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CARDIOVASCULAR MAGNETIC RESONANCE IMAGING IN THE ASSESSMENT OF PHYSIOLOGICAL AND PATHOLOGICAL CARDIAC ADAPTATIONS ASSOCIATED WITH COMPETITIVE SPORTS AND ATRIAL FIBRILLATION

Doctoral Dissertation

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Table of Contents

List of abbreviations

DOI:10.14753/SE.2022.2564

List of abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AF	atrial fibrillation
ARVC	arrhythmogenic right ventricular cardiomyopathy/ dysplasia
AUC	area under the curve
BMI	body mass index
BPM	beat per minute
BSA	body surface area
bSSFP	balanced steady-state free precession
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CMR	cardiac magnetic resonance
DCM	dilated cardiomyopathy
ECV	extracellular volume
EDV	end-diastolic volume
EDVi	end-diastolic volume index
EDWT	end-diastolic wall thickness
EF	ejection fraction
EF_{Active}	active ejection fraction
$EF_{Passive}$	passive ejection fraction

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EF_{Total}	total ejection fraction;
ECG	electrocardiogram
ESC	European Society of Cardiology
ESV	end-systolic volume
ESVi	end-systolic volume index
HCM	hypertrophic cardiomyopathy
HR	heart rate
M	mass
Mi	mass index
LA	left atrium
LAV	left atrial volume
LA-LGE	left atrial late gadolinium enhancement
LGE	late gadolinium enhancement
LV	left ventricular
LVNC	left ventricular noncompaction
LVOT	left ventricular outflow tract
MaxLAV	maximum left atrial volume
MaxLAVi	maximum left atrial volume index
MinLAV	minimum left atrial volume
MinLAVi	minimum left atrial volume index
OSA	obstructive sleep apnoe
RV	right ventricular

DOI:10.14753/SE.2022.2564

SCD	sudden cardiac death
SD	standard deviation
SV	stroke volume
SVi	volume index
PAF	paroxysmal atrial fibrillation
PFA	periprocedural fluid administration
PFB	periprocedural fluid balance
PLAS	peak longitudinal atrial strain
PVI	pulmonary vein isolation
TIA	transient ischemic attack
VF	ventricular fibrillation
VT	ventricular tachycardia

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1 Introduction

1.1 Cardiovascular magnetic resonance (CMR) imaging

Cardiovascular magnetic resonance (CMR) imaging has an emerging role in cardiovascular medicine by providing diagnostic and prognostic information of a wide variety of cardiac conditions(1). CMR is the sole non-invasive imaging modality offering precise anatomical, functional and hemodynamic assessment, tissue characterisation including oedema and viability assessment, and stress perfusion (Figure 1). It provides multiplanes coverage of the heart without applying ionizing radiation. CMR is considered to be the gold standard for structural and functional myocardial assessment (2). It is the superior modality for detecting left (LV) and right (RV) ventricular volumes, function and masses as well as atrial sizes and function. In addition to precise ejection fraction measurement, recent advancement of CMR feature tracking (CMR-FT) post-processing method has been proved to provide additional information of myocardial mechanics in different physiological and pathological cardiac adaptations(3, 4).

CMR is the primary non-invasive method to assess myocardial tissue characterization. Late gadolinium enhancement (LGE) imaging is part of the clinical routine for visualizing tissue damage in ischemic and non-ischemic processes(5). Due to the altered washout kinetics of gadolinium contrast relative to surrounding normal tissue, the detected LGE is representing structural remodeling of the ventricles. Using dedicated LGE sequences, myocardial fibrosis/scar can also be identified in the left atrial (LA) wall ((6, 7)).

The reproducibility of different CMR measurements is critical in establishing the feasibility of CMR imaging in clinical practice. Robust data are available regarding high reproducibility of volumetric and functional CMR parameters in healthy individuals and patients with various cardiovascular diseases(8-10). Excellent intra- and interobserver agreement have been reported in the detection of the presence/absence, location and extent of LGE in ischemic and non-ischemic cardiomyopathies(11-13). Considering the above mentioned advantages of CMR imaging, it is an optimal method to study various physiological and pathological cardiac adaptations.

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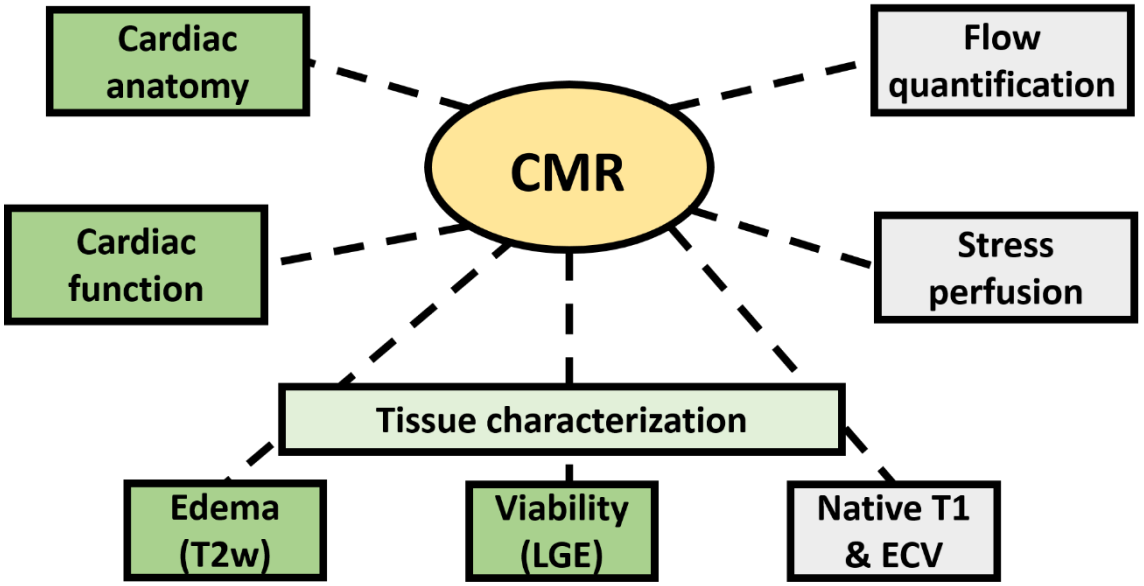

Figure 1: Clinical applications of cardiovascular magnetic resonance (CMR) imaging. The applied CMR techniques of the dissertation are highlighted with green. ECV, extracellular volume; LGE, late gadolinium enhancement; T1, T1 weighted and T2w, T2 weighted image.

1.2 Functional and structural characteristics of athlete's heart assessed by CMR imaging

1.2.1 Adult athletes

Performing regular and intense exercise training leads to a complex physiological adaptation of the heart including biventricular dilatation and hypertrophy (14-16). Physiological cardiac adaptation to exercise is a balanced adaptation (17-20). The specific characteristics of athlete's heart are influenced by multiple factors and are highly diverse among individual athletes exercising at high level (14, 17, 21-23). Numerous studies focus on how the athlete's heart responds to various amounts of strength- and endurance-training (15, 23-27). However, CMR imaging is the reference method to evaluate LV and RV volumes as well as masses(2), echocardiography data are more widely reported when discussing cardiac adaptation in male and female athletes (14-17, 22-24, 28). The currently available CMR studies mainly report data of male athletes (18, 28-31), whereas studies regarding female athletes' cardiac adaptation are still underrepresented in the literature (17, 19, 32). Physiological cardiac adaptation differs

based on the type of training among different sports, in order to facilitate increases in stroke volume and cardiac output demands. Based on the cardiovascular changes associated with intensive exercise training, sport disciplines could be categorized as skill, power, mixed and endurance sports (17, 33, 34). Derived RV/LV CMR parameters could address imbalances of adaptation without additional measurement or lengthening scan time (18, 31).

1.2.2 Adolescent athletes

As more young individuals are being encouraged to train intensely for sporting competitions from an early age, there is an utter need to precisely define the characteristics of physiological cardiac adaptation in this group(35). In young athletes, cardiac adaptation is not complete and defining the maximum limit of physiological cardiac adaptation might be challenging. Limited data are available reporting normal cardiac adaptation in healthy young individuals who exercise extensively (25, 26, 36, 37). Adolescence age as we defined in our study as age between 14 – 18 years old, is a key period for the emergence of different genetic cardiomyopathies characterized by LV hypertrophy and dilation. Therefore, differentiating early pathological signs from physiological cardiac adaptation in the young has a key role in improving risk stratification for sudden cardiac death (SCD).

1.2.3 Masters athletes

The beneficial impacts of exercise on cardiovascular health are well recognized(38). It is the most cost-effective and safe long-term intervention someone can do to minimize their lifetime cardiovascular risk. A number of studies comparing active subjects to sedentary controls consistently demonstrate upwards of 80% risk reduction in lifetime cardiovascular disease prevalence(39). Moreover, studies comparing professional athletes to the general population show a longevity benefit of 3-6 years(40). On the other hand, there is concern that athletes may also develop training related cardiac injury and despite the beneficial effects of moderate intensity exercise in a general population, vigorous exercise may prove to be harmful in some individuals(41). Masters (age > 35 years old) endurance athletes develop atrial arrhythmias

specifically atrial fibrillation (AF) at a higher rate than the general population(42). In fact, long term high intensity endurance training such as Nordic skiing, marathon running or professional cycling has been associated with as much as a 5-10 fold increase the prevalence of AF(43). This effect seems to be more pronounced in men than women(44). A "J-shaped" dose response pattern has emerged describing the relationship between exercise and AF in which a moderate dose of exercise is protective whereas higher lifetime doses increases risk(45). Risk of arrhythmia also increases with faster finishing times and number of races completed(43).
The cumulative effect of long-term high intensity training could be studied in masters athletes. As we discussed above, athletes typically develop biventricular increases in cavity size and wall thickness accompanied by increases in left atrial size(46). In addition to these structural transformations, ventricular myocardial fibrosis using LGE magnetic resonance imaging has also been detected in athletes, specifically those who participate in endurance sports(47). In the non-athletic population, a higher degree of left atrial fibrosis detected by LGE has been shown to be an independent risk factor for recurrence of atrial fibrillation(48).

1.3 The role of CMR imaging in athletes with suspected structural myocardial disease

Athletes are thought to represent the essence of health and vitality. However, athletes can be diagnosed with various cardiovascular conditions predisposing them to adverse cardiovascular event such as the rare but fatal SCD. The estimated incidence of SCD in athletes ranges from 1 in 40,000 to 1 in 300,000 per a year(49-52). In older athletes (>35 years), the incidence of SCD is 5-10 times higher and the most frequent aetiology is ischemic heart disease(53, 54). On the other hand, leading causes of SCD in young athletes (<35 year) are of non-ischemic origin such as hypertrophic (HCM), right ventricular arrhythmogenic (ARVC), dilated cardiomyopathy (DCM), genetic cardiac arrhythmias (e.g. long-QT-syndromes, channelopathies, Brugada-syndrome) or abnormal origin of coronary artery(55-58). Based on literature data, male athletes have a 2-25 times higher lifetime risk of SCD compared to females(50, 57, 59). Frequently, SCD is the sentinel event of the underlying pathology without any previous complain or symptom(55, 58). It has been also recognized that certain types of sports are associated with an increased risk of SCD(23, 60). Geographical variations and environmental factors may also influence the frequent aetiology of SCD in general population

and also in athletes(56, 61). In Hungary, the estimated incidence of SCD in athletes believed to be similar to international data(62). However, no comprehensive national database available regarding the frequency and aetiology of SCD in this unique population.

CMR imaging has a vital role in diagnosing cardiovascular diseases in athletes (Figure 2). Differentiating athlete's heart from pathological conditions often presents with a diagnostic challenge. Based on expert consensus guidelines, in clinical scenarios when the first line tests (e.g. 12-lead resting ECG, transthoracic echocardiography) cannot provide a clear diagnosis, CMR imaging should be performed(63-65).

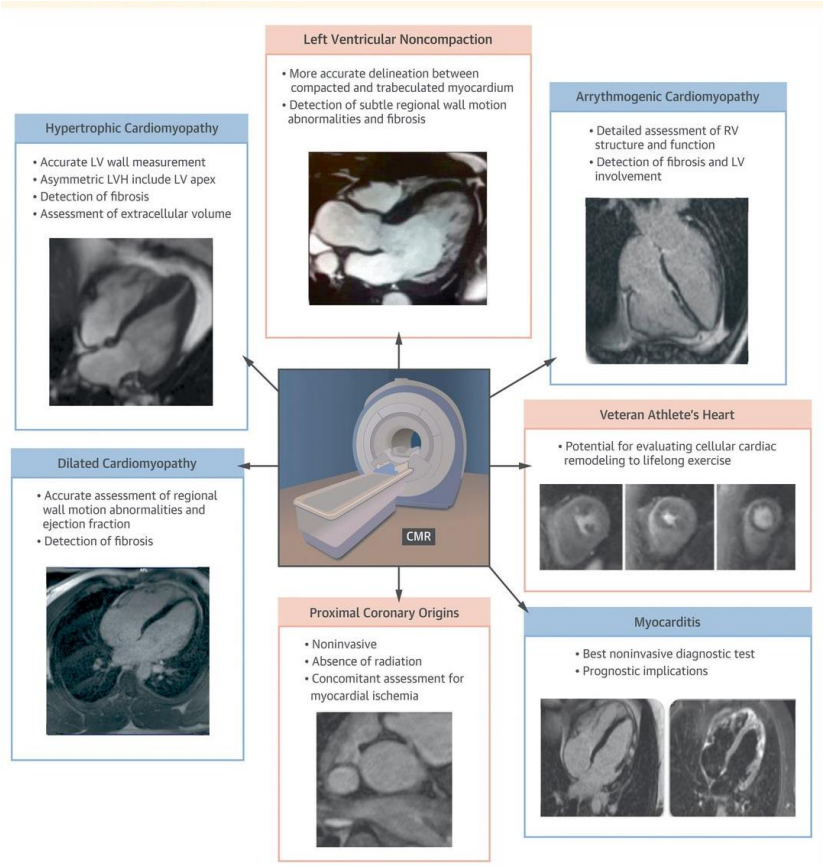

Figure 2: The role of CMR in the assessment of cardiovascular diseases in athletes(66). LV, left ventricle; LVH, left ventricular hypertrophy; RV, right ventricle.

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1.4 Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging

Atrial fibrillation is a progressive disease of the left atrium (LA) with complex morphological (dilatation), functional (ejection fraction, strain) and structural changes (fibrosis) (67). Catheter ablation is a well-established method of treating AF (67). However, the relationship between LA structural and functional remodeling pre- and post-ablation is not well understood. Limited data, primarily echocardiography studies are available characterizing changes in LA size and function after AF ablation (67, 68). As we discussed above, cine CMR is optimal to assess LA dimensons, and using special CMR sequences, LGE can also be identified in the thin LA wall. The extent of fibrosis in the LA can be quantified on pre-ablation LGE scans, and post-ablation scarring can be detected on post-ablation LGE images (6, 7). Despite the availability of advanced ablation catheters and techniques, the recurrence rate after AF ablation is significant 23 – 43% (69-71). Risk stratification of AF patients for catheter ablation is exceedingly complex and challenging, and optimal patient selection methods are still lacking.

DOI:10.14753/SE.2022.2564

2 Study aims

In our projects, we aimed to study various physiological and pathological cardiac conditions coupled with enlarged cardiac chambers using advanced CMR imaging techniques.

2.1 Functional and structural characteristics of athlete's heart assessed by CMR imaging

Our goal was to investigate the impact of sex, age, sport type and training hours on biventricular cardiac adaptation in a large cohort of healthy adult and adolescent athletes. We also aimed to study the morphological and structural characteristics of the left atrium in healthy masters athletes.

2.2 The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease

We aimed to investigate the diagnostic role of CMR imaging in athletes with suspected structural myocardial diseases, to identify the aetiology of sudden cardiac death (SCD) and to determine the frequency of detected pathological conditions in this unique group of athletes.

2.3 Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging

Our aim was to assess changes in left atrial volume and function after first AF ablation, to evaluate the association between longitudinal functional and structural remodeling and to detect potential predictors of recurrence using multiparametric CMR imaging.

3 Methods

3.1 Study design and study populations

3.1.1 Study design and study population of the "Functional and structural characteristics of athlete's heart assessed by CMR imaging" project

3.1.1.1 Adult and Adolescent athletes

The study was conducted at the Heart and Vascular Center of the Semmelweis University between January 2009 and January 2018. The institutional pre-screening consisted of a self-reported health questionnaire (focusing on previous and current cardiac symptoms, family history of cardiovascular diseases, especially cardiomyopathies and sudden cardiac death), physical examination and resting 12-lead ECG. All athletes were referred for further cardiac imaging tests, and participation in imaging studies was at the discretion of the athlete's or his/her legally authorised representatives. Caucasian athletes between the ages of 14 and 35 years at the time of the CMR scan were evaluated for the study. Athletes who did not perform regular exercise continuously 12 months prior to enrolment were not included in the study. Athletes who were free of complaints, without any cardiovascular diseases including hypertension and without definite pathological ECG signs were recruited in the study. ECG abnormalities were evaluated by an experienced cardiologist according to the pre-participation recommendation by the European Society of Cardiology (72). All athletes participating in the study denied the use of any anabolic steroid or other performance-enhancing drugs. The study protocol was approved by the Hungarian ethics committee (ETT-TUKEB 13687-0/2011-EKU).

Study population

A total of 327 Caucasian athletes (242 male, 21 ± 6 years) were studied. Athletes above the age of 18 years were classified as adult, younger athletes (≤18 years old) as adolescent. Table 1 shows the baseline characteristics of the groups; 145 adult male and 70 adult female athletes were studied. The average number of training hours was 22.5 ± 4 in male and 20 ± 6 hours per week in female athletes. In the adolescent group (n= 112, 97 male) the average number of training hours per week was 11.5 ± 5 in male and 16 ± 6 in female athletes. All athletes were previously or currently competing at a national or international level. Athletes were categorised

into the following sports disciplines (22): adult athletes: (a) skill n= 14 (13 male); (b) power n= 8 (4 male); (c) mixed n= 96 (45 male); (d) endurance n= 97 (83 male); adolescent athletes: (a) skill n= 3 (2 male); (b) power n= 1 male; (c) mixed n= 93 (85 male); (d) endurance n= 15 (9 male) disciplines. Rowers, canoe, kayak, water polo and soccer players (74% of whole cohort) made up the majority of the athletes who were studied.

Table 1: Baseline characteristics of male and female healthy athletes. (BSA= body surface area; mean values ± standard deviation)

Variables	Male Adult N = 145	Female Adult N = 70	Male Adolescent N = 97	Female Adolescent N = 15
Age (years)	24.5 ± 5	23 ± 4	15.9 ± 1	16 ± 1
Weight (kg)	82.7 ± 11	69 ± 10	71.2 ± 14	62 ± 8
Height (cm)	185.2 ± 8	175 ± 7	179.7 ± 10	172 ± 8
BSA (m^2)	2.1 ± 0.2	1.8 ± 0.14	1.9 ± 0.3	1.7 ± 0.13
Heart rate (bpm)	59 ± 9	56 ± 10	66.7 ± 11	57 ± 11
Training (hours/week)	22.5 ± 4	20 ± 6	11.5 ± 5	16 ± 6

3.1.1.2 Masters athletes

We recruited twenty healthy endurance masters athletes >35 years-old who have participated in at least 10-years of competitive endurance sports and actively train for ≥10 hours weekly(73). Endurance activities included: running, cycling, ski mountaineering, and Nordic skiing. Baseline vital signs were measured and questionnaires regarding medical history and training exposure were performed at the time of recruitment. Efforts were focused specifically on top finishers in local races. Baseline vital signs were measured and questionnaires regarding medical history and training exposure were performed at the time of recruitment. Quantification of exercise was determined by subject recollection and validated using training logs and race results.

Table 2: Baseline Characteristics of masters athletes and sedentary controls. BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; OSA, obstructive sleep apnoea. (P-values represent the comparison of the two groups with independent t-test; mean values ± standard deviation)

		Athlete (n=20)	Controls (n=20)	p-value
Age (year)		48.7 ± 8	48.3 ± 8	0.898
Gender	Male	15 (75%)	15 (75%)	1
	Female	5 (25%)	5 (25%)	1
BSA (m2)		1.9 ± 0.2	2.1 ± 0.2	0.011*
Weight (kg)		72 ± 11	85 ± 16	0.005*
Height (cm)		175 ± 5	181 ± 10	0.09
BMI (kg/cm2)		23 ± 3	26 ± 5	0.03*
COPD		0	1 (5%)	1
CHF		0	0	1
Diabetes Mellitus		0	0	1
Hyperlipidemia		0	1 (5%)	1
Hypertension		1 (5%)	0	1
OSA		0	0	1
Tobacco Use		1 (5%)	1 (5%)	1
Alcohol Use		11 (55%)	6 (30%)	0.2008

Endurance activities included those that were highly dynamic with low static component: running, cycling, ski mountaineering, and Nordic skiing. For the athlete cohort, recruitment was done through word of mouth at training clubs and at competitions. Twenty healthy age and gender matched control subjects from gastroenterology clinic were recruited into the study during screening colonoscopies. Inclusion criteria for controls was self-reported <3 hours of weekly cardiovascular exercise. Exclusion criteria included prior cardiac history including arrhythmia, cardiomyopathy, or heart failure symptoms. Overall, the two cohorts were very closely matched with few comorbidities. Athletes had significantly lower BMI and slightly more alcohol use (Table 2).

DOI:10.14753/SE.2022.2564

3.1.2 Study design and study population of "The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease" project

The study was conducted at the Heart and Vascular Center of the Semmelweis University between January 2011 and January 2016. A total of 153 athletes (112 males; 26.5 ± 10.5 years) were referred for CMR study due to the suspicion of structural myocardial disease (Table 3). The most common symptoms/complains were palpitation, dyspnoea, presyncope or syncope. Two athletes had documented sustained ventricular tachycardia (sVT) prior to CMR scan, and 10 athletes had aborted SCD.

Table 3. Baseline characteristics of athletes with suspicion of structural myocardial disease.

Variables		Athletes (n=153)
Age (year)		46.5 ± 10.5
Gender	Male	112 (73%)
	Female	41 (27%)
BSA (m2)		1.83 ± 0.16
BMI (kg/cm2)		24.5 ± 4
Olympic athletes and/or national/international championship medallists		64 (42%)

3.1.3 Study design and study population of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

Using the University of Utah Atrial Fibrillation Database, patients who underwent AF ablation between April 2015 and April 2017 were identified. Exclusion criteria were: 1) prior ablation procedure, 2) AF rhythm during CMR scan, 3) severe valvular disease, 4) implanted cardiac device, 5) electrical cardioversion within one month before the baseline CMR scan, and 6) severe CMR artefact on cine and/or LGE images. In this selected patient population, CMR

examination was performed in sinus rhythm at three time points: 1) Baseline (B) with a median 49 days before the ablation procedure, 2) Acute phase (A) within 24-hours after the procedure, and 3) at 3-months Follow-up (F) [median 98.5 days].

A total of 55 patients fulfilled the criteria and were recruited into the study (38 were male, patient age range 67 ± 10 years). Table 4 shows baseline clinical characteristics of the selected cohort. Patients were part of the Utah AF database, as approved by our institutional review board. Data handling methods were compliant with the Health Insurance Portability and Accountability Act.

Table 4: Baseline characteristics of patients with atrial fibrillation. AF, atrial fibrillation; LV, left ventricle; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.

Variables	Total N = 55
Age, years	67 ± 10
Male, n (%)	34 (62)
Type of AF	
PAF, n (%)	40 (73)
Non-PAF, n (%)	15 (27)
Hypertension, n (%)	20 (36)
Diabetes mellitus, n (%)	7 (13)
Hyperlipidaemia, n (%)	14 (25.5)
Congestive heart failure, n (%)	6 (11)
Vascular disease, n (%)	4 (7)
History of stroke or TIA, n (%)	2 (4)
Chronic renal disease, n (%)	3 (5.5)
CHA_2DS_2-VAS_C score, median (IQR)	2 (0 – 6)
LV ejection fraction, %	57 ± 8

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3.2 Image acquisition and analysis

3.2.1 Image acquisition and analysis of the "Functional and structural characteristics of athlete's heart assessed by CMR imaging" project

3.2.1.1 Adult and Adolescent athletes

CMR examinations were conducted on a 1.5 T MR scanner (Achieva, Philips Medical Systems, Best, The Netherlands) with a 5-channel cardiac coil. Retrospectively-gated, balanced steady-state free precession (bSSFP) cine images were acquired in conventional 2-chamber, 3-chamber and 4-chamber views. Short-axis cine images with full coverage of the left and right ventricle, and left and right ventricular outflow tract (LVOT, RVOT) movies were also obtained. Slice thickness was 8-mm without interslice gap, field of view 350 mm on average adapted to body size.

On cine short axis images, end-diastolic and end-systolic cardiac phases were identified and epicardial layer was detected along the compact myocardium including trabeculae and papillary muscles in the ventricular cavity using dedicated CMR software (Medis 8.0, Leiden, The Netherlands). The most basal section was required to show ≥50% visible myocardial circumference in order to be included. We measured the following CMR parameters of left and right ventricles: ejection fraction (EF), end-diastolic (EDV), end-systolic (ESV), stroke volumes (SV), cardiac output (CO) and myocardial mass in end-diastolic phase. Parameters corrected for body surface area were calculated. LVEDV/LVM and RVEDV/RVM ratios were created to assess the relative hypertrophy in relation with ventricular dilation. Balanced left-right adaptation was studied calculating RVEDV/LVEDV ratio. High intra- and interobserver agreement were detected for each LV and RV volumetric and functional parameters(74).

3.2.1.2 Masters athletes

Twelve of our athletes were scanned using a 1.5T scanner (Siemens Healthcare, Erlangen, Germany), were scanned using a 3T scanner; 14 of our controls were scanned using a 1.5T

scanner and were done using a 3T (Siemens Healthcare, Erlangen, Germany). High-resolution 3D LGE scan for assessment of LA fibrosis/scar was initiated 15-20 minutes following contrast agent injection (0.1 mmol/kg of gadobenate dimeglumine (Bracco Diagnostics Inc., Princeton, NJ, USA)) using a 3D inversion recovery-prepared, respiration-navigated, ECG-gated, gradient echo pulse sequence with fat saturation. The typical scan parameters were as follows: transverse imaging volume with field of view (FOV) = 400 x 400 x 110 mm and voxel size of 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm), inversion time (TI) = 270–320 ms, and GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisition) with reduction factor of 2. The other scan parameters for LGE-MRI performed with 1.5T scanner were: TR/TE = 5.2/2.4 ms, FA = 20º. The corresponding scan parameters for LGE-MRI performed with 3T scanner were TR/TE = 3.1/1.4 ms, FA = 14º. The TI value for LGE scan was identified using a TI scout scan of left ventricle acquired at short axis orientation.

MRI scans were evaluated for LGE using Corview image analysis software (MARREK, Inc., Salt Lake City, Utah). Quantification of LA remodeling was performed using methods previously described(6). Briefly, the LA wall was segmented manually from LGE-MRI scans by careful tracing of the LA contour without pulmonary veins (PVs). The LA outline was verified visually in the original image stack prior to rendering. LGE was distinguished from normal myocardium using an interactive tool for selecting intensity thresholds that correspond with LGE in the LA wall. A maximum intensity projection was used to assess contrast consistency throughout the image. A color lookup table mask was utilized in order to help differentiate between enhanced and non-enhanced tissue. On LGE-CMR images LA fibrosis was quantified as a proportion of the left atrial wall volume.

3.2.2 Image acquisition and analysis of “The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease” project

The image acquisition and cine image analysis protocol was same as described at the “Assessment of cardiac adaptation in healthy athletes” project. In conventional long- and short-axis planes, pre-contrast T2-weighted spectral inversion recovery (SPIR) images were acquired to detect acute myocardial oedema and post-contrast late gadolinium enhancement (LGE) images to assess myocardial necrosis/fibrosis (88% of cases). LGE images were

acquired using a segmented inversion recovery sequence 10–15 min after the administration of an intravenous bolus of 0.15 mmol/kg of the gadolinium-based contrast agent gadobutrol (Gadovist, Bayer-Schering Pharma) at a rate of 2–3 mL/s through an antecubital intravenous line. The inversion time was adjusted to provide optimal suppression of normal myocardium.

3.2.3 Image acquisition and analysis of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

The study protocol included cine CMR and 3D-LGE. The image acquisition protocol was same as described at the "Functional and structural characteristics of athlete's heart assessed by CMR imaging – Masters athletes" project.

Left atrial endocardial contours were manually traced on two- and four-chamber long axis cine images corresponding to atrial end-systolic and end-diastolic phases (Medis Suite 3.0 QMass 8.0 Leiden, The Netherlands). An automated tracking algorithm was applied, and LA endocardial border was evaluated in all cardiac phases. Tracking performance was reviewed and corrected manually in cases of insufficient automated border tracking. Maximum (MaxLAV), minimum (MinLAV) and pre-atrial contraction (Pre-aLAV) volumes were extracted from the volume/time curve, and total (EF_{Total}), active (EF_{Active}) and passive ($EF_{Passive}$) left atrial ejection fractions were calculated (Figure 3). LA myocardial feature tracking was performed using the same LA contours with dedicated software (Medis Suite 3.0 QStrain 2.0 Leiden, The Netherlands). This feature tracking technology was previously described by Kowallick et al (75). Similar to previous definitions from echocardiographic speckle tracking studies, longitudinal strain defined as the sum of passive and active LA strains was assessed. Mean peak global longitudinal atrial strain (PLAS) was calculated as the mean of two (2- and 4-chamber) longitudinal LA strain values. The observers evaluating the CMR functional and LGE data were blinded to other results. Inter- and intraobserver variability was tested on randomly selected scans by two experienced physicians (Table 5).

DOI:10.14753/SE.2022.2564

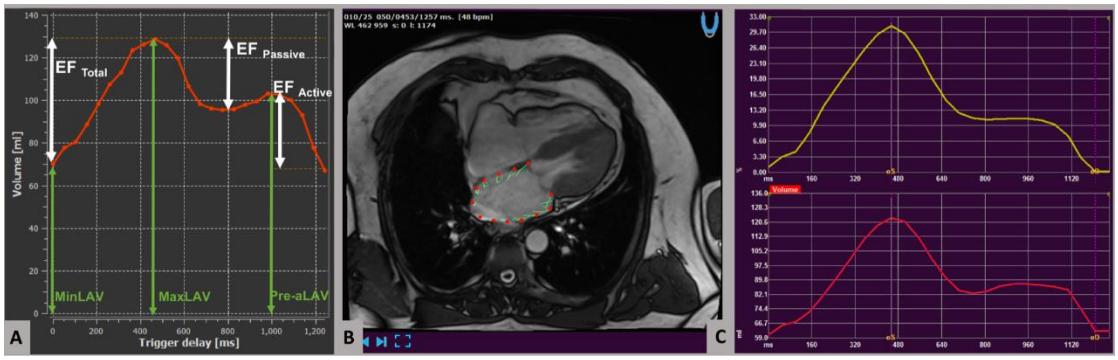

Figure 3. Atrial function measurement Maximum (MaxLAV), minimum (MinLAV) and pre-atrial contraction (Pre-aLAV) volumes were extracted from the volume/time curve and total (EFTotal), passive (EFPassive) and active (EFActive) ejection fractions were calculated (A). Image C shows the peak longitudinal strain curve (PLAS) (yellow) and volume curve (red) of the 4-chamber cine image (B).

MRI scans were evaluated for LGE using Corview image analysis software (MARREK, Inc., Salt Lake City, Utah). Quantification of LA remodeling was performed using methods previously described (3,4). On pre-ablation LGE-CMR scans and on 3-month post-ablation LGE-CMR scans, LA scar and LA fibrosis amounts, respectively, were reported as a proportion of left atrial wall volume (6, 7).

Table 5. Intraclass correlation coefficient (ICC) of each variable representing inter- and intraobserver agreement studied on randomly selected pre-ablation, acute and follow-up scans (n=20). EF_{Active}=active ejection fraction; $EF_{Passive}$=passive ejection fraction; $EF_{Total=}$total ejection fraction; ICC= intraclass correlation coefficient; MaxLAV=maximum left atrial volume; MaxLAVi=maximum left atrial volume index; MinLAV=minimum left atrial volume; MinLAVi=minimum left atrial volume index; PLAS=peak longitudinal atrial strain; Pre-aLAV= pre-atrial contraction volume. ICC [95% confidence intervals]

Variables	Interobserver variability	Intraobserver variability

MaxLAV (ml)	0.96 [0.90 to 0.98]	0.98 [0.94 to 0.99]
MinLAV (ml)	0.93 [0.83 to 0.97]	0.98 [0.96 to 0.99]
Pre-aLAV (ml)	0.91 [0.75 to 0.97]	0.97 [0.91 to 0.99]
EF_{Total} (%)	0.86 [0.67 to 0.95]	0.87 [0.68 to 0.95]
$EF_{Passive}$ (%)	0.76 [0.40 to 0.92]	0.78 [0.43 to 0.92]
EF_{Active} (%)	0.79 [0.45 to 0.93]	0.80 [0.48 to 0.93]
PLAS (%)	0.90 [0.73 to 0.96]	0.96 [0.88 to 0.98]

3.3 Additional study protocol to the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

3.3.1 Ablation protocol

We have only included patients with a first ablation procedure to avoid LA functional and structural remodeling changes related to prior ablation. Ablation was performed under general anaesthesia, as previously described (76). A circular mapping catheter and an irrigated ablation catheter were positioned in the left atrium, and electroanatomic mapping was performed using either CARTO (Biosense Webster, Diamond Bar, CA, USA) or ESI-NavX (St. Jude Medical, Minneapolis, MN, USA) systems. All patients underwent pulmonary vein isolation using wide area circumferential antral ablation technique (WACA). Additional linear ablations and/or substrate-based posterior wall debulking (based on pre-ablation LA LGE) was performed in selected patients at the operator's discretion (>80% of cohort). Linear ablations included the LA roof and mitral isthmus in patients with evidence of macro-reentrant arrhythmias after completion of pulmonary vein isolation. Ablations were done using either a non-contact force (Flexibility™ [St Jude Medical] and ThermoCool® NaviStar [Biosense Webster]), or a contact force (CF) sensing (Tacticath™ Quartz [St. Jude Medical], ThermoCool® SmartTouch™

NaviStar [Biosense Webster], and ThermoCool® SurroundFlow NaviStar [Biosense Webster]) catheter using standard irrigation flow rates recommended by the catheter manufacturer. Acute procedural success was defined as electrical isolation of all pulmonary veins, bidirectional block across all linear ablations, and completion of fibrosis-based substrate modification. We also analyzed the periprocedural fluid status of patients, and periprocedural fluid balance (PFB) was defined as the disparity of periprocedural fluid administration (PFA) and urine output (UO).

3.3.2 Clinical follow-up

Clinical follow-up protocol at the University of Utah involved assessing patients for AF recurrence at three, six, and twelve months after the ablation procedure using 12-lead ECG and 7-days Holter monitors. Additionally, telephone interviews were performed at one, two and nine months. With any patient complaints, additional resting ECGs and Holter monitors were obtained. Following hospital discharge after the ablation procedure, patients underwent 8-weeks of patient-triggered/auto-detected event monitoring. Procedural success was defined as freedom from AF, atrial tachycardia or atrial flutter while off of antiarrhythmic medication three months following PVI. AF recurrence was identified from patient symptoms or event/Holter/ECG data and was defined as any symptomatic or asymptomatic episode of AF, atrial tachycardia, or atrial flutter lasting > 30 seconds at 12-month follow-up. Time duration until the first recurrence of AF after index PVI procedure was recorded. The average follow-up in this study was 12.8 ± 3.7 months.

3.4 Statistical analysis

3.4.1 Statistical analyses the “Functional and structural characteristics of athlete’s heart assessed by CMR imaging” project

3.4.1.1 Adults and adolescent athletes

Statistical analyses were performed using MedCalc 13.2.2 (MedCalc Software, Ostend, Belgium). The Kolmogorov–Smirnov test was used to assess the normal distribution of the data. Continuous variables were reported as mean ± standard deviation and not normally distributed continuous variables as median value with interquartile range (IQR). The categorical and ordinal variables are reported as frequencies or percentage When continuous variables had a normal distribution, an unpaired (two sample) t-test was performed for comparison across groups. When continuous variables were non-normally distributed, Mann-Whitney U test was used. Differences between more than two groups were assessed by one-way analysis of variance (ANOVA) or Kruskal Wallis-test. Univariate and multivariate logistic regression models were performed to determine influencing factors of cardiac adaptive changes. P values of less than 0.05 were considered significant

3.4.1.2 Masters athletes

All statistical analysis were calculated with R (R Core Team (2013). R is a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Continuous variables are reported as mean ± standard deviation and categorical and ordinal variables are reported as frequencies or percentage. When continuous variables had a normal distribution, an unpaired (two sample) t-test was performed for comparison across groups. When continuous variables were non-normally distributed, Mann-Whitney U test was used. The distribution of continuous variables was tested with Kolmogorov-Smirnov test. For those parameters that were different in these two groups, univariate linear regression models were created to find the ones with correlation with an increased left atrial fibrosis. Any p-value below 0.05 is considered statistically significant.

3.4.2 Statistical analysis of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

Statistical analyses were performed using MedCalc 13.2.2 (MedCalc Software, Ostend, Belgium). The Kolmogorov–Smirnov test was used to assess the normal distribution of the data. Continuous variables were reported as mean ± standard deviation and p values of less

than 0.05 were considered significant. The comparison of baseline, acute and follow-up atrial functional data was performed with paired t or Wilcoxon tests. The differences between recurrence and non-recurrence groups were tested with independent sample t-tests. Logistic univariate regression test was applied to predict recurrence. We created a logistic multivariable model including individual predictors for AF recurrence. We aimed to create a model based on different characteristic features (size, function and structure) of the LA. Interobserver agreement was tested with intraclass correlation coefficient (ICC) score.

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4 Results

4.1 Results of the "Functional and structural characteristics of athlete's heart assessed by CMR imaging" project

4.1.1 Adult and Adolescent athletes

4.1.1.1 Sex-specific differences

We compared LV and RV parameters of males and females in adult and adolescent groups separately. Male adult athletes had higher LV and RV volumes and volume indices, and also higher masses compared to females (Table 6). LVEDV/LVM and RVEDV/RVM ratios were lower in males suggesting a more pronounced hypertrophy (Table 6). Adult male athletes had higher RVEDV/LVEDV compared to females. Figure 4 shows an example of cardiac adaptation of a same age male and female athlete. However, the two athletes were engaged in the same sport and trained under similar weekly training hours, female athlete had less pronounced LV hypertrophy.

Table 6: Sex-specific differences of left and right ventricular volumes, masses and ventricular ratios in adult athletes. LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVM, left ventricular mass; LVMi, left ventricular mass index; LVSV, left ventricular stroke volume; LVSVi, left ventricular stroke volume index; ns, non-significant; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVESVi, right ventricular end-systolic volume index; RVM, right ventricular mass; RVMi, right ventricular mass index; RVSV, right ventricular stroke volume; RVSVi, right ventricular stroke volume index.

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	Male Adult Athlete N=145		Female Adult Athlete N=70		p
Variables	Mean ± SD	95% CI	Mean ± SD	95% CI	
LVEF (%)	57 ±4	[50 - 65]	58 ± 5	[49 - 67]	ns
LVEDV (ml)	252 ± 38	[176 - 326]	193 ± 26	[140 – 244]	<0.0001
LVEDVi (ml/m2)	122 ± 15	[94 - 158]	106 ± 12	[82 – 128]	<0.0001
LVESV (ml)	108 ± 22	[65 - 152]	81 ± 16	[50 - 111]	<0.0001
LVESVi (ml/m2)	53 ± 10	[33 - 72]	44 ± 7	[29 - 59]	<0.0001
LVSV (ml)	143 ± 20	[103 - 182]	112 ± 16	[80 - 144]	<0.0001
LVSVi (ml/m2)	69 ± 8	[54 - 85]	61 ± 8	[46 - 76]	0.0019
LVM (g)	178 ± 38	[104 - 252]	115 ± 21	[82 - 155]	<0.0001
LVMi (g/m2)	86 ± 16	[56 - 116]	63 ± 10	[45 - 90]	<0.0001
maxEDWT	12.3 ± 1.5	-	10.1 ± 1.4	-	<0.001
LVEDV/LVM	1.43 ± 0.2	[0.97 – 1.9]	1.7 ± 0.26	[1.2 – 2.2]	<0.0001
RVEF (%)	55 ± 4	[47 - 64]	58 ± 5	[47 - 68]	0.0028
RVEDV (ml)	260 ± 41	[180 - 341]	194 ± 30	[136 - 252]	0.002
RVEDVi (ml/m2)	127 ± 17	[92 - 160]	106 ± 14	[79 - 133]	<0.0001
RVESV (ml)	117 ± 24	[69 - 164]	83 ± 20	[50 - 145]	<0.0001
RVESVi (ml/m2)	57 ± 11	[35 - 78]	44 ± 7	[27 - 63]	<0.0001
RVSV (ml)	144 ± 22	[100 - 187]	111 ± 17	[78 - 145]	<0.0001
RVSVi (ml/m2)	70 ± 9	[52 - 88]	61 ± 8	[45 - 77]	<0.0001
RVM (g)	49 ± 14	[23 - 76]	31 ± 10	[16 - 52]	<0.0001

RVMi (g/m2)	24 ± 6	[11 - 36]	17 ± 5	[10 - 28]	<0.0001
RVEDV/RVM	5.6 ± 1.7	[3.7 – 9.3]	6.6 ± 1.7	[4 - 10]	0.002
RVEDV/LVEDV	1.04 ± 0.09	[1.01 – 1.05]	1.01 ± 0.08	[1.00 – 1.03]	0.027

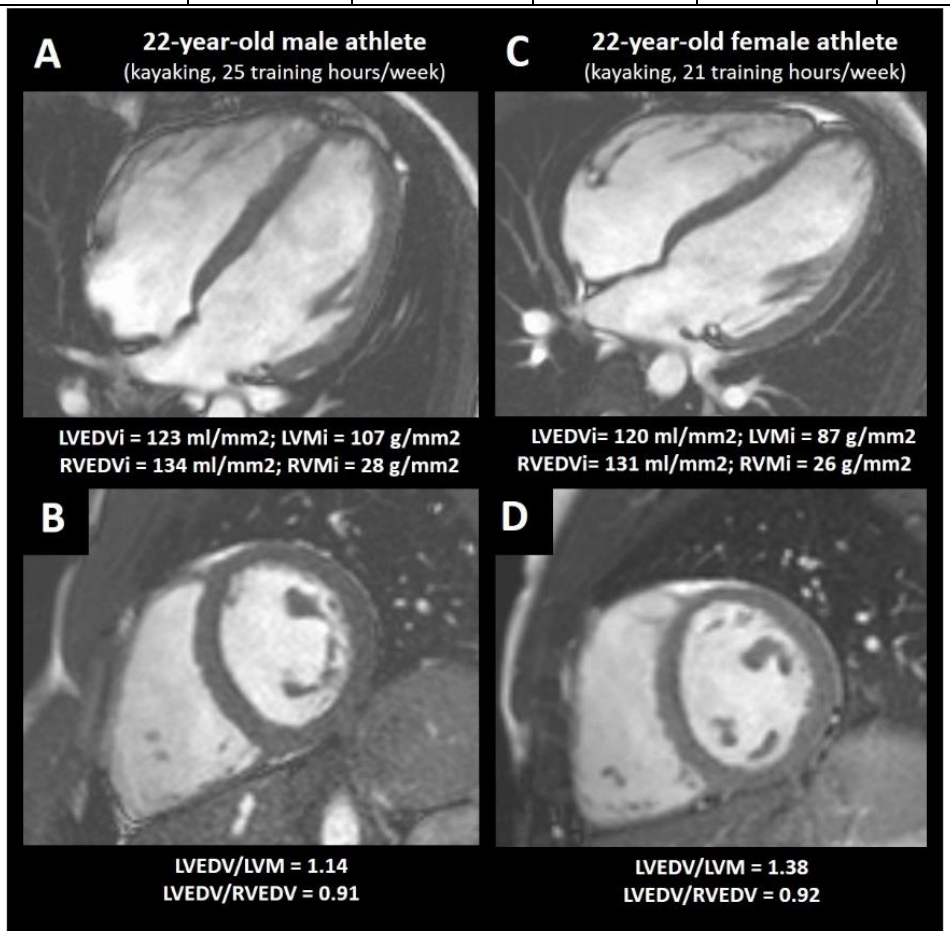

Figure 4: Representative examples of cardiac adaptation of a same age male and female athlete exercising in same sport with similar weekly training volume. Female athlete had less pronounced LV hypertrophy (Image A and C), and both athletes have balanced left and right ventricular dilation (Image B and D). LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVM, left ventricular mass; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume index.

In adolescent group, male athletes had higher LV and RV masses; however, indexed right ventricular volumes were not different between adolescent male and females (Table 7).

Comparing adolescent male and female athletes, the RV/LV ratios were not different (Table 7).

Table 7: Sex-specific differences of left and right ventricular volumes, masses and ventricular ratios in adolescent athletes. LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVM, left ventricular mass; LVMi, left ventricular mass index; LVSV, left ventricular stroke volume; LVSVi, left ventricular stroke volume index; ns, non-significant; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVESVi, right ventricular end-systolic volume index; RVM, right ventricular mass; RVMi, right ventricular mass index; RVSV, right ventricular stroke volume; RVSVi, right ventricular stroke volume index.

	Male Adolescent N=97		Female Adolescent N=15		p
Variables	Mean ± SD	95% CI	Mean ± SD	95% CI	
LVEF (%)	59 ± 5	[50 - 68]	60 ± 5	[51 - 68]	ns
LVEDV (ml)	212 ± 41	[132 - 292]	180 ± 32	[117 - 243]	0.0045
LVEDVi (ml/m2)	112 ± 13	[87 - 137]	103 ± 13	[77 - 129]	0.0193
LVESV (ml)	87 ± 19	[49 - 125]	73 ± 15	[43 - 102]	0.0060
LVESVi (ml/m2)	46 ± 8	[31 - 61]	42 ± 8	[27 - 56]	0.0471
LVSV (ml)	125 ± 26	[74 - 177]	108 ± 21	[67 - 149]	0.0155
LVSVi (ml/m2)	66 ± 9	[49 - 83]	62 ± 9	[50 - 87]	ns
LVM (g)	138 ± 30	[78 - 197]	107 ± 19	[70 - 145]	0.0003
LVMi (g/m2)	72 ± 11	[51 - 94]	62 ± 10	[43 - 81]	0.0005
maxEDWT (mm)	10.9 ± 1.7	-	9.5 ± 1.1	-	0.0037
LVEDV/LVM	1.57 ± 0.2	[1.16 – 1.98]	1.7 ± 0.27	[1.18 – 2.23]	0.0291
RVEF (%)	58 ± 5	[49 - 66]	59 ± 4	[52 - 65]	ns

RVEDV (ml)	214 ± 43	[130 - 298]	184 ± 32	[120 - 247]	0.0104
RVEDVi (ml/m2)	113 ± 14	[85 - 140]	106 ± 14	[86 - 146]	ns
RVESV (ml)	91 ± 22	[48 - 134]	76 ± 15	[46 - 106]	0.0124
RVESVi (ml/m2)	48 ± 9	[30 - 65]	42 ± 8	[29 - 58]	ns
RVSV (ml)	123 ± 25	[75 - 172]	108 ± 19	[70 - 146]	0.0252
RVSVi (ml/m2)	65 ± 8	[49 - 81]	62 ± 8	[49 - 87]	ns
RVM (g)	36 ± 10	[17 - 56]	28 ± 7	[14 - 42]	0.005
RVMi (g/m2)	19 ± 5	[11 - 30]	16 ± 5	[7 - 25]	0.0491
RVEDV/RVM	6.3 ± 1.7	[2.9 – 9.7]	7.0 ± 1.9	[3.3 – 10.7]	ns
RVEDV/LVEDV	1.01± 0.06	[1.00 – 1.02]	1.02 ± 0.06	[1.00 – 1.05]	ns

4.1.1.2 Adult vs. adolescent athletes

Adult male athletes had higher LV and RV volumes and volume indices (for all $p < 0.005$), and higher mass and mass indices (for all $p < 0.001$) compared to adolescent males. The ratio of LVEDV/LVM ($p<0.001$) and RVEDV/RVM ($p=0.002$) were lower in adult males suggesting marked biventricular hypertrophy. In this cohort, adolescent male athletes had perfectly balanced RV/LV dilatation (adult vs adolescent: RVEDV/LVEDV 1.04 ± 0.08 vs 1.01 ± 0.06 $p = 0.0075$). On the other hand, female adult and adolescent athletes' CMR parameters were not different. We performed a subgroup analysis categorising male endurance athletes by age quartiles, and indexed LV and RV masses and volumes were markedly increased between first and second quartiles in this homogenous subgroup of athletes (Figure 5).

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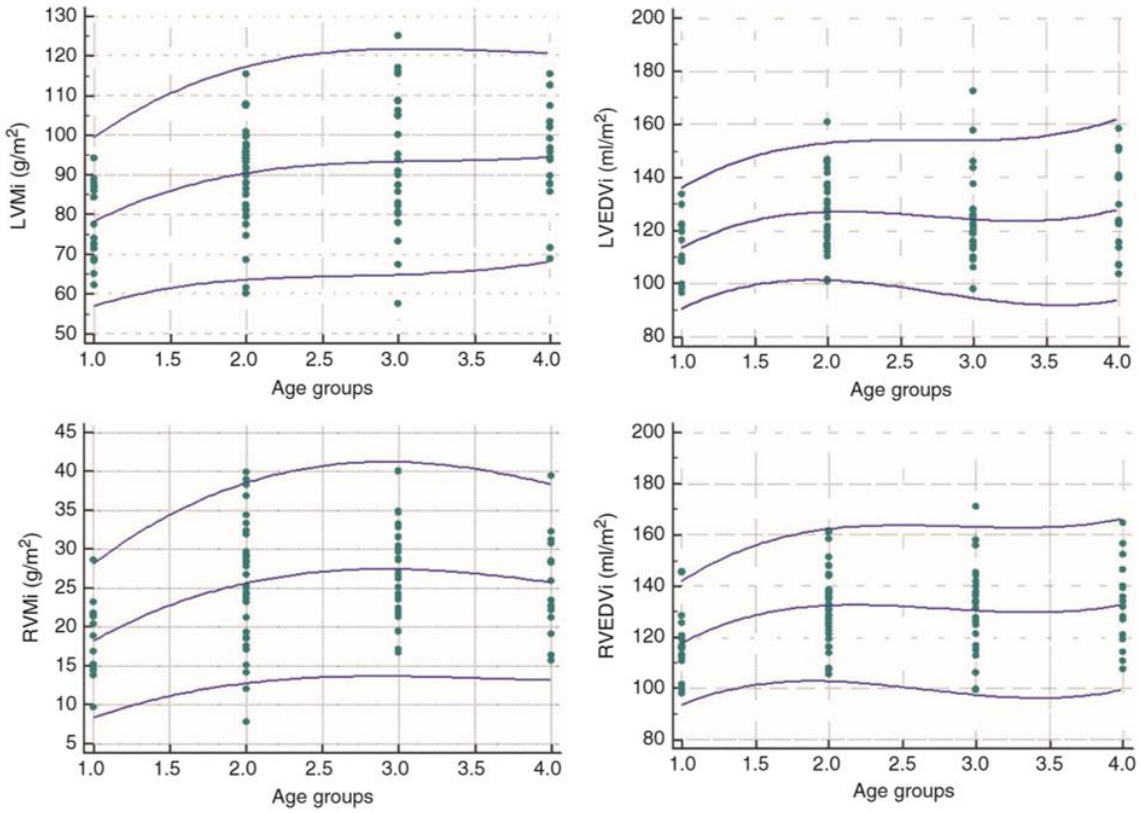

Figure 5: Indexed left (LV) and right (RV) ventricular masses and volumes of male endurance athletes grouped by age quartiles. LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; RVEDVi, right ventricular end-diastolic volume index; RVMi, right ventricular mass index.

4.1.1.3 Sport related differences

LVEDV/LVM ratio of endurance group was lower compared to mixed sport (1.40 ± 0.23 vs 1.44 ± 0.25 $p<0.05$) (Table 8.). In adult male athletes the six most frequent sports were: kayak-canoe (n=45), water polo (n=28), rowing (n=19), soccer (n=15) and cycling (n=8) while among female adults, water polo was the most popular sport (n=38).

Table 8: Different sport disciplines in male adult athletes. LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVM, left ventricular mass; LVMi, left ventricular mass index; LVSV, left ventricular stroke volume; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume index; RVM, right ventricular mass; RVMi, right ventricular mass index.

	Male Adolescent N=97		Female Adolescent N=15	
	Skill n= 13		**Power** n= 4	
Variables	Mean ± SD	95% CI	Mean ± SD	95% CI
LVEDVi (ml/m^2)	110 ± 15	[86 - 137]	117 ± 22	[93 - 142]
LVMi (g/m^2)	65 ± 22	[50 - 89]	71 ± 13	[60 - 91]
LVEDV/LVM	1.54 ± 0.2	[0.96 – 1.9]	1.64 ± 0.22	[1.37 – 1.89]
RVEDVi (ml/m^2)	116 ± 13	[90 - 141]	117 ± 20	[101 - 145]
RVMi (g/m^2)	19 ± 5	[9 - 29]	21 ± 3	[17 - 24]
RVEDV/RVM	6.35 ± 1.3	[3.78 – 8.90]	5.46 ± 0.7	[4.6 – 6.0]
LVEDV/RVEDV	0.95 ± 0.06	[0.84 – 1.06]	1.00 ± 0.10	[0.81 – 1.19]
	Mix n= 45		**Endurance** n= 83	
Variables	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
LVEDVi (ml/m^2)	119 ± 13	[93 - 145]	126 ± 16	[100 - 160]
LVMi (g/m^2)	84 ± 13	[59 - 109]	92 ± 14	[64 - 119]
LVEDV/LVM	1.44 ± 0.25	[1.1 – 2.2]	1.40 ± 0.23	[1.04 – 1.97]
RVEDVi (ml/m^2)	121 ± 16	[90 - 151]	132 ± 17	[100 - 170]
RVMi (g/m^2)	22 ± 5	[13 - 31]	26 ± 7	[13 - 39]
RVEDV/RVM	5.67 ± 1.3	[3.75 – 9.20]	5.49 ± 2	[3.36 – 11.12]
LVEDV/RVEDV	0.99 ± 0.07	[0.86 – 1.13]	0.96 ± 0.08	[0.80 – 1.12]

4.1.1.4 Determining factors of cardiac adaptation in adult and adolescent athletes

We performed univariate analysis in adult (n=215) and adolescent (n=112) athletes separately aiming to study the biventricular adaptation of athlete's heart. In adult group, BSA, sex and age correlated with left and right ventricular dilation and hypertrophy (Table 9). More training per week related to higher LVEDV, RVEDV and LVM. Mixed, power and skill sports correlated negatively with LVM. Regarding ventricular ratios, male sex associated with higher LV and RV volume/mass ratios and higher RVEDV/LVEDV. Endurance sport correlated with a lower ratio of LVEDV/LVM and RVEDV/RVM, and weakly associated with right dominant dilation (Table 9).

In adolescent group, positive correlations were found between training hours and left ventricular hypertrophy (LVM r=0.39 p<0.0001; LVMi r=0.33 p=0.0013), and between training hours and biventricular dilation (LVEDV r=0.34 p=0.0008; LVEDVi r=0.25 p=0.0159; RVEDV r=0.36 p=0.0004; RVEDVi r=0.28 p=0.0066). Male sex related to higher LV and RV volumes (LVEDV r=0.27; LVEDVi r=0.22; RVEDV r=0.24; all < 0.05) and masses (LVM r=0.38; LVMi r=0.32; RVM r=26; RVMi=0.19; all p<0.05) in adolescents too. While in adult athletes, body size (BSA and BMI) was strongly associated of cardiac adaptation, in adolescents either BSA or BMI did not correlate with CMR values. Also, in adolescent athletes age did not correlate with indexed ventricular parameters or ventricular ratios. Since in adolescent group mainly mixed athletes were recruited, we were not able to adequately study sport related differences.

Table 9: Univariate analysis of determining factor of ventricular dilation and hypertrophy in adult athletes (n=215). BSA, body surface area; C, coefficient; ns, non-significant.

Table 8/A						
Covariates	LVEDV		LVM		LVEDV /LVM	
	C	p	C	p	C	p
Age (years)	0.19	0.0043	0.25	0.0002	-0.20	0.004

Sex	-0.62	<0.0001	-0.67	<0.0001	0.48	<0.0001
BSA (kg/m^2)	0.72	<0.0001	0.65	<0.0001	-0.3	<0.0001
Training /week (hours)	0.18	<0.05	0.16	<0.05	0.05	ns
Endurance (yes/no)	0.25	<0.001	0.38	<0.0001	-0.38	<0.0001
Mixed (yes/no)	-0.15	<0.05	-0.23	0.0008	0.26	0.0002

Table 8/B

Covariates	RVEDV		RVM		RVEDV /RVM		RVEDV /LVEDV	
	C	p	C	p	C	p	C	p
Age (years)	0.20	0.004	0.20	<0.005	0.12	ns	0.045	ns
Sex	-0.64	<0.0001	0.57	<0.0001	0.26	<0.0001	0.17	<0.05
BSA (kg/m2)	0.69	<0.0001	0.53	<0.0001	0.21	0.0019	-0.05	ns
Training /week (hours)	0.19	0.007	0.07	ns	0.03	ns	0.07	ns
Endurance (yes/no)	0.30	<0.0001	0.36	<0.0001	0.17	<0.05	0.17	<0.05
Mixed (yes/no)	-0.21	0.0018	-0.26	0.0002	0.11	ns	-0.20	0.005

4.1.1.5 Multivariate model to predict left and right ventricular dilation and hypertrophy in adult athletes

For adult athletes, multivariate models were created to study the significance of the individually correlating factors regarding cardiac adaptation. Including age, sex, training hours, endurance and mixed sports (all significant independently), all factors stayed significant in the model and correlated with LVMi except training hours. Sex and endurance sports were the strongest contributors: both factors associated with an increase of 20 g/m^2 LVMi. Mixed sport was associated with an increase of 11 g/m^2 LVMi.

We applied the same model to study biventricular dilation: sex and endurance sports were the strongest contributors and associated with a 13.5 ml/m^2 higher LVEDVi and 16 ml/m^2 higher RVEDVi; endurance sport associated with 15 ml/m^2 higher LVEDVi and 16 ml/m^2 higher RVEDVi. Participating in mixed sport had lower impact and was related to a 9 ml/m^2 increase of LVEDVi, and was not a significant contributor of RVEDVi. Each additional training hour was associated with an increase of 0.5 ml/m^2 LVEDVi and 0.7 ml/m^2 RVEDVi. The multivariate models (combination of age, sex, training hours, endurance and mixed sport) explained 30% of the variance of LVEDVi (r=0.30 p=<0.0001), RVEDVi (r=0.34 p=<0.0001) and RVMi (r=0.30 p=<0.0001); and as much as 53% of LVMi (r=0.53 p=<0.0001).

4.1.2 Masters athletes

Participants in the athlete cohort reported training regularly for an average of 29 ± 9 years and a mean of 15.5 ± 7 hours each week (Table 10). The majority of that time was spend training in endurance activities. Most athletes train in more than one sport but of those who focus on one sport, skiing was the most common. Half of the participants engaged in high school or college varsity athletics.

Table 10: Masters athletes sport participation.

Athletes (n=20)		n (%)
Type of the Primary Sport		
	Running	2 (10%)
	Cycling	7 (35%)
	Ski mountaineering	2 (10%)
	Cycling/Nordic skiing	9 (45%)
Varsity College Athletes		10 (50%)
Varsity High School Athletes		10 (50%)
Years in Endurance Sport		29 ± 9
Total training hours/week (mean ± SD)	Total	15.5 ± 7

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	Primary (mean ± SD)	12.5 ± 6
	Strength (mean ± SD)	3.5 ± 4
	Other (mean ± SD)	2 ± 2

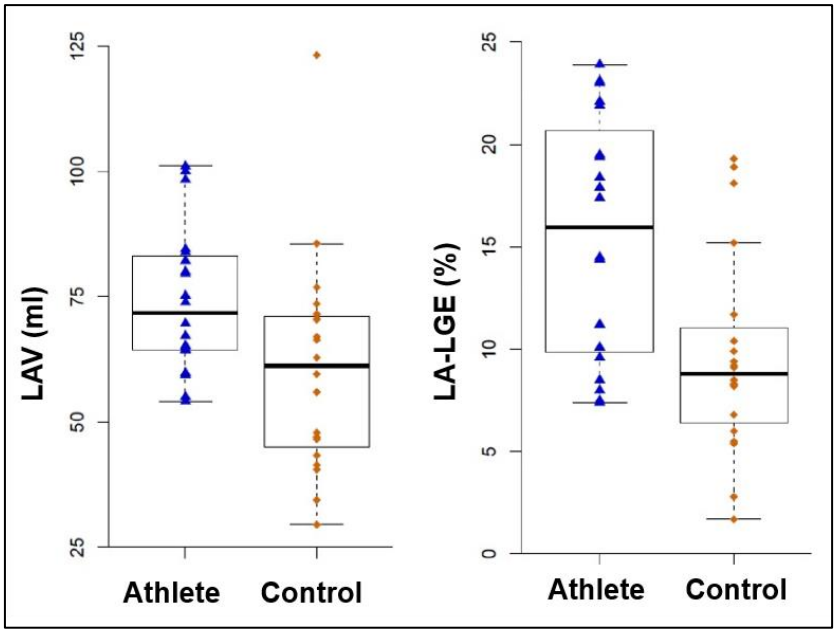

Figure 6: Left atrial volume (LAV) and late gadolinium enhancement (LA-LGE) of athletes compared to control group. The average left atrial volume in athletes is significantly higher compared to controls (p=0.02). Box and whisker plot showing that the average percentage of LA-LGE is significantly greater in athletes as compared to controls (p=0.002).

Left atrial volumes were significantly larger in the athletes (74 ± 14 ml^3) as compared to the healthy control subjects (60 ± 22 ml^3) (Figure 6). Mean LA fibrosis score, reported as a percentage of the LA, was higher in the athlete cohort compared to controls (p=0.001). Figure 7 shows representative examples of an endurance athlete (left) with higher LA-LGE% and healthy control (right) with smaller extent of LA-LGE%. Importantly, the LV parameters of the two groups and right atrial size were not different (Table 11).

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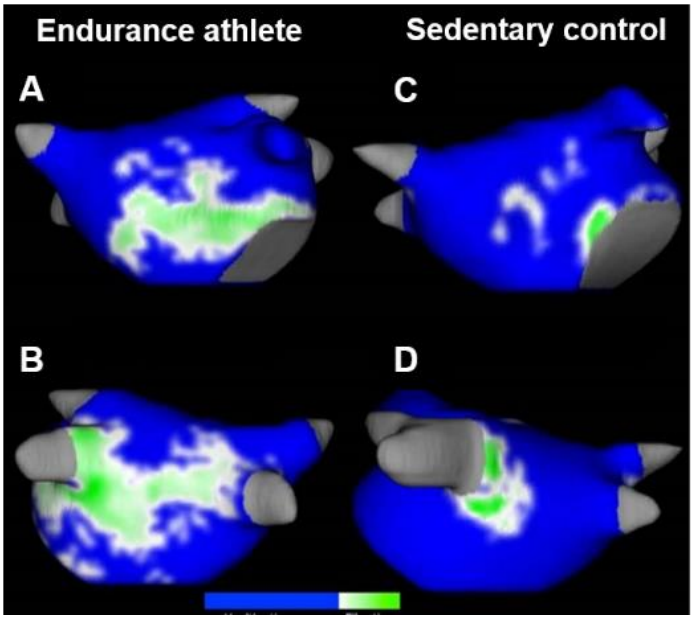

Figure 7: Colorized image of left atrial enhancement. Anterior images are above (A, C) and posterior images (B, D) below of endurance athlete (left) and healthy control (right). Blue color represents healthy areas of tissue and areas of white and green signify locations of late gadolinium enhancement with green demonstrating the densest areas of fibrosis.

Table 11: CMR parameters of masters athletes and sedentary controls. Masters athletes had higher left atrial volume (LAV) and volume index (LAV index) as higher left atrial late-gadolinium enhancement% (LA-LGE%).

	Masters Athlete (n=20)	Control (n=20)	p-value
LAV (mL)	74 ± 14	61 ± 21	0.02*
LAV index (mL/m^2)	41 ± 9	33 ± 10	0.012*
LA-LGE (%)	16 ± 6	10 ± 5	0.002*
RA area (cm^2)	25 ± 6	23 ± 5	0.27
LVEDV (mL)	142 ± 25	166 ± 44	0.29
LVEDV index (mL/m^2)	90 ± 8	87 ± 11	1.00
LVEF (%)	63 ± 5	60 ± 5	0.14

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4.2 Results of "The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease" project

CMR confirmed the diagnosis of structural myocardial disease in 39 athletes (25.5%) (37 male, 27 ± 17 years) (Figure 8).

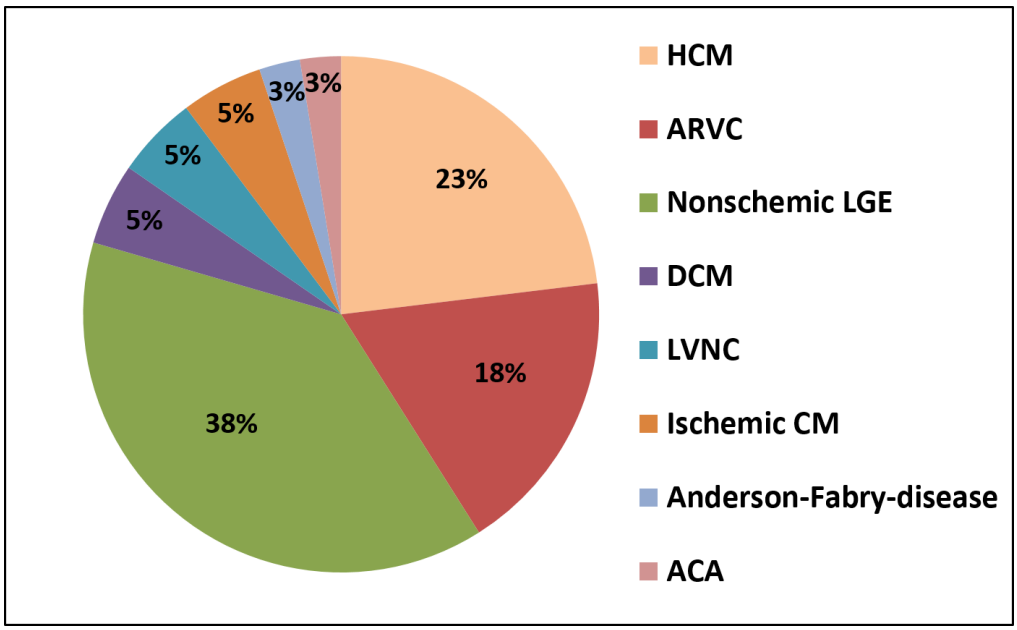

Figure 8: Athletes with structural myocardial diseases. Athletes were diagnosed with hypertrophic cardiomyopathy (HCM), prior myocarditis (typical late-gadolinium enhancement (LGE) pattern of prior myocarditis), arrhythmogenic right ventricular cardiomyopathy (ARVC), atypical LGE pattern, ischemic cardiomyopathy, idiopathic dilated cardiomyopathy (DCM), left ventricular noncompaction cardiomyopathy (LVNC), Anderson-Fabry disease and anomalous origin of the coronary artery (ACA)

Nine athletes (23%) have been diagnosed with hypertrophic cardiomyopathy (7 male; 18.5 ± 7.8 years). Three athletes had asymmetric septal hypertrophy, another three athletes concentric left ventricular hypertrophy (LVH) and four athletes had apical HCM (Figure 9). Figure shows an example of an athlete with apical HCM. The average LVM index in HCM group was 84 ± 2 g/m^2, and the maximum end-diastolic wall thickness (EDWT) was 17 ± 0.5 mm. The maxEDWT/LVEDVi ratio was higher than 0.15 in eight athletes. Seven athletes had LGE in

the LV. Two athletes without LGE had repeated CMR scan following a 6-weeks long deconditioning period when CMR parameters when LVMi and EDWT were detected in pathological range.

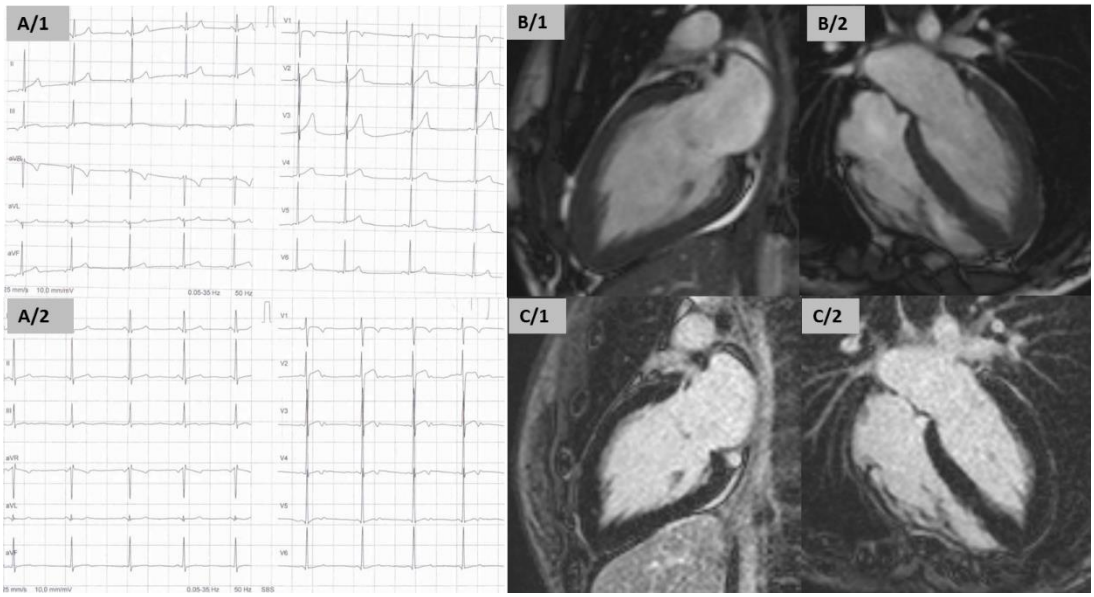

Figure 9: Female athlete with apical hypertrophic cardiomyopathy. Compared to the normal baseline 12-lead resting ECG (A/1), three-years later the follow-up ECG demonstrates left ventricular hypertrophy and biphasic T waves in V3 and V4. The cine long-axis CMR images (B/1 and B/2) show apical LVH without fibrosis on late gadolinium images (C/1 and C/2).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) was diagnosed in 7 athletes (18%) (6 male, 28 ± 1.4 years). Two athletes had biventricular ARVC (Figure 10). In addition, three athletes had a documented history of aborted SCD and another two athletes had prior sustained VT.

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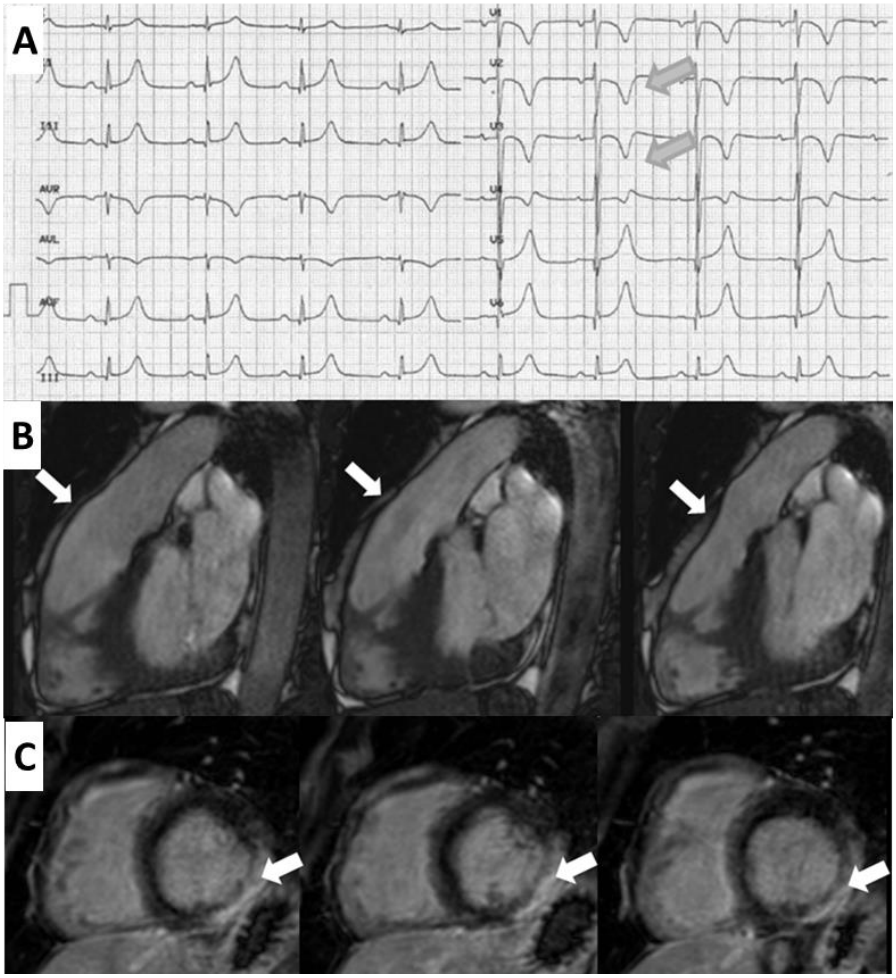

Figure 10: Triathlete with biventricular arrhythmogenic right ventricular cardiomyopathy. The resting 12-lead ECG shows inverse T waves in V2 and V3 leads (A). Right ventricular dysynchrony was detected in the basal right ventricular wall/right ventricular outflow tract (B), and subepicardial late gadolinium enhancement (LGE) in the inferolateral basal left ventricular wall (C).

Two athletes had LV hypertrabecularization indicating for left ventricular noncompaction cardiomyopathy (LVNC) based on the current CMR criteria(77). Two athletes have been diagnosed with idiopathic dilated cardiomyopathy (DCM) (LVEF 49% and 47%; LVEDVi 131 and 153 ml/m2). Two male marathon runners (39 and 50 years old) had subendocardial LGE suggesting prior myocardial infarction with corresponding hypokinesia (Figure 11). Non-ischaemic LGE pattern was detected in 15 athletes (38%). Patchy subepi-midmyocardial LGE was found in 8 athletes suggesting prior myocarditis and atypical LGE pattern in 7 cases

(Figure 11). One athlete had midmyocardial LGE in the basal inferolateral segment of the LV which is typical for Anderson-Fabry-disease (Figure 11). The diagnosis was confirmed with enzyme assay test. One athlete was diagnosed with an anomalous origin of the coronary artery (ACA) when right coronary artery originated from the left sinus Valsalva with an interatrial course between the aorta and the pulmonary artery. In two athletes with the history of documented sustained VT, ARVC were diagnosed. Among ten athletes with the history of aborted SCD, three athletes had ARVC and two of them had atypical LGE on CMR images.

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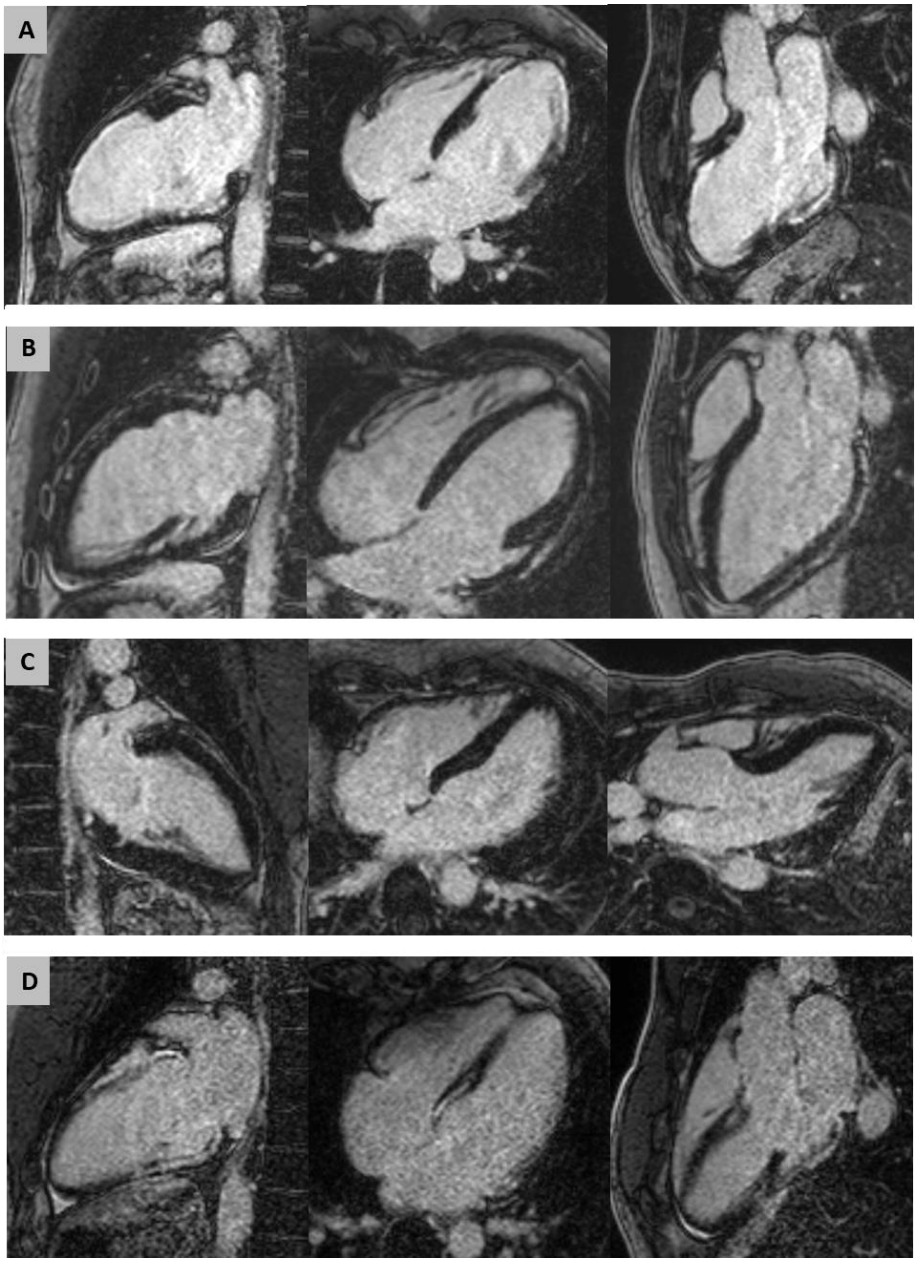

Figure 11: Marathon runner with subendocardial late gadolinium enhancement (LGE) suggesting prior myocardial infarction (A). Dilated cardiomyopathy with subepicardial LGE in the lateral left ventricular (LV) wall and midmyocardial basal streak in basal septum (B). Athlete with midmyocardial LGE in the basal inferolateral segment of the LV, specific sign of Anderson-Fabry-disease (C). Atypical LGE pattern in a pentathlon athlete in the basal and mid anterior, antero-and inferoseptal and inferior segments midmyocardially (D).

4.3 Results of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

4.3.1 Longitudinal changes of left atrial volumes and function in the whole cohort

4.3.1.1 Baseline vs. acute atrial volumes and function

The maximum LA volume did not change acutely, but MinLAV and MinLAVi increased immediately after the ablation procedure. In the acute phase, all of the LA functional parameters decreased except passive ejection fraction (Table 12). The EF_{Total} decreased by 13.5%, EF_{Active} decreased by 36% and PLAS decreased by 17% acutely.

Table 12: Left atrial volumes and function at baseline (B) before the procedure, in acute phase (A) and at follow-up (F) in the whole cohort. EFActive, active ejection fraction; EFPassive, passive ejection fraction; EFTotal, total ejection fraction; MaxLAV, maximum left atrial volume; MaxLAVi, maximum left atrial volume index; MinLAV, minimum left atrial volume; MinLAVi, minimum left atrial volume index; PLAS, peak longitudinal atrial strain.

Variables	Baseline N = 55	Acute N = 55	Follow-up N = 55	B vs A p	B vs F p
MaxLAV (ml)	107 ± 34	109 ± 36	94 ± 35	NS	0.003
MaxLAVi (mL/m^2)	51 ± 15	52 ± 15	45 ± 15	NS	0.003
MinLAV (ml)	66 ± 30	74 ± 34	60 ± 32	0.003	NS
MinLAVi (mL/m^2)	32 ± 14	35 ± 15	29 ± 15	0.003	NS
EF_{Total} (%)	39 ± 14	33 ± 12	38 ± 14	0.001	NS
$EF_{Passive}$ (%)	21 ± 8	23 ± 10	23 ± 10	NS	NS
EF_{Active} (%)	23 ± 14	15 ± 11	20 ± 13	0.001	NS

PLAS (%)	27 ± 10	17 ± 8	19 ± 9	0.010	NS

4.3.1.2 Baseline vs. follow-up atrial volumes and function

No significant difference was detected between baseline and follow-up atrial function except LAV and LAVi (Table 12). Regarding periprocedural fluid status, PFA (median, first and third quartile: 800 ml [500 to 1100]) and PFB (500 ml [390 to 860]) did not correlate with acute volumes or function (acute minLAVi, maxLAVi, EF_{Total}, $EF_{Passive}$, EF_{Active}, PLAS), either with pre- and post-ablation volume or functional changes (ΔminLAVi, ΔmaxLAVi, ΔEF_{Total}, $\Delta EF_{Passive}$, ΔEF_{Active}, ΔPLAS).

4.3.1.3 Atrial function vs. LA-LGE

Higher baseline LA-LGE% correlated with lower baseline EF_{Total} ($r=0.37$ $p=0.012$), $EF_{Passive}$ ($r=0.51$ $p<0.001$) and PLAS ($r=0.34$ $p<0.002$), but not with EF_{Active}. Figure 12 shows an example of LGE distribution in a patient with good (Patient A) and poor (Patient B) baseline atrial function.

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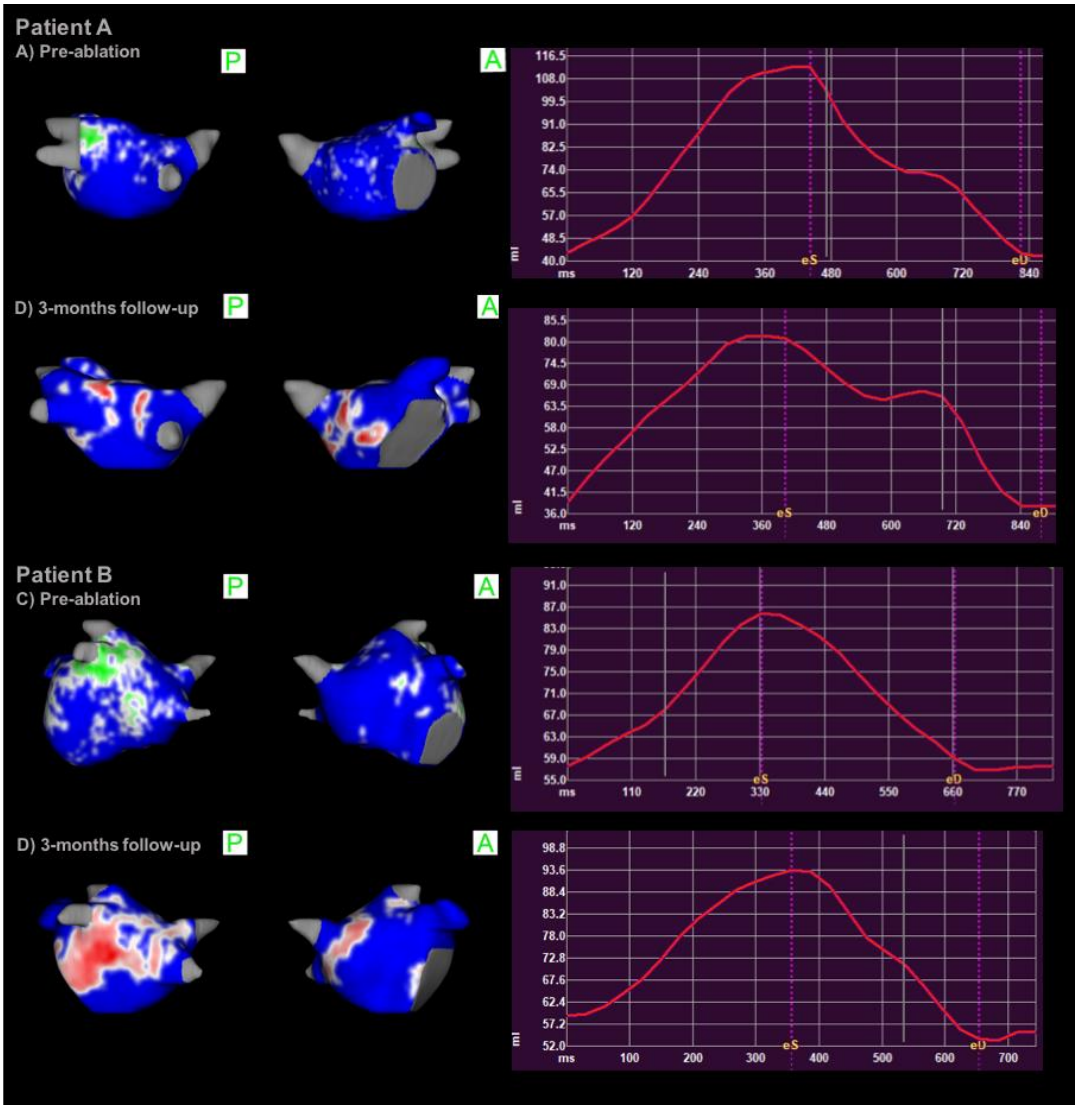

Figure 12: Association between left atrial (LA) function and structure. Patient A with low baseline fibrosis (green=fibrosis; blue=healthy tissue) and good LA function (image A: EF_{Total}=62%) (A=anterior, P=posterior view). Patient B with higher baseline fibrosis and poor LA function (image C: EF_{Total}=33%). Image B and D show ablation scar (red) and follow-up function (Patient A: EF_{Total}=53% and Patient B: EF_{Total}=42%).

4.3.2 Longitudinal changes of left atrial volumes, function and structure in recurrence and non-recurrence groups

Table 13: Left atrial volumes and function baseline (B) before ablation procedure, in acute phase (A) and at follow-up (F) in non-recurrence (n=26) and recurrence (n=24) groups.

EFActive, active ejection fraction; EFPassive, passive ejection fraction; EFTotal, total ejection fraction; MaxLAV, maximum left atrial volume; MaxLAVi, maximum left atrial volume index; MinLAV, minimum left atrial volume; MinLAVi, minimum left atrial volume index; PLAS, peak longitudinal atrial strain.

Variables	Baseline		Acute		Follow-up		B vs A		B vs F	
	NR	R	NR	R	NR	R	NR	R	NR	R
							p	p	p	p
MaxLAVi (mL/m^2)	50 ± 19	53 ± 14	49 ± 16	53 ± 13	39 ± 11	51 ± 18	ns	ns	0.002	ns
MinLAVi (mL/m^2)	28 ± 13	36 ± 14	31 ± 16	39 ± 14	24 ± 9	37 ± 17	ns	0.018	0.019	ns
EF_{Total} (%)	43 ± 12	33 ± 15	38 ± 11	28 ± 10	44 ± 12	29 ± 13	0.001	0.026	ns	ns
$EF_{Passive}$ (%)	24 ± 9	18 ± 7	26 ± 10	19 ± 8	27 ± 9	19 ± 9	ns	ns	ns	ns
EF_{Active} (%)	28 ± 12	18 ± 15	19± 12	11 ± 8	24 ± 11	14 ± 10	0.003	0.001	ns	ns
PLAS (%)	24 ± 10	17 ± 10	20 ± 7	13 ± 6	24 ± 8	14 ± 7	0.017	0.014	ns	ns

Of the total of 55 patients, 91% (50 patients) fulfilled the 12-months clinical follow-up criteria. Of these 50 patients with complete follow-up, 24 patients experienced AF recurrence. Comparing baseline characteristics of the recurrence (R) and non-recurrence (NR) groups, patients with recurrence had higher baseline MinLAVi and lower total, passive and active LA ejection fractions as well as PLAS (Table 13).

4.3.2.1 Baseline vs. acute atrial volumes and function

In the acute time period, MinLAVi increased in patients with recurrence but did not change in non-recurrence group (Table 13). Also in the acute phase, atrial function was lower in patients who had recurrence [R vs NR: EF_{Total} 28 ± 10% vs 38 ± 11% p=0.002; EF_{Active} 10.5 ± 8% vs 19 ± 12% p=0.007; $EF_{Passive}$ 19 ± 8 vs 26 ± 10 p=0.021; PLAS 13± 6% vs 20 ± 7% p=0.004].

4.3.2.2 Baseline vs. follow-up atrial volumes and function

In non-recurrence group, both the MaxLAVi and MinLAVi were significantly decreased at the time of the follow-up scan (Table 13). Figure 13 depicts the mean LA volume and strain curves for recurrence and non-recurrence groups separately at baseline (in the acute phase) and during follow-up. It is clearly seen by comparing volume and strain curves that active atrial ejection fraction is impaired acutely in both groups (Figure 13).

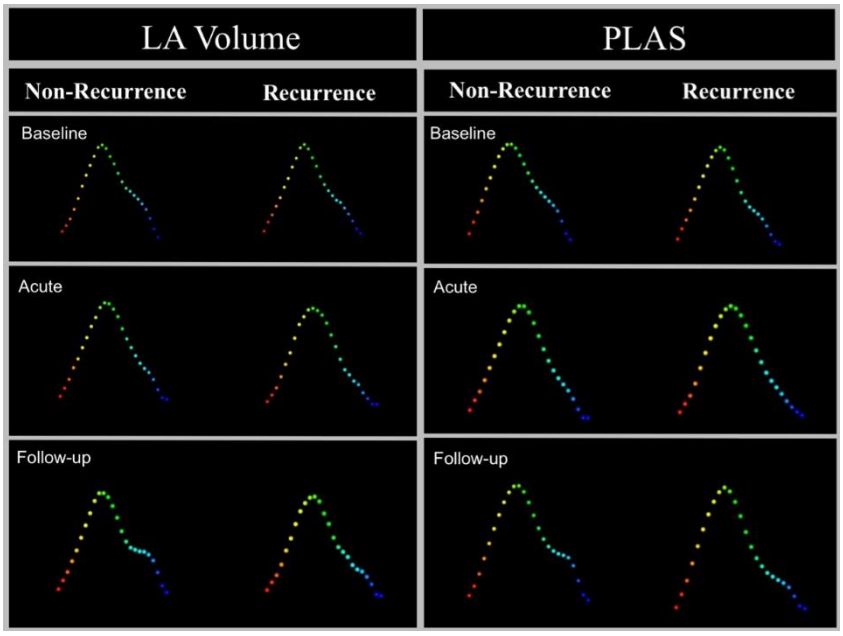

Figure 13: Changes of mean left atrial (LA) volume and peak atrial longitudinal strain (PLAS) before and after ablation. Analyzing individual volume and PLAS curves of each patient, representative mean curves were created for recurrence (R) and non-recurrence (NR) groups regarding pre-ablation, acute and follow-up values. Active atrial function (second loop of the curves) was impaired in both R and NR groups acutely (flattened second loop) and improved markedly at 3-month follow-up in NR group.

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4.3.2.3 Atrial fibrosis and post-ablation scar

Baseline LA-LGE% was higher in patients who had AF recurrence compared to those without AF recurrence (17± 6% vs 13 ± 5% p=0.015). The amount of left atrial ablation scar (quantified on 3-months follow-up scan) was not significantly different in patients with and without recurrence (21.5 ± 7% vs 22 ± 6%), moreover post-ablation scar did not correlate either with 3-months follow-up function (follow-up EF_{Total}, $EF_{Passive}$, EF_{Active}, PLAS) or baseline - follow-up LA functional changes (delta values).

4.3.2.4 Predictors for recurrence

With univariate regression, baseline MinLAV and MinLAVi, each baseline LA functional parameter (EF_{Total}, $EF_{Passive}$, EF_{Active}, PLAS) and also baseline LA-LGE% were significant predictors for arrhythmia recurrence (Table 14).

Table 14: Univariate analysis to predict the recurrence of atrial fibrillation. EFActive, active ejection fraction; EFPassive, passive ejection fraction; EFTotal, total ejection fraction; MaxLAV, maximum left atrial volume; MaxLAVi, maximum left atrial volume index; MinLAV, minimum left atrial volume; MinLAVi, minimum left atrial volume index; PLAS, peak longitudinal atrial strain.

Variables	AUC	[95% CI]	p-value
Age	0.567	0.420 to 0.707	0.5345
Sex	0.510	0.364 to 0.654	0.8769
AF type	0.591	0.443 to 0.728	0.1489
CHA_2DS_2VASc	0.522	0.759 to 1.833	0.2999
Baseline MaxLAVi (mL/m^2)	0.601	0.453 to 0.737	0.4860
Baseline MinLAVi (mL/m^2)	0.689	0.542 to 0.812	0.0402*
Baseline EF_{Total} (%)	0.713	0.568 to 0.832	0.0070*

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Baseline $EF_{Passive}$ (%)	0.723	0.578 to 0.840	0.0053*
Baseline EF_{Active} (%)	0.681	0.534 to 0.806	0.0215*
Baseline PLAS (%)	0.696	0.549 to 0.818	0.0225*
Baseline LA-LGE (%)	0.685	0.526 to 0.818	0.0112*
Acute EF_{Total} (%)	0.753	0.611 to 0.864	0.0014*
Acute $EF_{Passive}$ (%)	0.671	0.524 to 0.798	0.0188*
Acute EF_{Active} (%)	0.702	0.556 to 0.823	0.0049*
Acute PLAS (%)	0.742	0.599 to 0.855	0.0031*

Acute LA function (EF_{Total}, $EF_{Passive}$, EF_{Active}, PLAS) also predicted arrhythmia recurrence (Table 14). In a multivariate model including MinLAV, EF_{Active} and LA-LGE (all at baseline), LA-LGE was an independent predictor for recurrence (AUC: 0.768 [0.615 to 0.883]; p=0.0322).

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5 Discussion

5.1 Discussion of the "Functional and structural characteristics of athlete's heart assessed by CMR imaging" project

5.1.1 Adult and adolescent athletes

5.1.2 Sex-specific differences and female athlete's heart

In this study, all LV and RV volumes and masses were different between adult male and female athletes. Male adults had marked left and right ventricular hypertrophy represented by the lower LVEDV/LVM and RVEDV/RVM ratios compared to females. In adolescent group, male athletes also had higher LV and RV masses; however, indexed right ventricular volumes were not different between sexes may suggesting that cardiac adaptation is not as clearly separated as in adults. Although, female adolescent group was smaller and they exercised vigorously. In adolescent athlete's heart, CMR derived RVEDV/LVEDV ratio was one in both sexes.

Due to the lack of literature data, the recently published meta-analysis does not provide normal CMR values for female athletes (78). In our study, highly trained Caucasian female athletes (n=96; 26% of cohort) were investigated. We found that in contrast with male athletes, female adult and adolescent athletes' LV and RV volumes and masses were not different. It could be explained by that physiological cardiac adaptation is less remarkable in female athletes, and cardiac adaptation did not change as much with age as in males. Although, the small sample size of adolescent females, and high weekly training volume may impact the result. In a large echocardiography study, Finocchiaro et al. reported that female athletes have eccentric LV hypertrophy more often than males (21). In accordance, this study reports higher LV volume/mass ratio in both female adult and adolescent athletes measured by CMR imaging. Moreover, we also found that adult female athletes had higher RVEDV/RVM compared to males.

5.1.3 Sport-related differences

In accordance with literature data, we found that sport disciplines, endurance and mixed sports are significant contributors of LV and RV dilation and hypertrophy in adult athletes (18, 23). Due to the variable categorization of sport disciplines in the literature (17, 18, 34, 79), it is challenging to compare sport-related differences between studies. In this study we report mean value and confidence intervals of highly trained endurance and mixed male athletes. A recently published study showed that even mortality was different between athletes engaged in different sport disciplines (80).

5.1.3.1 Adolescent athletes

Cardiac adaptation in young athletes is a dynamically changing process, and studying the transformation of 'immature' athlete's heart into a complete morphological and structural adaptation what can be seen in adult athletes, is challenging. Limited, mainly echocardiography data available regarding cardiac adaption of young athletes (25, 36). In adolescent athletes, more training hours correlated with higher biventricular sizes and hypertrophy. Previous echocardiography study shows that body size reported as body mass index (BMI) was not correlated with ventricular dimensions in healthy young adolescent athletes (36). We also found that BMI and additionally BSA did not correlate with CMR values. This result may suggest that cardiac adaptation was disproportionate compared to overall body size (and muscular hypertrophy) represented by BMI and BSA in adolescent group. In addition, using chronological age to discriminate the two groups could be debatable. Recent ECG publication reported that interpretation of ECG regarding isolated T-wave inversion using current recommendations (chronological age <16 years) warrants caution, and applying biological age improves diagnostic accuracy (81). LVEDV/LVM was higher in adolescent athletes compared to adults which could support the hypothesis as in young athletes the dilation of the ventricles is more remarkable than ventricular hypertrophy.

5.1.3.2 Biventricular sizes and balanced cardiac adaptation

Recent meta-analysis on CMR studies defined the normal limit of biventricular size and function in competitive white male athletes (78). Compared to the meta-analysis data, we observed higher LVMi in our study. This difference could be because the training hours in the current study population was above the average of the studies included in the meta-analysis, or due to the high participation of endurance athletes. Studying LVEDV/LVM and RVEDV/RVM ratios, pronounced LV hypertrophy is associated with higher age, BSA, male sex, endurance and mixed sports. In accordance with literature, we found a balanced biventricular cardiac adaptation in adult athletes (18). Male athletes and athletes participating in endurance sport had slightly right dominant dilation, although the correlations were weak. Calculating RV/LV volume ratio is a quick and reliable method to determine imbalances of the biventricular adaptation. Differentiating physiological cardiac adaptation from different pathologies like arrhythmogenic right ventricular cardiomyopathy (ARVC), is challenging (82, 83). Based on literature data, the RVEDV/LVEDV value of 1.3 could suggest pathological right ventricular dilation (82). In our study two athletes had a RVEDV/LVEDV equal with 1.3 (both of them were male adults), and none of the athlete had a higher RVEDV/LVEDV value than 1.3.

5.1.3.3 Determining factors

Physiological cardiac adaptation due to regular and high-volume exercise is influenced by multiple factors such as age, ethnicity, sex, body weight and height, sport category, the intensity and duration of physical activity (14, 17, 23, 84, 85). As the main characteristic features of ventricular adaptation are ventricular dilation and hypertrophy, we created models to study the variation of LVEDVi, RVEDVi, LVMi, and RVMi parameters. We found that age, higher BSA, male sex, higher weekly training hours, and endurance or mixed sports associated with higher LV and RV end-diastolic masses and volumes in adult athletes. A combination of age, sex, training hours, endurance and mixed sport explained 30% of the variance of LV and RV dilation, and RV hypertrophy; and as much as 53% of LV hypertrophy.

An important determinant of physiological cardiac adaptation in athletes is ethnicity: ethnic differences are clinically relevant in case of left ventricular adaptation and slightly different regarding RV parameters (32, 81, 85). Advocating the diversity of cardiac adaptation in

athlete's heart, recent study reported that electrical (prevalence of pathological ECG) and structural (LV hypertrophy) adaptation to exercise training were not uniform among black athletes from different geographical location (86).

Determining the physiological limit of cardiac adaptation in athlete's heart is challenging. Quantitative assessment of LV and RV parameters in healthy athletes is vital to better understand the physiological limit of cardiac adaptation to exercise. Our study highlights the necessity of establishing age-, sex, and sport related normal values for healthy athletes. In the future, multicentric follow-up studies could help us to better understand the specific characteristics and physiological limit of athlete's heart.

5.1.4 Masters athletes

This study demonstrated an increased level of atrial fibrosis in masters endurance athletes as compared to healthy non-athletic controls. The cardiovascular benefits of daily exercise are well recognized. However, endurance athletes appear to develop atrial arrhythmias at higher rates compared to the general population, with an estimated 5-10 fold increase the prevalence of AF amongst endurance athletes (42-45, 87). While there are speculations regarding atrial remodeling contributing to such increased rates of atrial arrhythmia, our study is the largest to date to describe and characterize fibrotic changes within the LA of endurance athletes. We demonstrated that masters athletes have a significantly greater degree of LA fibrosis as compared to healthy age and gender matched controls. Additionally, the athletic cohort had significantly larger LA volumes ($p=0.02$) consistent with physiological changes that have previously been described in the trained heart(88). Our athletes did not have larger absolute LV volumes as might be expected.

Ventricular fibrosis in athletes is not a new findings and was introduced several decades ago(89). The literature focusing on myocardial fibrosis in athletes, using both CMR and biopsy, suggest variation in patterns and location of fibrosis(90). The majority of studies found fibrosis in the septum and right ventricular insertion point. There are few studies comparing ventricular fibrosis in athletes to age and gender matched controls, but at least two studies have shown fibrosis prevalence to be greater in athletes(91). More recently, investigators found that

competitive triathletes demonstrated greater levels of focal, “non-ischemic” late-gadolinium enhancement (LGE) of the left ventricle as compared to normally active controls(92). Interestingly, LGE correlated closely with lifetime competition distance and was only seen in the male population. These findings, including male predominance and correlation with lifetime high intensity activity exposure, parallel the body of evidence linking endurance exercise to atrial remodeling and development of atrial arrhythmias(93).

The higher risk of AF associated with endurance sports has been confirmed in numerous populations(42-45). However, our population was specifically screened to select athletes without a prior diagnosis of arrhythmia but at high risk for future development due to their training habits. The exact mechanism by which athletic training increases an individual’s risk for AF is not entirely understood. One current hypothesis is that elevated blood pressure and repetitive atrial stretching during exercise in addition to left ventricular enlargement lead to atrial remodeling(94, 95). Another theory put forward by Andre La Gerche describes a “dam wall” effect. He argues that during exercise, the proportion of time spent in systole increases and thus the mitral valve is closed for a greater percentage of the cardiac cycle. This alteration in timing leads to elevated pressures in the LA, upstream of the mitral valve. Thus the thin walled LA is thus subject to stretch and remodeling(96). Interestingly, recent data by MacNamara et al. artfully reported the evolution of LA remodeling in sedentary individuals who began high-intensity training (HIT)(97). They found that despite significant LA mechanical remodeling, there was no change in non-invasive markers of electrical remodeling during the 2-year training period. They hypothesized that the increased susceptibility to AF may require prolonged exposure to exercise or is a late downstream effect of mechanical remodeling rather than a concomitant effect of HIT. Lastly, atrial ectopy which can act as a trigger for sustained atrial arrhythmias has been shown to increase with the number of marathons run(98). These factors may help explain the pattern of increased atrial arrhythmias seen in highly trained athletes.

Previous studies have shown that patients with AF have a significantly higher fibrosis burden than control groups of the same age(99). In patients with known AF, a higher degree of atrial fibrosis is associated with an increased risk of major adverse cardiovascular and cerebrovascular events as well as recurrence of AF about successful ablation(100). Degree of

LA fibrosis has been further classified in 4 stages (I: 0-10%, II: 10-20%, III: 20-30%, IV: >30%)(101). Using this classification system, the athlete group (total fibrosis 15.5%) would be considered Utah Stage II whereas controls (total fibrosis 9.6%) would be Utah Stage I. An absolute 5% difference in atrial fibrosis appears to be clinically significant in those with AF who have undergone an ablation. Whether this difference is clinically significant in athletes is yet to be determined. While total burden of LA fibrosis appears to have clinical significance, the implications of a specific LA fibrosis pattern are still not understood. It is believed that AF induces electrophysiological changes in the atrial myocardial cells as well as structural changes such as fibrosis and LA dilation. These changes together are thought to reduce the effective refractory period and likely lead to a propensity for increased risk of arrhythmia. Lastly, atrial remodeling resulting in atrial fibrosis has also been observed in patients without AF but with other stressors on the heart including hypertension, valvular disease or heart failure(102). Perhaps extensive endurance training creates a similar environment which then leads to atrial fibrosis formation. Despite our ability to detect left atrial fibrosis in endurance athletes, the clinical implications remain unclear. In the initial longitudinal case-controlled study by Svedberg et al. in which investigators reported a higher prevalence of AF in male cross-country skiers as compared to controls, they also found that participation in sports was protective against stroke(103). As Pelliccia and colleagues concluded, “left atrial remodeling in competitive athletes may be regarded as a physiologic adaptation to exercise conditioning, largely without adverse clinical consequences”(104).

5.2 Discussion of “The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease” project

Differential diagnosis between athlete’s heart and structural myocardial diseases may be challenging due to overlapping features. Distinguishing athlete’s heart from HCM is one of the main diagnostic dilemmas in the field of sports cardiology. HCM is the most common cause of SCD in young competitive athletes(56, 105). As a first line diagnostic tests, resting 12-lead ECG and echocardiography can help the differential diagnosis. The physiological upper limit of maximal end-diastolic wall thickness (EDWT) is 15 mm thus athletes with a maxEDWT >15 mm may be considered to have pathological left ventricular hypertrophy(106-108). HCM has diversity in morphological expression and certain phenotypes such as apical hypertrophy

might be difficult to diagnose with first line screening tests. CMR imaging is superior to echocardiography in differentiating athlete's heart from HCM(64, 65). LGE could provide incremental information beyond morphological CMR measures(64, 65). Importantly, the absence of LGE does not exclude the diagnosis of HCM. In one athlete the pathological LVH with basal inferolateral mid-myocardial LGE suggested Anderson-Fabry disease, a glycosphingolipid storage disease. The diagnosis was confirmed by laboratory testing and enzyme replacement therapy was initiated.

Due to eccentric RV remodeling is a known phenomenon in athletes, diagnosing ARVC in athletes is more challenging compared to non-athletes(65, 79). ARVC is a clinical diagnosis, however, current Task Force document is lacking special consideration of athletes(109). In our study, seven athletes were diagnosed with ARVC. CMR imaging helped to establish the diagnosis by providing precise RVEF, and in selected cases detecting fibrosis/fat in the ventricles. Our research group previously reported data that regional strain and strain rates may help to identify ARVC even in highly trained athletes with preserved RVEF(80).

CMR can be useful in the differentiation of athlete’s heart from DCM providing accurate volumetric and functional measurement, and in about one third of the cases identifying mid-myocardial LGE as we have seen in the two athletes in our study group(110-112). In two athletes (age > 35 years) ischemic cardiomyopathy based on the subendocardial LGE. These athletes were referred for CMR viability study due to ECG abnormalities, and they did not have any symptoms or complain prior to the CMR scan. Importantly, both athletes were older (39 and 50 years-old) and they were engaged in endurance sport.

Abnormal origin of the coronary arteries are congenital disorders, usually underdiagnosed cardiovascular disease due to the lack of symptoms. However, literature data suggest that after HCM, ACA is the second most common aetiology of sport-related SCD in young athletes(113, 114). CMR imaging can visualize the origin of the coronary arteries without radiation exposure and can play an important role of diagnosing ACA in young individuals(115). In athletes with nonischemic LGE pattern, 8 athletes had subepicardial patchy LGE suggesting prior acute myocarditis. Although, acute myocarditis is an absolute contraindication of intense physical exercise, limited data available regarding the safetiness of recreational and professional sport in individuals with post-myocardial LGE(65, 116). CMR imaging is excellent technique to

detect oedema in acute myocarditis and is useful to identify post-myocardial scar formation(65, 115, 117).

To the best of our knowledge, this was the first national study reporting data of the etiology and frequency of structural myocardial diseases in a large group of Hungarian athletes using CMR imaging. In athletes with suspected structural myocardial abnormality, CMR imaging can detect myocardial fibrosis/scar without the presence of myocardial wall motion abnormalities and/or pathological ECG signs. We found that the most frequently diagnosed cardiomyopathy was HCM, while the most common structural disorder related to aborted SCD was ARVC.

5.3 Discussion of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

5.3.1 Longitudinal changes of LA volumes

Recently, large population-based studies have provided normal values of LA dimensions measured by CMR (78, 118). According to the literature, LA function can be impaired even with normal LA size and sinus rhythm (119). A recent CMRi study showed that in an asymptomatic multi-ethnic population, elevated LA volumes and decreased LA function are associated with AF (120). Data regarding post-ablation changes of LA volumes and function are controversial and mainly have been reported using transthoracic echocardiography (121, 122). Using cardiac MRI, we demonstrated that minimum LA volume and volume index changed in the acute phase. Due to impaired contractility, it is possible that the ablated, dilated LA could not shrink acutely. However, at 3-months follow-up in patients without recurrence, the MaxLAV and MaxLAVi decreased, likely as part of reverse remodeling.

According to current task force guidelines (123), peak longitudinal left atrial strain (PLAS) is the most reliable deformation parameter for clinical application when evaluating LA function. Histologic analysis has demonstrated that LA function as measured by FT-CMRi, especially PLAS, strongly correlates with the degree of fibrofatty infiltration of the left atrial wall (124). In our AF cohort, higher pre-ablation LA-LGE% correlated with lower PLAS and with total

and passive ejection fractions at baseline. Higher LA-LGE amount suggests that higher amounts of fibrosis make the LA wall rigid. The lack of association between baseline EF_{Active} and baseline LA-LGE% might suggest that passive ejection fraction is more dependent on structural alterations of the myocardium, while active atrial ejection is able to compensate and does not show definite impairment even in cases of higher LA fibrosis. However, in this study the vast majority of patients had paroxysmal AF and due to this bias we might miss the group of patients with high baseline fibrosis and low EF_{Active}. Also, patients with very advanced atrial disease (extremely dilated atrium, highly depressed function with apparently poor active contractile function and possibly high LA wall fibrosis), are less likely referred for invasive ablation procedure.

5.3.2 Acute functional impairment and left atrial functional recovery

Limited data are available about the impact of AF catheter ablation on LA size and function measured acutely after an ablation procedure. The only available CMR study measured thickened LA wall within 24-hours after the procedure, consistent with edema (125). In our study ablation injury caused impaired EF_{Active} while $EF_{Passive}$ did not change acutely, suggesting that active atrial ejection function is the dynamically changing component of LA function. In the acute time period, all measured functional parameters were predictive of AF recurrence. Acutely after a successful AF ablation, most patients are in sinus rhythm, which is optimal for accurate evaluation of LA function by CMRi. Additionally, LGE-CMR assessment in the acute phase after the ablation procedure makes possible the evaluation of esophageal injury (76), which likely provides additional benefit to this CMRi obtained post-ablation.

Comparing baseline and follow-up atrial function, no functional improvement was detected in the whole cohort or even in the non-recurrence group. However, between the acute and follow-up scans, LA function improved, and follow-up LA function was not lower compared to baseline levels. In this cohort the majority of patients had paroxysmal AF, and significant functional improvement would have been detectable in patients with persistent AF. Also, baseline LA function in patients with recurrence was primarily lower.

This study reports functional data of the whole cardiac cycle representing mean values of volume and strain curves measured by FT-CMRi. Our data suggest that active atrial kicking is the dynamically changing component of LA function in both recurrence and non-recurrence groups. Since no correlation was found between periprocedural fluid status (PFA, PFB) and acute LA volumes or function, we can conclude that acute volume and functional measurements were not influenced by periprocedural volume status in this particular study.

5.3.3 Predictors for AF recurrence and the complexity of left atrial structural and functional recovery

In a previous echocardiography study, pre-ablation LA midlateral strain inversely correlated with LA-LGE% and was related to AF recurrence (126). Similar to previously reported studies (127), we found a significant correlation between pre-ablation global LA function (PLAS and EF_{Total}) and fibrosis. However, while lower $EF_{Passive}$ was also associated with higher baseline LA-LGE, no association was found between EF_{Active} and LA-LGE. Habibi et al. reported that atrial function and strain parameters measured by tissue tracking CMRi are predictors for AF/AT in a drug-refractory AF population (128). In our study, in addition to baseline atrial function, acute functional impairment was also predictive for recurrence. In a multivariate model including baseline LA size (MinLAV), function (EF_{Active}) and structural remodeling (LA-LGE%) CMR parameters, LA fibrosis was the only independent predictor for recurrence. After AF ablation procedure, new LGE on 3-months post-ablation scan can be detected as LA scar formation(7). In this cohort, there was no significant difference between recurrence and non-recurrence groups regarding amount of LA scar after the ablation procedure. In patients with high baseline LA-LGE%, the more fibrotic and rigid LA wall seems to be more fragile/sensitive to acute ablation injury and showed poor functional recovery regardless of the ablation scar amount.

A few studies have reported that after a certain point, further increases in atrial volume associate with lower LA function (129). Fibrotic elements in the LA wall and also ablation scarring seem to contribute to abnormalities in LA function/contractility. In this patient cohort, we did not find any differences in outcome regarding ablation scarring. Further studies are needed to look for an association between the amount and localization of ablation scar in

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relation to LA function. In the future, a comprehensive 4D (CMR) evaluation of LA morphology, structure and function may help better classify AF patients and might have additional implications for optimal treatment selection.

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6 Limitations

6.1 Limitations of the “Functional and structural characteristics of athlete’s heart assessed by CMR imaging” project

6.1.1 Adult and adoselcent athletes

This is a single-center study, and selected sport disciplines were studied according to the popular sports in Hungary. We did not have enough athletes in each sport, therefore we grouped them as skill, power, mixed and endurance athletes. Due to the small sample size of skill and power sports, we could not include them in the statistical analysis. All Caucasian athletes were recruited in the study, thus no ethnicity related differences were studied. Due to the exact years in training were not recorded in all athletes, we could not calculate the impact of long-term exercise training quantitatively. Gadolinium contrast administration was up on the athlete’s or his/her legally representative’s discretion, and 211 athletes (65%) agreed to get contrast agent. We did not find definite pathological LGE in this subset of the cohort; however, the prevalence of incidental/asymptomatic LGE could be underestimated. The assessment of myocardial fibrosis using native T1 mapping is an excellent technique for imaging athlete’s heart as providing tissue specific information without the need of contrast injection (130). Unfortunately, due to technical limitations we were not able to acquire T1 map in our athletes.

6.1.2 Masters athletes

This study had a number of important limitations. The first was limited patient number. Due to monetary constraints, our cohort was limited to forty. In addition, we did not have a third group of endurance athletes with atrial fibrillation. The second limitation was that exercise exposure was self-reported. There are inherent bias in self-reported data, particularly in quantifying an exercise regimen over a number of years. We attempted to ensure our cohort had a high level of exercise exposure through recruitment of athletes who were top finishers in recent competitions within their respective sports as well as through verification of activity using

training logs. This could have been avoided if we had access to VO2 max data in the athletic cohort. Similarly, we could not verify the activity level of the control group, although in our estimation it would be highly unlikely that they would have participated in such extreme training as our athlete populations. In addition, LGE cannot easily differentiate between fibrosis and edema. We did not have a specific required gap between long endurance training and the subject's scan so the LGE we are detecting could be due to edema from recent training or competition. A fourth limitation was that while we screened for patients who did not have a history of arrhythmias, we did not confirm patient were arrhythmia free using remote telemetry monitoring. Finally, our athlete cohort is predominantly Caucasian males thus we could not report on gender or ethnicity specific differences.

6.2 Limitation of "The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease" project

The single-center nature and the relatively limited number of patients are the major limitations of the study. Native T1 mapping and extracellular volume measurement could have provide additional tissue specific information without the need of contrast injection. As we have mentioned above, due to technical limitations we were not able to acquire T1 map in our athletes.

6.3 Limitations of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

In order to accurately evaluate LA function, cine images need to be obtained in sinus rhythm; assessment is therefore limited in patients who are in AF during the baseline scan, and this could introduce bias into the AF groups (in our cohort non-paroxysmal AF vs paroxysmal AF: 27% vs 73%). The ablation lesion set was not entirely homogeneous in this cohort, although all patients underwent complete PVI and in the vast majority of patients (>80%) radiofrequency application was extended to fibrotic areas of the left atrium along the posterior wall and interatrial septum methodically. We performed the follow-up CMRi at the time of the 3-month return visit consistently for all patients, and we did not perform additional CMRi scans

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thereafter. Quantification and detection of LA size and function is more accurate and credible after the blanking period (as obtained in our study), but further functional improvement could possibly be detected at even longer duration follow-up. In this study, the follow-up methodology for arrhythmia recurrence was guideline-directed but did not involve continual monitoring, and we might have missed some asymptomatic recurrences.

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7 Conclusion

7.1 Conclusion of the "Functional and structural characteristics of athlete's heart assessed by CMR imaging" project

7.1.1 Adult and adolescent athletes

In our first CMR study, we observed sex and age-related differences in the physiological adaptation of adult as well as adolescent athlete's heart. Male sex and endurance sport were major contributors of cardiac adaptation in adult athletes. In adults, a combination of sex, training volume, endurance and mixed sports explained about 30% of the variance of left and right ventricular dilation, and as much as 53% of LV hypertrophy. In adolescent athletes, sex and training volume were correlated with ventricular dilation and hypertrophy.

7.1.2 Masters athletes

Our second study describes and characterizes fibrotic changes within the LA of highly trained endurance athletes. We have shown that in otherwise healthy participants, with no history of arrhythmia, endurance training is associated with a higher level of atrial fibrosis as compared to age and gender matched controls. Atrial fibrosis seen in this population could be an early indicator for those athletes at highest risk for arrhythmia development. To our knowledge, this is the first study which demonstrated an increased level of atrial fibrosis in masters endurance athletes as compared to healthy non-athletic controls. Future longitudinal studies should focus on understanding the relationship between existing atrial fibrosis and development of arrhythmia specifically in the athletic population.

7.2 Conclusion of "The role of CMR imaging in the assessment of athletes with suspected structural myocardial disease" project

To the best of our knowledge, this was the first national study reporting data of the etiology and frequency of structural myocardial diseases in a large group of Hungarian athletes using CMR imaging. In athletes with suspected structural myocardial abnormality, CMR imaging can detect myocardial fibrosis/scar without the presence of myocardial wall motion abnormalities and/or pathological ECG signs. We found that the most frequently diagnosed cardiomyopathy was HCM, while the most common structural disorder related to aborted SCD was ARVC.

7.3 Conclusion of the "Functional and structural characteristics of the left atrium in patients with atrial fibrillation assessed by CMR imaging"

In our fourth study we were focusing on LA remodeling in patients with AF. We found that pre-ablation baseline LA function, acute functional impairment, and atrial fibrosis were related to post-ablation AF recurrence. In patients with high baseline LA-LGE, the more rigid LA wall appeared more sensitive to acute ablation injury and showed poor functional recovery regardless of the extent of ablation scar. To the best of our knowledge this is the first CMR study that provides detailed information about the longitudinal assessment of LA function and structure acutely and at follow-up.

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8 Summary

In athletes, intensive and regular physical exercise can lead to a physiological cardiac adaptation which may mimic pathological conditions causing differential diagnostic dilemmas. Determining the physiological upper limit of athletic sport adaptation is critical in order to accurately distinguish athlete's heart from cardiac diseases with an increased risk to adverse cardiovascular event.

We studied physiological cardiac adaptation in a large group of healthy athletes with CMR imaging. We found that the normal ranges/limits of cardiac adaptation differ in healthy highly trained male and female athletes in adults and also in adolescents. In adults, a combination of sex, training volume, endurance and mixed sports explained about 30% of the variance of left and right ventricular dilation, and as much as 53% of LV hypertrophy. In adolescent athletes, sex and training volume were correlated with ventricular dilation and hypertrophy.

In a study comparing endurance masters athletes to age and gender matched sedentary controls, we found that athletes had higher LA size. In addition, our study was the first to demonstrate that in otherwise healthy athletes, with no history of arrhythmia, long-term endurance training is associated with a higher degree of atrial fibrosis detected by LGE CMR imaging. The increased atrial fibrosis seen in this population may be an early indicator for endurance athletes at risk of developing atrial arrhythmias.

CMR is a valuable tool to diagnose structural abnormality in athletes. In our single center CMR study investigating 153 athletes with suspected structural myocardial disease, CMR findings confirmed the diagnosis in 39 athletes (25.5%). The most commonly diagnosed cardiomyopathy was HCM. However, in athletes with aborted SCD, ARVC was the most frequent pathology. To the best of our knowledge, this was the first national study reporting data of the etiology and frequency of structural myocardial diseases in Hungarian athletes using CMR imaging. In our study focusing on LA remodeling in AF patients before and after ablation procedure, we found that pre-ablation LA function inversely correlated with LA fibrosis and was related to procedural. In addition, patients with a baseline higher MinLAVi, lower LA function and higher LA-LGE% related to higher rate of arrhythmia recurrence during follow-up. This study was the first to report multi-parametric and longitudinal CMR assessment of LA function and structure in AF patients pre- and postablation. Our data suggest that in patients with AF, CMR measures of LA remodeling could be helpful in the selection of optimal treatment strategies for AF patients by predicting outcomes.

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9 Összefoglaló

A rendszeres és intenzív sporttevékenység hatására a szív komplex strukturális és funkcionális átalakuláson megy keresztül, mely változások összességét sportszívnek nevezzük. Nagyszámú élsportoló bevonásával készült vizsgálatunkban férfi és női sportolók eltérő MR normálértékeit ismertettük mind felnőtt, mind ifjúsági sportolókban. Felnőttekben a vizsgált paraméterek közül a nem, a heti edzési óraszám és a terhelés típusa bizonyultak a bal és jobb kamrai dilatáció és hipertrófia legmeghatározóbb tényezőinek: a fenti paraméterek összessége mintegy 53%-ban határozta meg a bal kamra hipertrófia mértékét.

Master sportolók körében a pitvarfibrilláció magasabb prevalenciája régóta ismert. Kutatásunkban master sportolókat, valamint korban és nemben egyeztetett egészséges kontroll személyeket vizsgáltunk szív MR technikával. Master sportolókban mind a bal pitvari volumen, mind pedig a kalkulált LGE% magasabb volt, mely kifejezett pitvari adaptációra és kiterjedtebb pitvari fibrózisra utal. Elsőként igazoltuk, egészséges, panaszmentes sportolók kiterjedtebb bal pitvari fibrózisát. A bal pitvar ezen strukturális változásai növelhetik a sportolók körében előforduló pitvarfibrilláció kialakulásának kockázatát, ezen hipotézis megerősítésére további utánkövetéses vizsgálatok szükségesek.

A szív mágneses rezonanciás vizsgálat diagnosztikus szerepét célzó kutatásunkban strukturális szívizombetegség gyanúja miatt vizsgált sportolóknál az MR vizsgálat az esetek 25,5%-ában (39/159) igazolt eltérést. A cardiomyopathiák közül az általunk vizsgált csoportban a leggyakoribb kórkép a HCM, míg a hirtelen szívhalál hátterében álló leggyakoribb strukturális eltérés az ARVC volt. Magyarországon ez az első, sportolók körében végzett, szív MR diagnosztikát alkalmazó strukturális szívizombetegség gyakoriságát célzó tanulmány.

Pitvarfibrilláló betegekben vizsgáltuk a bal pitvari remodellinget abláció előtt, illetve beavatkozás után közvetlenül az akut fázisban majd utánkövetés során. Az ablációt megelőző minimum pitvari volumen, bal pitvari funkcionális paraméterek, valamint a pitvari fibrózis (LGE%) a pitvarfibrilláció rekurrencia független prediktorai voltak. Az ablációt megelőző csökkent bal pitvari funkció negatívan korrelált a pitvari fibrózis kiterjedésével. A jelen tanulmány az első, amely a pitvarfibrilláló betegek pitvari remodellingjét tanulmányozza egy longitudinális szív MR vizsgálat keretében. Eredményeink alapján a bal pitvari funkció és struktúra szív MR vizsgálattal történő meghatározása a jövőben segítheti a pitvarfibrilláló betegek esetén az optimális terápia kiválasztását, valamint a hatékony rizikóstratifikációt.

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