial fibrosis in athletes—Current perspective. Clin Cardiol. 2020 Mar 19;43(8):882–8.

62. Mordi I, Carrick D, Bezerra H, Tzemos N. T_1 and T_2 mapping for early diagnosis of dilated non-ischaemic cardiomyopathy in middle-aged patients and differentiation from normal physiological adaptation. Eur Heart J Cardiovasc Imaging. 2016 Jul;17(7):797–803.

63. Tahir E, Starekova J, Muellerleile K, von Stritzky A, Münch J, Avanesov M, Weinrich JM, Stehning C, Bohnen S, Radunski UK, Freiwald E, Blankenberg S, Adam G, Pressler A, Patten M, Lund GK. Myocardial Fibrosis in Competitive Triathletes Detected by Contrast-Enhanced CMR Correlates With Exercise-Induced Hypertension and Competition History. JACC: Cardiovascular Imaging. 2018 Sep;11(9):1260–70.

64. Banks L, Goodman J, Altaha M, Yan A, Dorian P, Connelly K. T1-MAPPING DERIVED CARDIAC EXTRACELLULAR VOLUME IN MIDDLE-AGED ENDURANCE ATHLETES AND RECREATIONALLY-ACTIVE ADULTS. Canadian Journal of Cardiology. 2017 Oct;33(10):S24.

65. Görmeli CA, Görmeli G, Yağmur J, Özdemir ZM, Kahraman AS, Çolak C, Özdemir R. Assessment of myocardial changes in athletes with native T1 mapping and cardiac functional evaluation using 3 T MRI. Int J Cardiovasc Imaging. 2016 Jun;32(6):975–81.

66. Gastl M, Lachmann V, Christidi A, Janzarik N, Veulemans V, Haberkorn S, Holzbach L, Jacoby C, Schnackenburg B, Berrisch-Rahmel S, Zeus T, Kelm M, Bönner F. Cardiac magnetic resonance T2 mapping and feature tracking in athlete's heart and HCM. Eur Radiol. 2021 May;31(5):2768–77.

67. Fogante M, Agliata G, Basile MC, Compagnucci P, Volpato G, Falanga U, Stronati G, Guerra F, Vignale D, Esposito A, Dello Russo A, Casella M, Giovagnoni A. Cardiac Imaging in Athlete's Heart: The Role of the Radiologist. Medicina. 2021 May 7;57(5):455.

68. Cipriani A, Zorzi A, Sarto P, Donini M, Rigato I, Bariani R, De Lazzari M, Pilichou K, Thiene G, Iliceto S, Basso C, Corrado D, Perazzolo Marra M, Bauce B. Predictive value of exercise testing in athletes with ventricular ectopy evaluated by cardiac magnetic resonance. Heart Rhythm. 2019 Feb;16(2):239–48.

69. Crescenzi C, Zorzi A, Vessella T, Martino A, Panattoni G, Cipriani A, De Lazzari M, Perazzolo Marra M, Fusco A, Sciarra L, Sperandii F, Guerra E, Tranchita E, Fossati C, Pigozzi F, Sarto P, Calò L, Corrado D. Predictors of Left Ventricular Scar Using Cardiac Magnetic Resonance in Athletes With Apparently Idiopathic Ventricular Arrhythmias. JAHA. 2021 Jan 5;10(1):e018206.

70. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. European Heart Journal. 2006 Nov 13;27(23):2879–88.

71. Maceira A, Prasad S, Khan M, Pennell D. Normalized Left Ventricular Systolic and Diastolic Function by Steady State Free Precession Cardiovascular Magnetic Resonance. Journal of Cardiovascular Magnetic Resonance. 2006 Jul 1;8(3):417–26.

72. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. J Magn Reson Imaging. 2009 Feb 25;29(3):552–9.

73. Maceira AM, Cosín-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2010 Nov 11;12(1):65.

74. Maceira AM, Cosín-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference right atrial dimensions and volume estimation by steady state free precession cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance. 2013 Apr 8;15(1):29.

75. Abdel-Aty H, Boyé P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, Bock P, Dietz R, Friedrich MG, Schulz-Menger J. Diagnostic Performance of Cardiovascular Magnetic Resonance in Patients With Suspected Acute Myocarditis: Comparison of Different Approaches. Journal of the American College of Cardiology. 2005 Jun 7;45(11):1815–22.

76. Rosmini S, Bulluck H, Captur G, Treibel TA, Abdel-Gadir A, Bhuva AN, Culotta V, Merghani A, Fontana M, Maestrini V, Herrey AS, Chow K, Thompson RB, Piechnik SK, Kellman P, Manisty C, Moon JC. Myocardial native T1 and extracellular volume with healthy ageing and gender. European Heart Journal - Cardiovascular Imaging. 2018 Jun 1;19(6):615–21.

77. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging:, Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, et al. Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart: A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002 Jan 29;105(4):539–42.

78. Herzog BA, Greenwood JP, Plein S. Cardiovascular Magnetic Resonance Pocket Guide.

79. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the royal statistical society Series B (Methodological). 1995;289–300.

80. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing [Internet]. 2022; Available from: https://www.R-project.org/

81. Maron BJ. Structural features of the athlete heart as defined by echocardiography. Journal of the American College of Cardiology. 1986 Jan 1;7(1):190–203.

82. Miller CA, Naish JH, Bishop P, Coutts G, Clark D, Zhao S, Ray SG, Yonan N, Williams SG, Flett AS, Moon JC, Greiser A, Parker GJ, Schmitt M. Comprehensive Validation of Cardiovascular Magnetic Resonance Techniques for the Assessment of Myocardial Extracellular Volume. Circ: Cardiovascular Imaging. 2013 May;6(3):373–83.

83. Abergel E, Chatellier G, Hagege AA, Oblak A, Linhart A, Ducardonnet A, Menard J. Serial left ventricular adaptations in world-class professional cyclists: Implications for disease screening and follow-up. Journal of the American College of Cardiology. 2004 Jul 7;44(1):144–9.

84. Pujadas S, Doñate M, Li CH, Merchan S, Cabanillas A, Alomar X, Pons-Llado G, Serra-Grima R, Carreras F. Myocardial remodelling and tissue characterisation by cardiovascular magnetic resonance (CMR) in endurance athletes. BMJ Open Sport Exerc Med. 2018 Oct 25;4(1):e000422.

85. McDiarmid AK, Swoboda PP, Erhayiem B, Lancaster RE, Lyall GK, Broadbent DA, Dobson LE, Musa TA, Ripley DP, Garg P, Greenwood JP, Ferguson C, Plein S. Athletic Cardiac Adaptation in Males Is a Consequence of Elevated Myocyte Mass. Circ: Cardiovascular Imaging. 2016 Apr;9(4):e003579.

86. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the Cardiologist. JACC Basic Transl Sci. 2020 Apr 10;5(5):518–36.

87. Halle M, Binzenhöfer L, Mahrholdt H, Johannes Schindler M, Esefeld K, Tschöpe C. Myocarditis in athletes: A clinical perspective. Eur J Prev Cardiol. 2020 Apr 17;2047487320909670.

88. Marijon E, Tafflet M, Celermajer DS, Dumas F, Perier MC, Mustafic H, Toussaint JF, Desnos M, Rieu M, Benameur N, Le Heuzey JY, Empana JP, Jouven X. Sports-related sudden death in the general population. Circulation. 2011 Aug 9;124(6):672–81.

89. Domenech-Ximenos B, Sanz-de la Garza M, Prat-González S, Sepúlveda-Martínez A, Crispi F, Duran-Fernandez K, Perea RJ, Bijnens B, Sitges M. Prevalence and pattern of cardiovascular magnetic resonance late gadolinium enhancement in highly trained endurance athletes. J Cardiovasc Magn Reson. 2020 Sep 3;22(1):62.

90. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, Daniels CJ. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. JAMA Cardiol. 2021 Jan 1;6(1):116–8.

91. Pan C, Zhang Z, Luo L, Wu W, Jia T, Lu L, Liu WV, Qin Y, Hu F, Ding X, Qin P, Qian L, Chen J, Li S. Cardiac T1 and T2 Mapping Showed Myocardial Involvement in Recovered COVID-19 Patients Initially Considered Devoid of Cardiac Damage. J Magn Reson Imaging. 2021 Aug;54(2):421–8.

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