ΑΝΑΣΚΟΠΗΣΗ

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REVIEW

ECHOCARDIOGRAPHIC LEFT VENTRICULAR ADAPTATIONS TO EXERCISE

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ABBREVIATIONS AND ACRONYMS

AF	atrial fibrillation
BSA	body surface area
BMI	body mass index
CVD	cardiovascular disease
EF	ejection fraction
FFM	fat free mass
HTN	hypertension
HFrEF	heart failure reduced ejection fraction
HfpEF	heart failure preserved ejection fraction
IVS	intraventricular septum
IVRT	isovolumic relaxation time
GLS	global longitudinal strain
LV	left ventricle
LA	left atrium
LAVi	left atrium volume index
LVESD	left ventricular end systolic diameter
LVEDD	left ventricular end diastolic diameter
LVH	left ventricular hypertrophy
LVM	left ventricle mass
RV	right ventricle
RA	right atrium
PWT	posterior wall thickness
RWT	relative wall thickness
TDI	tissue doppler imaging
SCD	sudden cardiac death
SV	stroke volume
SR	strain rate
LVMi	left ventricle mass index
LVRI	left ventricle remodeling index

INTRODUCTION

Exercise and athletic training induce alterations in ventricular function and structure that are most commonly known as the athlete's heart. This term has been used for over four decades, ever since Morganroth et al. presented a dichotomous view of athletic activity, dividing it predominantly to endurance and strength training. According to Morganroth, endurance exercise inflicts an increase in LV end diastolic volume and LV mass due to volume overload, while strength exercise leads to an increase in left ventricular wall thickness due to pressure overload. Although this view has been widely accepted over the years, recent studies tend to question their findings, due to the complexity of the nature of exercise and the large spectrum of factors affecting sports activity.

Before analyzing the concepts of the athlete's heart, one should define what constitutes athletic training. The European Society of Cardiology aids towards this direction, by setting the standard for minimum exercise for healthy individuals of all ages at a minimum of 150 min of moderate-intensity endurance exercise training split over 5 days or 75 min of vigorous exercise per week split over 3 days. Further benefit could be obtained by increasing the amount of exercise to 300min of moderate-intensity or 150 min of vigorous-intensity aerobic exercise per week. The cardiovascular effects of training that are known as the athlete's heart, however, present with physical activity surpassing the above baseline routine. Some authors propose a minimum of 20h a week of exercise capacity of 15METS to inflict changes upon the left ventricle on trained individuals, although the baseline could be set significantly lower for untrained subjects. Furthermore, an increase in haemodynamic load, as reflected by a systolic BP of approximately ≥150 mmHg, should be achieved in order to inflict structural and functional changes upon the heart (Lovic et al., 2017). Evaluating exercise intensity remains to this day a challenge, although there are methods to approximate it, such as calculating the percentage of maximal oxygen capacity (V02max) by Cardiopulmonary exercise test, or using the equation [HRmax= 220 − age].

The physiologic pathways that lead to left ventricular alterations during exercise are complex, with a distinct correlation to type of training, and expand from volume and pressure load dynamics to myocyte anatomy and function. There are mainly four types of exercise: skill (such as golf, sailing and bowling), power (such as weight lifting, wrestling and boxing), endurance (such as jogging, cycling and swimming) and combined (including soccer, basketball and tennis). More explicitly, endurance training initially provokes an increase in cardiac output, maximum oxygen consumption and peripheral vasodilatation, in order to compensate for the increased tissue oxygen demand. Over time, the sustained elevation of preload, due to increased venous return, leads to volume overload, resulting in addition of sarcomeres in series, and therefore, an increase in left ventricular dimensions with a proportional increase in wall thickness. On the other hand, strength training, does not inflict sustained elevation of cardiac output, since it most commonly comes in short intervals, and therefore ventricular dilatation, although present, is less profound. There is however, an increase in left ventricular wall thickness, that resembles the one seen in pressure overload cardiac disease, such as systemic hypertension and aortic stenosis. This is justified by the contraction of myocytes in order to develop tension against the

increase in afterload. Moreover, there is a relative increase in thickness to dimension ratio, probably due to the higher exercise blood pressures associated with these activities. Mixed types of sports combine elements of endurance and strength exercise resulting in an intermediate phenotype of left ventricular adaptation. Finally, skill training does not induce considerable left ventricular alterations. (Colan et al., 1987) More recent studies however, are doubting the former classification, supporting that pressure overload can be observed in endurance exercise as well, and volume overload can found in strength training. (Haykowsky et al., 2018)

A vast bibliography around training has been constructed over the years, with authors trying to define and predict the models of left ventricular adaptation to exercise. Most studies coincide that these adaptations are profoundly benign and even more, that systematic exercise is associated with reduced cardiovascular (CV) and all-cause mortality, as well as a reduced prevalence of some malignancies.(Antonio Pelliccia et al., 2021) Therefore, exercise is an adjunctive therapy for most cardiovascular diseases, included in rehabilitation programs after acute events. However, in some cases, athletic activity, can lead to pathology, especially in the elite level, or can be hazardous in specific patient populations with underlying pathology. More specifically, exercise can rarely induce sudden cardiac death in individuals with underlying cardiovascular disease (80% of SCD), channelopathies, cardiomyopathies and coronary anomalies. The incidence of SCD in athletes has been reported between 1/1.000.000- 1/5000 athletes per year. Furthermore, athletic activity can promote acute coronary events, such as coronary ischaemia, due to underlying atherosclerotic cardiovascular disease, or due to oxygen supply and demand mismatch. Moreover, transient ischaemic attacks, cerebrovascular events and supraventricular arrythmias can also occur during athletic activity. In younger athletes arrythmiogenic genetic disorders such as Wolf Parkinson White syndrome and arrythmiogenic right ventricular dysplasia prevail, along with hypertrophic caridomyopathy , coronary anomalies and other congenital heart diseases. Nonetheless, physical activity should be encouraged in all patients with cardiovascular disease with appropriate risk stratification and optimal medical therapy prescription. Pre-participation screening should be performed in selective patients, depending on exercise intensity, medical history and cardiovascular risk factors, and varies from physical examination and 12-lead ECG, to exercise testing, cardiopulmonary exercise test and more advanced techniques, according to underlying pathology. (Antonio Pelliccia et al., 2021)

The purpose of this review is to evaluate left ventricular alterations occurring during excessive exercise, predominantly in competitive athletes. These alterations include left ventricular hypertrophy, increase in internal dimensions, left ventricular mass and volume, alterations in diastolic function, aortic root dimensions and left atrial properties. These adaptations resemble the ones encountered in echocardiographic evaluation of hypertensive patients (and other diseases such as hypertrophic cardiomyopathy) and can therefore lead to diaforodiagnostic struggle when encountered in a typical exam. Echocardiographic findings of the two entities, the athlete’s heart and hypertensive heart disease will be compared, targeting to provide useful diaforodiagnostic tools in clinical practice.

2.THE LEFT VENTRICLE IN ATHLETES

2.1 GEOMETRY

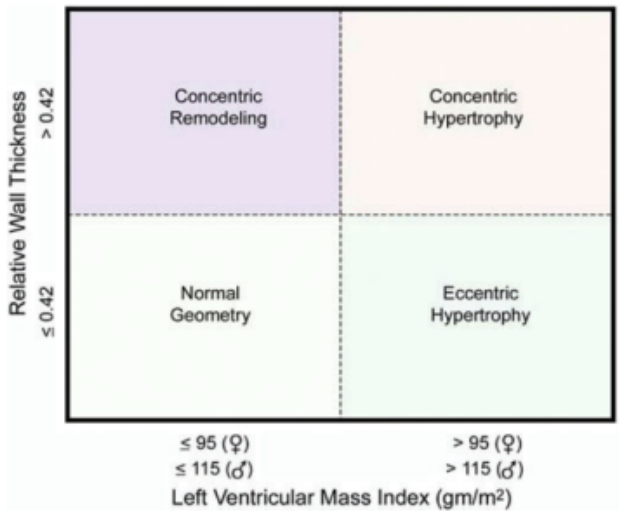
Strenuous and chronic exercise induces alterations in the shape, size and function of the left ventricle in order to adapt to the increased workload of athletic training. Those alterations mainly include reduction in heart rate and enlargement of the heart, also known as the athlete's heart.(A Pelliccia et al., 1999) Moreover, chronic athletic training leads to an increase in stroke volume and a reduction in systemic vascular resistance in order to adapt to the increased oxygen demand during exercise. Other haemodynamic changes during athletic activity, include an increase in cardiac output, defined as the product of stroke volume and heart rate, as well as elevation of blood pressure. Chronically, in order to adapt to the increased wall stress induced by the aforementioned changes, the left ventricle will dilate and increase its wall thickness. Genetic predisposition and hormonal alterations, also play a role in these changes. Ultrasound seems to be the gold standard in evaluating both size and function of the left ventricle, taking into account its ability to show real time images of the beating heart, while having a wide availability, portability and low cost.(Galderisi et al., 2015)

Before analyzing the parameters of left ventricular geometry in athletes, normal echocardiographic values and standardized methods of acquiring them, should be defined. According to the EACVI Recommendations for Cardiac Chamber Quantification linear measurements of the left ventricle are performed in the parasternal long-axis view, at the level of the mitral valve leaflet tips. Calculations are made for end-diastole and end-systole and they should be indexed for BSA. Volumetric measurements should apply the biplane method of disks summation (modified Simpson's rule) usually based on tracings of the blood-tissue interface in the apical four- and two-chamber views.(Lang et al., 2015)

A calculation of the LV mass can be obtained from M-mode echocardiography, 2DE, and 3DE. The Cube formula -(LV mass = 0.8 · 1.04 · [(IVS + LVID + PWT) 3 − LVID3] + 0.6 g Where IVS is interventricular septum; LVID is LV internal diameter, and PWT is inferolateral wall thickness) is the most popular method for LVM. As with wall thickness, linear internal measurements of the LV ought to be obtained perpendicular to the LV long axis, at the level of the mitral valve leaflet tips. All measurements should be performed at end-diastole. When the entire ventricle is measured from 2D echocardiographic images, either the area-length or truncated ellipsoid technique is used, whereas when measurements are made using M-mode and 2D measurements of LV diastolic diameter and wall thickness geometric formulas are used to calculate the volume of LV myocardium, although 3DE can obtain those measurements directly. Volume is converted to mass by multiplying the volume of myocardium by the myocardial density (approximately 1.05 g/mL).(Lang et al., 2015)

Relative wall thickness (RWT) is estimated using the formula 2 × (posterior wall thickness)/(LV internal diameter at end diastole). Using relative wall thickness and left ventricular mass index, one can classify ventricular morphology into 4 categories: concentric hypertrophy (RWT> 0,42 and LVMi> 95gm/m2 for women or >115gm/m2 for

men) or eccentric hypertrophy (RWT< 0,42 and LVMi> 95gm/m2 for women or >115gm/m2 for men), concentric remodeling (RWT> 0,42 and LVMi<95gm/m2 for women or <115gm/m2 for men) and normal geometry (RWT< 0,42 and LVMi<95gm/m2 for women or <115gm/m2 for men), as shown in the following image. (Lang et al., 2015)Some writers, recognize a fifth morphological type, concentric remodeling, with LVMi< <95gm/m2 for women or <115gm/m2 for men and a RWT<0,30.(Douglas et al., 1997)



The four types of left ventricular remodeling according to RWT and LVMi (Lang et al., 2005)

Normal values for 2D echocardiographic parameters of LV size and function according to gender (Lang et al., 2015)

	males		**females**	
parameter	Mean+/-SD	2-SD range	Mean+/-SD	2-SD range
LV internal dimension				
Systolic dimension (mm)	50.2+/-4.1	42.0– 58.4	45.0+/-3.6	37.8– 52.2
Diastolic dimension (mm)	32.4+/-3.7	25.0– 39.8	28.2+/-3.3	21.6– 34.8
LV volumes (biplane)				
LV EDV mm	106+/-22	62-150	76+/-15	46– 106
LV ESV mm	41+/-10	21– 61	28+/-7	14-42
LV volumes normalised by BSA				
LVEDV (ml/m2)	54+/-10	34-74	45+/-8	29-61
LVESV(ml/m2)	21+/-5	11– 31	16+/-4	8-24
EF(%) biplane	62+/-2	52-72	64+/-5	54-74

Normal ranges for LV mass indices Women Men (Lang et al., 2015)

	women	**men**
Linear method		
LV mass (g)	67–162	88– 224
LV mass/BSA (g/m2)	43 –95	49–115
Relative wall thickness (cm)	0.22-0.42	0.24-0.42
Septal thickness (cm)	0.6–0.9	0.6-1
Posterior wall thickness (cm)	0.6-0.9	0.6-1
2D method		
LV mass (g)	66-150	96-200
Lvmass/BSA (g/m2)	44-88	50-102

2.1.1 WALL THICKNESS AND INTERNAL DIMENSIONS

The thickness of the LV wall is long known to be one of the main features of the athlete' s heart and has been inspected in a vast number of studies. The commonly used measuremnts to assess LV wall thickness are posterior wall thickness, intraventricular septum wall thickness and relative wall thickness (defined as 2 times posterior wall thickness divided by the left ventricular (LV) diastolic diameter). In clinical practice, the relative wall thickness may be used to characterize the morphologic remodeling of the left ventricle, with values between 0.30 and 0.45 compatible with physiologic remodeling. (Antonio Pelliccia et al., 2018)

About 30 years ago, Pellicia et al. in a cohort of 947 elite athletes, found LV wall thickness minimal and within normal range, since only 1,7% of the athletes were found to have LV wall thickness more than 13mm. More specifically, posterior wall thickness ranged from 7-13mm in men and 6-10mm in women, and septal wall thickness was 7-16mm in men and 6-11mm in women. The greatest value of LV wall thickness among the athletes was 16 mm, measured in one athlete. Wall thicknesses compatible with hypertrophic cardiomyopathy (greater than or equal to 13 mm) were identified in only 16 of the 947 athletes (1,7%). Notably, the athletes who presented with such values also presented with marked athletic achievements (8 of them , which accounts for 50%, were olympic medalists or world champions). Left ventricular end diastolic dimension ranged from 44-66mm in men ,and from 40 to 61mm in women, exceeding normal values (>54mm) in 38% of athletes. As far as gender is concerned, men tend to have increased wall thickness compared to women (0,9mm mean difference). However, gender specific aspects of the

athlete's heart will be discussed in the following chapters.(Spirito et al., 1994)*(A Pelliccia et al., 1991)*

Douglas and colleagues examined 235 highly trained triathlon participants and found that 32 (16%) had septal wall thickness above 1.1 cm and only 2 (1%) had septal wall thickness exceeding 1.3 cm. As for posterior wall thickness, 7 athletes (3%) excibited values greater than 1.1 cm, and only 1 had a posterior wall thickness above 1.3 cm. Increase in left ventricular cavity size was more common than increase in wall thickness, with 61 athletes (30%) excibiting mild dilation. Compatible with the previously mentioned study by Peliccia et al, increase in internal dimensions of the left ventricle is much more common than left ventricular hypertrophy in athletes. Only 4 athletes (2%) had concentric remodeling (relative wall thickness >0.45), whereas eccentric remodeling (relative wall thickness less than 0.30) was more common (15 athletes-7%), but still quite rare. (Douglas et al., 1997)

A large metanalysis that encompassed 59 studies and 1451 athletes showed that There was a significant difference between endurance, strength trained and combined endurance and strength trained athletes and control subjects in terms of left ventricular internal diameter (53,7mm in endurance trained athletes, 52.1mm in strength trained athletes and 56,2mm in combined endurance and strength trained athletes.) Interventricular septum thickness was measured at 8,8mm in control subjects, and 10,5mm in endurance-trained athletes and 11,8 in strength-trained athletes, suggesting an increase in athletes compared to controls, with mildly elevated values (above normal ranges) in strength trained athletes. Posterior wall thickness was 8,8mm in control subjects and 10,3mm in endurance-trained athletes and 11mm in combined endurance- and strength trained athletes and 11mm in strength trained athletes. Compatible with septum thickness measurements, posterior wall was increased in athletes compared to controls. (Pluim et al., 2000)

Another study of 3500 highly trained British athletes(Basavarajaiah, Wilson, et al., 2008) found that 1,5% of athletes had a left ventricular wall thickness (LVWT) of over 12mm. This study was designed to explore the prevalence of hypertrophic cardiomyoppathy in elite athletes, the diagnosis of which was excluded by echocardiography in (98.5%) on the basis of a LV wall thickness <12 mm, and other echocardiographic features suggestive of hypertrophic cardiomyopathy. The maximal value found was 16 mm suggesting that this value should be considered pathological. In those athletes, LV internal cavity dimension at end diastole was 45-65mm, while those who had LVWT<12mm presented with LVIDd <56mm. In other words, the higher the degree of hypertrophy, the higher was the degree of increase in left ventricular internal diameter.

Echocardiographic Features in Athletes With Left Ventricular Wall Thickness >12mm (Basavarajaiah, Wilson, et al., 2008)

	Mean ± Standard Deviation (Range)
LVWTd (mm)	13.6 ± 0.9 (13–16)
LVIDd (mm)	58.5 ± 5.14 (45–65)
LVIDs (mm)	31.6 ± 4.1 (22–42)
Left atrial diameter (mm)	32 ± 4.8 (21–47)
E-wave (m/s)	0.87 ± 0.2 (0.5–1.5)
A-wave (m/s)	0.45 ± 0.2 (0.17–0.9)
E/A ratio	2.32 ± 0.94 (1.8–4.5)

A study of 446 elite british athletes, designed to identify the physiological upper limits of cardiac hypertrophy, demonstrated that 2,5% of athletes, competing in judo, skiing, cycling, triathlon, rugby and tennis, presented with a wall thickness >13 mm, compatible with a diagnosis of hypertrophic cardiomyopathy. A 5,8% of male athletes presented with a left ventricular internal diameter during diastole (LVIDd) >60 mm, with the highest limit being 65 mm. Of the 136 female athletes, none where found to have a maximum wall thickness >11 mm, while left ventricular internal diameter was <60 mm in all female athletes. These values are slightly higher than those found by Basavarajaiah et al, which may be attributed to the smaller number of participants in the Whyte et al study. Consequently, the study concludes that upper normal limits for left ventricular wall thickness and LVIDd should be considered to be that of 14 mm and 65 mm accordingly, for elite male British athletes, and 11 mm and 60 mm for elite female British athletes. (Whyte et al., 2004). Interestingly, these values are well above the normal range of the general population, implying that hypertrophy and dilation of the left ventricle are a normal adaptation in athletes and only values that are above these limits should prompt further investigation to exclude pathology. As has been previously derived from different studies, women athletes tend to excibit LVH to a lesser degree than male athletes.

Utomi et al, published a systematic review and metanalysis, encompassing 92 studies, examined the morphologic adaptation of the male athlete's heart. Results showed that intraventricular septum wall thickness (IVSWT) was 11mm (10.8 to 11.3mm), posterior wall thickness (PWT) was 10.6mm (10.3 to 10.9mm), and left ventricular end diastolic diameter (LVEDD) was 54.8mm in endurance athletes, while in resistance trained athletes IVSWT was 11mm (10.3 to 11.8mm), PWT was 10,4mm (9.8 to 10.9mm) and LVEDD was 52,4mm, with the the greater value being 55,6mm in endurance trained athletes. Main results suggested that both endurance and resistance-trained athletes present with greater LV structures than non-athletes, and endurance is the athlete group with the higher dimensions, compatible with eccentric hypertrophy. The two athlete groups present with insignificant differences in left ventricular wall thickness. Therefore to support that resistance athletes present with concentric hypertrophy is not strongly supported. (Utomi et al., 2013)

Left ventricular structural and functional data in male endurance-trained, resistance-trained and sedentary control subjects(Utomi et al., 2013)

Parameter	Endurance-trained (ET)	Resistance-trained (RT)	Sedentary controls (CT)	p Value (All groups)
LV mass (g)	232 (200 to 260) [n=64; 1099]	220 (205 to 234) [n=25; 510]	166 (145 to 186) [n=59; 1239]	< 0.001
IVSWT (mm)	11.0 (10.8 to 11.3) [n=68; 1802]	11.0 (10.3 to 11.8) [n=19; 408]	9.2 (8.9 to 9.5) [n=63; 1352]	< 0.001
PWT (mm)	10.6 (10.3 to 10.9) [n=57; 1928]	10.4 (9.8 to 10.9) [n=14; 370]	8.8 (8.6 to 9.1) [n=53; 1433]	< 0.001
LVEDD (mm)	54.8 (54.1 to 55.6) [n=61; 1548]	52.4 (51.2 to 53.6) [n=17; 384]	50.1 (49.5 to 50.7) [n=56; 1174]	< 0.001
LVEDV (ml)	171 (157 to 185) [n=34; 493]	131 (120 to 142) [n=14; 189]	135 (125 to 145) [n=34; 539]	< 0.001
LV SV (ml)	106 (97 to 116) [n=28; 479]	86 (77–95) [n=9; 125]	83 (77 to 90) [n=27; 590]	< 0.001
LVEF (%)	63 (61 to 64) [n=42; 1330]	66 (62–70) [n=7; 85]	64 (62 to 65) [n=37; 878]	0.365
LV E/A	2.0 (1.9 to 2.1) [n=34; 844]	1.9 (1.7–2.0) [n=8; 214]	1.8 (1.7 to 1.9) [n=34; 868]	0.014
LV E'	13.6 (12.3 to 14.9) [n=7; 204]	*	11.0 (9.4 to 12.6) [n=4; 183]	0.014

Most recently, in a study conducted in 1118 university athletes, athletes were categorized in two groups, normal and abnormal LV geometry, and in particular concentric

remodelling, concentric hypertrophy, or eccentric hypertrophy versus normal LV structure (Cho et al., 2019) LVEDD (left ventricle end diastolic diameter), LVESD (left ventricle end systolic diameter) and RWT (relative wall thickness) were 46,4-55.6mm, 28,5-36,9 mm, 0,27-0,36, respectively. When compared with the normal reference value of the EACVI guidelines, increased LVEDD was found in 12%, LVESD in 10,2% and RWT in 8,3%. The thickness of the LV interventricular septum was 6,3-9,7mm and the thickness of the posterior wall were and 6,7-9,9mm. In 1,9% of the athletes, thickness of the LV interventricular septum and in 2% posterior wall thickness were found to be above 12 mm. However, no athletes were identified with LV wall thickness >15 mm (in basavarajiah et al, the highest value was 16mm) Therefore, structural pathological conditions such as hypertrophic cardiomyopathy should be carefully investigated in athletes with LV wall thickening above 15 mm, while values of 13-15mm suggest a gray zone between extreme physiologic hypertrophy and hypertrophic cardiomyopathy. In this study there was no gender difference in geometric changes of the Left Ventricle. All in all, in this study abnormal LV geometry in general, is relatively common (13.2%) and concentric remodeling is the most common pattern of LV adaption to exercise in young trained university athletes. (Cho et al., 2019)

In conclusion, athletes exhibit a 15–20% increase in septal and left ventricular posterior wall thickness. However, the mean LVWT in athletes is between 10 and 11 mm, identical with the normal range for sedentary subjects, and the vast majority has a LVWT<12mm. However, a small minority of athletes, LVWT measurements show increased values (13-16mm) that overlap with those observed in patients with morphologically mild HCM. (John Rawlins et al., 2009). As for left ventricular internal diameter values above 60mm at end diastole are rare and are more often found in mixed endurance and resistance trained athletes. Internal dimanesions in athletes have a tendency towards the upper physiological limits but rarely surpass 55mm end diastolic diameter.

2.1.2. CARDIAC MASS

Cardiac mass is most often calculated using the cube formula : Mass = 0.8 x (1.04 x (((LVEDD + IVSd +PWd)3 - LVEDD3))) + 0.6). Nonetheless, whichever method the echocardiographer chooses to apply, left ventricular internal diameter and left ventricular wall thickness are the major determinants of cardiac mass. Therefore, it seems reasonable to assume that increased cardiac mass is a common finding in subjects with increased LV size (Atchley & Douglas, 2007) . As shown in previous chapters, whether within normal ranges or beyond them, athletes tend to excibit an increase in both wall thickness and internal dimension, suggesting that an increase in cardiac mass would be well anticipated.

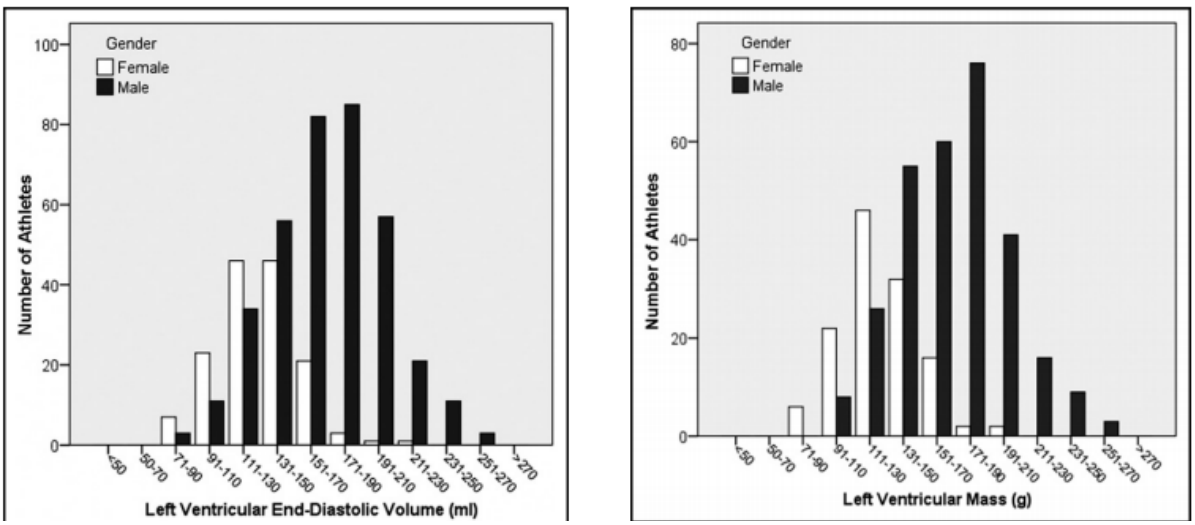
Among 235 triathlon participants studied by (Douglas et al., 1997) mild elevations in cardiac dimensions were common, but marked increases were rare, except for left ventricular mass which was commonly increased (49% of total subjects.). In this study, 43% of females had an absolute LV mass greater than the accepted upper limits of normal (198 g) and only 17% of males had an absolute LV mass that exceeded accepted upper limits of normal (294 g), and this gender difference was not previously noted.

Normal ranges for LV mass indices (Lang et al., 2015)

	Women	Men
Linear method		
LV mass (g)	67–162	88–224
LV mass/BSA (g/m²)	***43–95***	***49–115***
Relative wall thickness (cm)	0.22–0.42	0.24–0.42
Septal thickness (cm)	***0.6–0.9***	***0.6–1.0***
Posterior wall thickness (cm)	***0.6–0.9***	***0.6–1.0***
2D method		
LV mass (g)	66–150	96–200
LV mass/BSA (g/m²)	***44–88***	***50–102***

In a meta-analysis of 59 studies including more than 1450 athletes, Pluim and colleagues demonstrated a highly significant difference in cardiac mass between trained athletes (249 g)(strength trained, endurance trained and mixed endurance and strength trained athletes) when compared with control subjects (174 g).This difference seems to be more pronounced in female athletes, because cardiac mass can vary significantly with respect to height and body surface area. LVM did not seem to show a significant difference between strength, endurance and mixed-type athletes.(Pluim et al., 2000)

In a comparative study using 3-dimensional echocardiography in 511 olympic athletes, excibited LV remodeling in athletes in terms of LVM. Specifically, controls had a LVM of 90+/- 13mm, skill athletes 107 +/-17mm, power athletes 117+ /-20mm, mixed athletes 145 +/-23mm and endurance athletes 130+/-16mm. Obviously mixed and endurance athletes were found to have the largest LVM. Moreover, in this study LVRI (left ventricle remodeling index) (the ratio between LV mass to end-diastolic volume) showed no difference between athletes as a group and controls proving that the model of physiologic LV adaptation to exercise, is harmonious in most sport types. (Caselli et al., 2011)



Distribution of LV end diastolic volume(left) and LV mass (right) in athletes (Caselli et al., 2011)

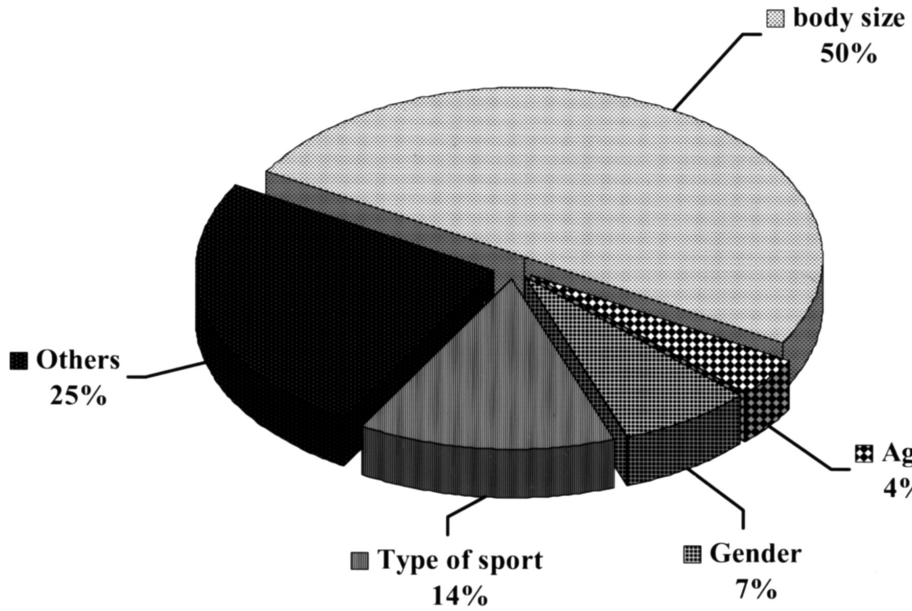
A small study by (Kreso & Arslanagić, 2008)conducted in 150 subjects, of those 100 were active athletes and 50 were in control group. LVMI in g/m2 (± SD) is 196,05±35,42

grams in athletes and 83,98±19,48 grams in non-athletes suggests statistically significant increase in LVMI in athletes versus non athletes.

In 947 elite, highly trained athletes who participated in a large spectrum of sports showed that, while both the thickness of the left ventricular wall and the internal diameter of the left ventricle were elevated, the increased left ventricular mass among the football players was primarily attributable to increased left ventricular internal dimensions. This is an important point, as highly trained competitive athletes (particularly rowers and cyclists) without other features to suggest heart disease can develop significantly thickened ventricular walls that may mimic hypertrophic cardiomyopathy. (Maron & Pelliccia, 2006)

2.1.3 PREDICTORS OF LV GEOMETRY

Upto this point, it has been clearly stated, that left ventricular geometry does indeed alter in athletes, even though it is usually within normal range. However, this statement alone is not enough to qualify the adaptations of the left ventricle to exercise. A lot of different parameters, including, predominantly, type of sport, body size, ethnical characteristics, age and gender are also to be taken into account in order to properly assess these alterations.



Impact of different clinical variables on LV end-diastolic cavity dimensions in a large population of male and female elite athletes. The relative impact of the examined variables (body size, gender, age, and type of sport) are shown here as a proportion of overall variability in LV cavity size.(Maron & Pelliccia, 2006)

2.1.3.1 TYPE OF SPORT

Before analysing the different aspects of exercise-induced cardiac remodeling, one must define the different concepts of remodeling depending on the type of exercise that is being pursued. The concept of a dichotomous classification of sports and their impact on cardiac remodeling, was first introduced by (Morganroth et al., 1975) over 40 years ago. In short, the Morganroth Hypothesis divides sports in two categories: isotonic or dynamic or endurance sports such as walking, swimming, jogging, biking and isometric or static or

strength or resistance exercise such as weight lifting. According to Morganroth, isotonic exercise results in an increase in cardiac output and decrease in peripheral vascular resistance, resulting in volume overload and increased diastolic stress, whereas isometric exercise results in less increase in cardiac output, increased systolic wall stress and a transient increase in peripheral resistances; therefore, strength training enforces pressure overload. As a result, isotonic exercise induces enlargement of the LV chamber with increased wall thickness and eccentric LV hypertrophy whereas strength training, such as weight lifting, induces a model of LV remodeling that consists of thickening of the LV wall and increase of the LV cavity size, causing concentric hypertrophy. This dichotomous classification of sports and their impact on heart morphology is undoubtedly based on exercise physiology. However, vast bibliography published ever since doubts this simplistic approach to the athlete's heart.

The "Morganroth Hypothesis" has been proved to have limited support by later on studies, because some sport disciplines, such as cycling and rowing, have both endurance and strength compounds, resulting in an intermediate phenotype of remodeling. Furthermore, especially with strength exercise, the phenotype could be misinterpreted, since excessive drug abuse (mostly anabolic androgenic hormones, peptide hormones, growth factors, erythropoietin or its derived, and stimulants), alters LV remodeling, the pathways of which are difficult to comprehend and distinguish. Moreover, compared to recreational athletes, it is elite and competitive athletes that exhibit the largest degree of remodeling, but also it is them who are most prone to be found using steroid drugs. (*Sage_cprb13_687*, n.d.) (Urhausen et al., 1989) (Antonello D'Andrea et al., 2017). The cardiac output of trained endurance athletes may increase from 5 to 6 L/min at rest, which is similar to that of untrained healthy subjects, to up to 40 L/min during maximal exercise. (Ekblom & Hermansen, 1968) Accordingly, the heart will adapt to this excessive increase in volume with an increase in internal diameter. On the other hand, blood pressure is another parameter that also increases during endurance exercise, with readings of up to 175/69 mm Hg during treadmill running, as was recorded by (Palatini et al., 1989), This increase, however, does not match the readings documented during strength training. Nonetheless the readings are high enough to alter the phenotype of the endurance trained heart, to that of an intermediate type. In other words, pure volume load during endurance training does not exist; during long distance running, aerobic exercise, etc., the heart has to adapt to both volume and pressure load increase, resulting in an increase in both left ventricular internal diameter and left ventricular wall thickness, both of which are consequently aspects of the endurance heart.

The rise of blood pressure and cardiac output during resistance exercise, such as weight lifting, can explain the model of left ventricular hypertrophy, consisting of a slight increase in left ventricular internal diameter and a large increase in left ventricular wall thickness. Mac Dougall et all, long ago measured blood pressure in weight lifters at the time of maximal exercise. What was demonstrated is that BP was vastly increased, (mean value of 255/190 mmHg when repetitions were continued to failure) peaking to values of even 480/350 mm Hg, a seemingly unrealistic finding, which was found in only one athlete. (MacDougall et al., 1985) Moreover, in the same study, the heart rate of the weight lifters was also measured and values ranging from 102 to 170 bpm where found, suggesting that pure pressure load during strength training does not exist.

(A Pelliccia et al., 1991) demonstrated that the highest contribution on LV mass- meaning an increase in left ventricular internal diameter and wall thickness- is related to some endurance disciplines such as cycling, rowing, swimming, and cross-country skiing, that are all characterized by a high degree of both dynamic and static components and a high degree of exercise performance in these athletes, due to greatly increased cardiac output, induced by the combination of both isotonic and isometric exercise. Endurance cyclists, rowers, and swimmers were the athlete groups with the largest LV diastolic internal dimensions and wall thickness. Athletes training in sports associated with larger LV internal diameter also had increased wall thickness. Athletes training in isometric sports, such as weightlifting and wrestling, increased wall thickness in relation to internal diameter, but their absolute wall thickness remained within normal limits. Maximal oxygen uptake, a marker of cardiorespiratory fitness and endurance capacity in exercise performance, is higher in these athletes, suggesting a superior exercise performance, which can explain their prominent cardiac remodeling (Steding et al., 2010)(Antonio Pelliccia et al., 2018)

A large meta-analysis by (Pluim et al., 2000) included endurance-trained athletes, strength-trained athletes and combined endurance and strength trained athletes. Endurance and strength trained athletes presentedwith a noteable difference in terms of mean relative wall thickness (0.39 versus 0.44, P=0.006) and interventricular septum thickness (10.5 versus 11.8 mm, P=0.005) and less in posterior wall thickness (10.3 versus 11.0 mm, P=0.078), suggesting that strength trained athletes had the largest degree of LVH. The difference in mean relative wall thickness between endurance and combined endurance and strength-trained athletes was not significant. Endurance trained athletes showed a slight increase in LVIDd (53,7mm) versus strength-trained athletes (52,1mm), but mixed trained athletes exhibited the highest LVIDd (56,2mm). Moreover, strength trained athletes also showed LV dilatation, however the mixed athlete type had the largest LV cavity. Consequently, there is no sport-specific model of LV adaptation to exercise according to pluim et al.

An other study, conducted by Caselli et al in 511 olympic athletes using 3D echocardiography showed that type of sport, as well as age, gender and BSA had a relevant impact on LV remodeling. In male athletes, the most significant LV remodeling was exhibited in endurance exercise, such as cycling, rowing and canoing, and long-distance running, where LV volumes and masses had the greatest values. Results were similar in female athletes. Moreover, in male and female power athletes, the difference in LV mass and end diastolic volume was not statistically significant, when compared to other sport disciplines. This finding is different from what was described in previous studies showing that primary isometric activities (i.e., power, such as weightlifting) had the highest LV mass and end-diastolic volume, and confirms what was previously described, that strength exercise does not result only in LV wall thickness alterations and, frthermore, endurance exercise does not only alter the LV cavity diameter. Moreover, the ratio between LV mass and end-diastolic volume remains sustained, regardless of the type of sport, reflecting the balanced remodelling of physiologic LV hypertrophy in most sport disciplines. (Caselli et al., 2011)

Three-dimensional echocardiographic data in male untrained controls and athletes according to type of sport(Caselli et al., 2011)

Variable	Controls (n = 106)	Skill (n = 50)	Power (n = 48)	Mixed (n = 97)	Endurance (n = 168)
LV end-diastolic volume (ml)	121 ± 24$^{\dagger,\ddagger,\S,\|}$	138 ± 29$^{*,\S,\|}$	150 ± 27$^{*,\|}$	164 ± 29$^{*,\dagger,\|}$	186 ± 28*,†,‡,§
	(73–191)	(89–221)	(90–209)	(109–240)	(119–268)
LV end-diastolic volume index (ml/m^2)	64 ± 11$^{\dagger,\ddagger,\S,\|}$	73 ± 11$^{*,\|}$	77 ± 11$^{*,\|}$	78 ± 12$^{*,\|}$	93 ± 12*,†,‡,§
	(41–100)	(49–102)	(55–98)	(53–113)	(56–136)
LV ejection fraction (%)	62 ± 5	64 ± 6	63 ± 6	64 ± 5	64 ± 5
	(51–71)	(53–71)	(50–73)	(51–71)	(50–78)
LV mass (g)	123 ± 22$^{\ddagger,\S,\|}$	152 ± 27$^{\S,\|}$	152 ± 27$^{*,\|}$	169 ± 28$^{*,\dagger,\|}$	185 ± 28*,†,‡,§
	(67–175)	(93–197)	(98–237)	(118–245)	(116–266)
LV mass index (g/m^2)	65 ± 11$^{\ddagger,\S,\|}$	72 ± 10$^{\S,\|}$	81 ± 11$^{*,\|}$	81 ± 11$^{*,\dagger,\|}$	93 ± 13*,†,‡,§
	(38–94)	(51–91)	(56–104)	(53–112)	(60–134)
LVRI (g/ml)	1.01 ± 0.08	1.01 ± 0.06	1.03 ± 0.09	1.01 ± 0.06	1.01 ± 0.07
	(0.84–1.20)	(0.84–1.10)	(0.83–1.32)	(0.84–1.18)	(0.78–1.28)
SDI (%)	1.37 ± 0.41	1.15 ± 0.43	0.94 ± 0.26	1.05 ± 0.41	1.05 ± 0.41
	(0.66–2.43)	(0.42–2.27)	(0.46–1.47)	(0.27–2.49)	(0.26–2.87)

A meta analysis of 92 studies by (Utomi et al., 2013) showed tha both IVSWT and PWT were greater in resistance-trained and endurance trained athletes than controls. Cavity dimension, but not volume, was greater in endurance athletes than resistance athletes. This might be explained by taking into account the greater overall training time in endurance athletes leading to an eccentric type of hypertrophy, whereas the lack of concentric-type hypertrophy in resistance athletes might be due to a limited exposure time to increased haemodynamic afterload because of the intermittent nature of strength training.

In a study conducted by(A Pelliccia et al., 1999) upon 1309 elite Italian athletes, showed that the impact on left ventricular dimensions differed greatly among different sport types: some endurance sports such as cycling, crosscountry skiing, and canoeing seemed to have the greatest impact on left ventricular cavity. On the other hand, other sports, such as table tennis, alpine skiing, yachting, and equestrian had the minimum effect. When these findings were statistically analyzed, those differences were proved to be statistically significant. Athletes with left ventricular internal diameter of 60 mm or more were 185 and participated in various sporting disciplines, of which road cycling (49% of cyclists), ice hockey (42%), basketball (40%), rugby (39%), canoeing (39%), and rowing (34%) were the most notable. As with previous studies, a significant amount of them (26%) had exceeding recognition and high success rates in athletic competitions.

A recent article by (Naylor et al., 2008) suggests that the morganroth hypothesis might be partly recognized, at least for the endurance part, since eccentric hypertrophy does indeed seem to occur in endurance training. However to reject the resistance training part of the hypothesis, further longitudinal studies must be performed. Endurance athletes are less included in studies and strength exercise with its intermittent pattern, requires an observation of the LV remodeling over a greater amount of time, perhaps using the newest imaging modalities available.

The haemodynamic overload caused by endurance training is also applicable in changes found in LA size. Left atrium volume index is increased in endurance athletes, whereas strength trained athletes do not show a substantial increase in LA size. The range of LA volume index was 26 to 36 mL/m in men and 22 to 33 mL/min women ($P < .01$) in a study of 615 eltite athletes, conducted by (Antonello D'Andrea, Riegler, et al., 2010)

Accordingly, RA and RV dilatation was greater in endurance athletes vs strength athletes in a study conducted by (Pagourelias et al., 2013) in a 108 elite athletes.

Aortic root parameters are also increased in endurance versus strength athletes, who tend to show no alteration in aortic root dimensions. The impact of endurance exercise on aortic root size however is only mild, mainly in male versus female athletes, as shown in a study conducted in 2137 athletes. (Antonio Pelliccia et al., 2010)

2.1.3.2 BODY SIZE

In healthy sedentary subjects, some parameters of left ventricular geometry such as LV mass and left ventricular end diastolic dimensions are closely related to body size parameters such as body surface area, fat free mass and height. These parameters must be taken into account when evaluating geometrical features of the left ventricle and findings should be indexed to those parameters in order, not only to avoid miscalculations, but also in order to make these results comparable between subjects of different body features.

a. Body surface area

Body surface area, is usually calculated using the The Mosteller formula, that takes the square root of the height (cm) multiplied by the weight (kg) divided by 3600. In echocardiography the effect of BSA has been found to be statistically significant in many measurements, and nowadays, these parameters, such as LV and LA volume and LV mass are indexed to BSA. When evaluating the adaptations of the left ventricles in athletes, BSA has been found by many studies to be an independent predictor of left ventricular geometry.

In a group of 1309 Italian athletes, stepwise multiple regression analysis of continuous variables showed that only body surface area, heart rate, and age were significantly associated with left ventricular cavity dimension. Statistical analysis of these variables (body surface area, heart rate and age) as well as the categorical variables type of sport and sex, showed that more than 70% of the variability in left ventricular cavity dimension was explained by the continuous and categorical variables combined. Covariance analysis with these variables identified the regression coefficients (that describe the relation between left ventricular cavity dimension and all of these variables) and 95% confidence intervals (that defines a range of values that one can be 95% certain contains the population mean) that describe the relation between left ventricular cavity dimension and all of these variables. Using these coefficients one could predict the left ventricular cavity dimensions of a hypothetical athlete of a given age, sport, sex, BSA and heart rate, using a mere equation. According to covariance analysis and the Wald test, the most important determinants of left ventricular cavity dimensions were body surface area and type of sport. Heart rate, sex and age, were less significant, but still important determinants.(A Pelliccia et al., 1999)

Maron and Pelliccia, studied 947 elite athletes, and found that BSA has the most significant positive relationship with LV cavity size, with other factors such as type of

sports, gender and age being less eminent. Therefore all measurements should be indexed to BSA. Larger athletes (particularly men) will generally demonstrate greater absolute LV cavity and wall thickness dimensions.(Maron & Pelliccia, 2006)

In a study conducted in 156 football players, it was shown that Left ventricle internal diameter, wall thickness and left ventricle mass were correlated to BSA and body weight and therefore all measurements were indexed to BSA. (Abernethy et al., 2003)

A systematic review and meta-analysis by Utomi et al using multiple meta-regression data showed that increased BSA leads to increased measurements of cardiac structure. Whether this is attributable to higher total body mass or to a higher lean body mass(excluding body fat) in the athlete groups cannot be determined by using solely BSA. These data suggest that in order to compare cardiac dimensions one must take into account variability in body size between individuals in order to avoid misinterpretations and flawed conclusions. However, in this review it is not determined whether body mass, BSA or lean mass is the best approach to scaling and suggests the need for further studies on the topic. (Utomi et al., 2013)

b. Fat Free Mass

Fat free mass expresses the metabolically active tissue in the body, which accounts for total body weight minus body fat. Methods for calculating FFM are complex and require multiple regression equations, that are beyond the purposes of this review.

Whalley et al. conducted a study of 30 endurance athletes compared to sedentary controls matched for age, gender and body size to assess body fat. The only predictor for LVM and LVEDD was fat free mass, with BSA, weight and height being also correlated to these values. Interestingly, LVM and LVEDD were not different between athletes and non-athletes when indexed to height or FFM, indicating that the size of LV remodeling and the athletes heart are the result of a physiologic response to extended FFM induced by training.(Whalley et al., 2004)

A study of 30 female swimmers of national competitions, showed that there was a significant relation of left ventricular end diastolic diameter,posterior wall thickness and left entricle mass with fat free mass and body surface area. When multivariative regression analysis was performed, FFM was the only independent predictor of both LVM and LVEDD. Consequently, when assessing LVM and LVEDD, correction for FFM in athletes should be performed and may be more appropriate than other measurements of body size, in order to index absolute size of LV. (Sheikhsaraf et al., 2010)

Left ventricular mass (LVM), septal wall thickness (ISWT) and end-diastolic diameter (LVEDD) were measured by echocardiography in 1051 elite athletes and in 338 sedentary controls matched for age, gender and body size. Body fat was determined by skinfold thickness measurements. The results showed that LV geometry is vastly influenced by body composition, and therefore before advising athletes to de-train to reverse LV remodeling, physicians should scale cardiac dimensions. FFM was found to have the strongest influence on LVEDD, ISWT and LVM and is therefore recommended as the primary choice for correction. However, although differences in cardiac size disappear when corrected for body size, high dynamic excersice induces increase in LVM that exceeds the mere influence of body composition.(Pressler et al., 2012)

2.1.3.4 ETHNICITY

Ethnical differences are an emerging factor that contributes to left ventricular remodeling during exercise. White, Black and asian athletes, although they share basic echocardiographic characteristics, also present with significant differences. Therefore, it is important to underline these differences in order to evaluate adaptation to athletic training in these populations and avoid misinterpretation of findings.

A study of 240 black and 200 white female athletes, demonstrated that black athletes exhibit increased left ventricular wall thickness (8-10.4 versus 7,4-9,8mm, P<0.001) and left ventricular mass (145,2-229,2g versus 130,3-214,3g, P=0.008) than white athletes. 3% of black athletes had a left ventricular wall thickness above 11 mm (maximum of 13 mm) compared with white athletes, none of which had LVWT above 11mm. Systolic and diastolic function was normal in all athletes.(J Rawlins et al., 2010)

Comparison of Echocardiographic Cardiac Dimensions Between Black and White Female Athletes(J Rawlins et al., 2010)

	Black Athletes (n=240)	White Athletes (n=200)	*P*
Ao, mm	27.2±2.9 (23, 38)	26.4±3.5 (17, 33)	0.21
LA, mm	35.3±4.7 (21, 41)	32.5±4.8 (25, 47)	<0.0001
LVED, mm	48.6±3.9 (39, 60)	48.2±3.5 (40, 62)	0.93
LVES, mm	27.3±4.0 (21, 44)	30.5±4.7 (20, 44)	0.47
IVSd, mm	9.0±1.3 (6, 13)	8.4±1.2 (6, 11)	<0.001
PTWD, mm	8.7±1.3 (6, 12)	8.4±1.2 (6, 11)	0.14
Max LVWT, mm	9.2±1.2 (6, 13)	8.6±1.2 (6, 11)	<0.001
LVM, g	187.2±42 (95, 322)	172.3±42 (86, 293)	0.008
E wave, m/s	0.89±0.2 (1.36, 0.6)	0.90±0.2 (1.33, 0.53)	0.49
A wave, m/s	0.41±0.1 (1.1, 0.2)	0.44±0.1 (0.9, 0.2)	0.076
E/A ratio	2.3±0.8 (5.5, 1.1)	2.2±0.8 (5.5, 1.1)	0.15
E′, m/s	0.22±0.03 (0.25, 0.13)	0.23±0.03 (0.28, 0.17)	0.40
A′, m/s	0.07±0.03 (0.16, 0.02)	0.06±0.03 (0.13, 0.03)	0.43
E:E′	4.41±0.71 (5.61, 2.30)	4.46±0.74 (5.55, 1.96)	0.39
EF, %	67±6.7 (41, 78)	66±6.9 (44, 76)	0.48

Similar to the previous study, basavarajaiah et al also suggested that black athletes exhibit an appreciable increase in LV wall thickness in response to exercise, compared to white athletes. In a study of 300 black and 300 white athletes, black athletes excibited higher values of LV wall thickness, and a higher incidence of LVH>13mm (18% in blsck athletes versus 4% in white). Interestingly, values of LVH >15mm were observed in 3% of black athletes as opposed to white athletes, none of whom excibited such values. Black athletes with increased wall thickness also displayed enlarged LV internal diamensions with normal diastolic function. No athlete, black or white, had LVH>16mm. (Basavarajaiah, Boraita, et al., 2008) .(Sheikh & Sharma, 2014) Black athletes excibited increased measurements in all sports categories, despite having the same blood pressure values, implying a genetic predesposision to LVH in black athletes.(John Rawlins et al., 2009)

Ethnic differences extend beyond black and caucasian athletes. A study of 282 professional soccer players (Japanese, african-carribean and Caucasian) demonstrated that morphologic cardiac remodeling is different, despite similar type and magnitude of training, in athletes of different ethnic origin. Specifically, larger left ventricular cavity dimensions were illustrated in Japanese playeres compared with AfroCarribean and Caucasian players (55.2 ± 3.3 versus 52.2 ± 3.8 and 53.9 ± 3.7 mm, accordingly, $p < 0.01$), with over 4% of these, exhibiting profoundly increased cavity dimensions (>60 mm), in the presence of normal systolic/diastolic function, excluding, thus, dilated cardiomyopathy. Japanese athletes presented with a more eccentric type of remodeling compared with African-Carribean who tend towards a more concentric LV remodeling compared to Caucasian.(Kervio et al., 2013)

A study conducted in 1185 university athletes, found that left ventricular and left atrium dimensions, left ventricular volumes, LV wall thickness, and LV mass were vastly increased in non-Asian than in Asian athletes, but when indexed to BSA LV end diastolic diameter, LV end systolic diamete , LA dimension and LV wall thickness were similar, but LV end-diastolic and end-systolic volume and LV mass index remained increased in non-Asian athletes. Right ventricular size and wall thickness and inferior vena cava size were significantly smaller, and TAPSE was significantly lower in Asian compared with non-Asian athletes, and these differences were preserved even after indexing for BSA. Cho et al conclude that different normal reference values for cardiac chamber quantification should therefore be adopted in regard to racial origin(Cho et al., 2019)

A single centre cross-sectional case-control study performed in 2004 at athletes from Changi Sports Medicine Center in Singapore demonstrated for the first time that the Singapore-asian athlete's heart appears to undergo similar remodeling induced by exercise as non-Asians, although It might appear that the remodeling extends to a lesser degree than non-Asians. However, these results need further data to strongly support such a conclusion . (Keh et al., 2018))

600 high-level Arabic, 415 Black African, 160 Caucasian male athletes were evaluated by echocardiography in the Riding et al study. 9 athletes (0.7%) were identified with a cardiac pathology associated with sudden cardiac death. Two athletes of arabic descend (0.3%) and five of Black African descend (1.2%) were diagnosed with hypertrophic cardiomyopathy; the prevalence of which was four times greater in Black African compared to Arabic athletes. All athletes, irrespective of ethnicity had increased LVEDD, LV wall thickness and LV mass compared to controls, however arabic athletes exhibited the lowest values compared to african and caucasian athletes. The incidence of Left ventricle hypertrophy (above 12mm) was similar between Arabic, Black African and Caucasian populations (0.5%, 0.5% and 0.6%, respectively). In conclusion, arabic athletes tend to express significantly smaller cardiac dimensions than Black African and Caucasian athletes. (Riding et al., 2014)

Comparison of echocardiographic parameters between Arabic, Black African and Caucasian athletes, and Arabic controls(Riding et al., 2014)

Parameter	Arabic (n=596)	Black African (n=410)	Caucasian (n=160)	Arabic controls (n=201)
Ao (mm)	26.8±2.4* (18–39)	27.4±2.6† (21–36)	28.2±2.6†‡ (22–34)	25.9±2.7 (21–34)
LA (mm)	33.4±3.9* (20–47)	34.4±3.7† (22–45)	34.4±3.8† (24–48)	31.5±4.0 (18–42)
LA vol D (ml)	46.0±14.2* (12–117)	52.8±16.0† (20–118)	50.8±16.8† (15–101)	37.8±11.9 (15–77)
RA area (mm^2)	15.6±2.9* (7–27)	17.8±3.2† (10–29)	17.5±3.6† (10–27)	13.9±3.2 (8–37)
LVED (mm)	52.7±4.2* (39–65)	53.9±3.9† (41.1–63)	55.8±3.7†‡ (40–63)	49.4±4.1 (41–60)
LV vol D (ml)	122±25* (40–236)	130±24† (60–209)	143±29†‡ (81–271)	106±22 (47–175)
mLVWT (mm)	8.9±0.9* (5.7–14)	9.3±1.1† (6.3–14)	9.2±0.8† (7–13)	8.6±0.9 (6.3–12)
mLVWT≥10 mm (%)	12*	25§	14	6
mLVWT≥12 mm (%)	0.5	0.5	0.6	0
LVM (g)	164±34* (54–262)	182±38† (71–291)	193±32†‡ (96–276)	143±33 (78–286)
LVM/BSA (g/m^2)	86.8±14.3*	89.7±14.8	90.8±13.3	77.3±14.8
E/A	2.07±0.42*	2.07±0.38	2.05±0.41	1.97±0.46
E/E′	4.8±0.8	4.9±0.9	4.6±0.7‡	5.1±0.9

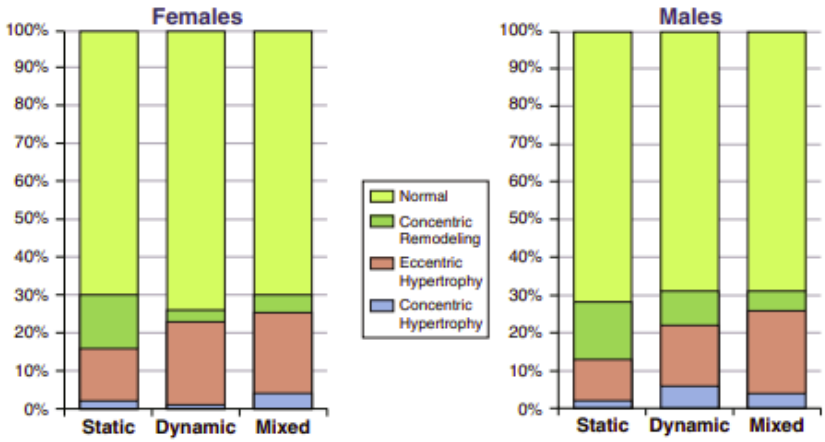
2.1.3.4 GENDER

With regard to previously mentioned parameters that influence left ventricular remodeling, it should be anticipated that gender specific differences in exercise induced remodeling do exist. Male and female athletes differ in terms of body surface area and fat free mass since their distribution of fat and muscle differs significantly. The difference between female and male athletes also depicts the difference between male and female in the amount of circulating endogenous anabolic hormones, resulting in excessive muscle growth and therefore higher intensity training in male. Therefore,it stands to reason left ventricular cavity dimensions and wall thickness would present with different values in men and women. However, to blindly conclude that men present with greater degree of remodeling than women, has been found to be inconclusive.

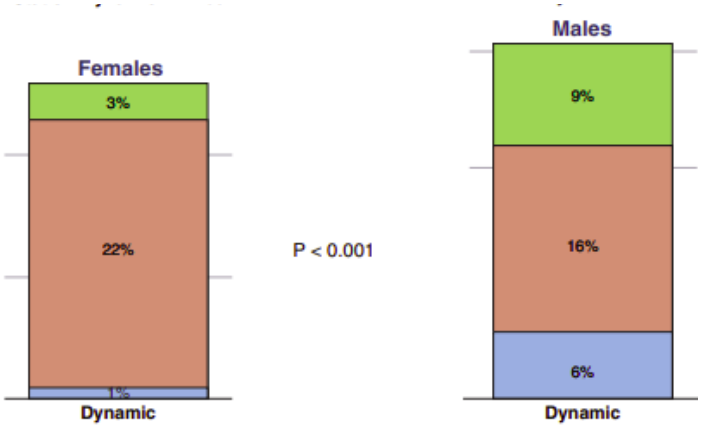
In a study conducted in 600 elite female athletes, it was demonstrated that female athletes exhibited significantly smaller left ventricle dimensions and wall thickness compared to previous studies that included male athletes. These alterations were found to be a normal adaptation to training, since increased cavity dimensions were outside normal values for only 8% of female athletes, and wall thickness, though relatively increased, was always within normal limits. Hence, differentiating hypetrophic cardiomyopathy from the female athlete' s heart is not an issue.(A Pelliccia et al., 1996)

In the recent study by (Finocchiaro et al., 2017) Females exhibited lower LVM and RWT and absolute LV dimensions, but when compared to BSA, the indexed dimensions were greater in females. Most athletes showed normal LV geometry. Eccentric hypertrophy was more common in female dynamic athletes and concentric hypetrophy was more common in male dynamic athletes. Concentric hypertrophy in female symptomatic athletes may be a sign of disease.

A study conducted in 1185 university athletes through the Check-up Your Heart Program during the 2015 Gwangju Summer Universiade, showed no difference in male versus female athletes in terms of LV geometrical adaptation to exercise. Concentric remodeling was the dominant form of LV adaptation that was shown in both male and female athletes..(Cho et al., 2019)



Left ventricular geometry in males and females according to type of sport(Finocchiaro et al., 2017)



Concentric hypertrophy/remodeling and eccentric hypertrophy in athletes involved in dynamic sport (Finocchiaro et al., 2017)

All in all, female athletes tend to have small absolute increases in LV wall thickness , cavity size, right ventricular (RV) and right and left atrial cavity size in comparison with sedentary women, but to a lesser extend than male athletes, in absolute values.(Lang et al., 2015)

2.1.3.5 AGE

Advance of age goes along with a decreased rate of myocardial relaxation, increased LV stiffness, and a more prominent role of the atrial pump to left ventricular filling. Elder athletes present with lower left ventricular volumes and mass compared with the younger athletes, but in both groups these values are higher compared to sedentary subjects.

In a study conducted in athletic seniors and controls as well as athletic youths and controls, showed that left ventricular mass was greater in young athletes than senior

athletes and greater in senior athletes than senior sedentary subjects. Left ventricular ejection fraction was similar in all groups. Left ventricular stroke volume was greater in the athletic than in the sedentary groups, global longitudinal strain during exercise was (-22,4 to -17,6)% in the senior athletic group and (-24.2 to -20)% in the young athletic group. The septal annular e' and lateral annular e' velocities were greater in youth than seniors, irrespective of exercise. However master athletes tend to exhibit smaller *E* and *e'* waves and higher *A* and *a'* waves and are compatible with normal aging of the left ventricle that also applies to untrained subjects. All of the above, conclude that young people adapt to regular exercise, in terms of systolic and diastolic function more than older aged training matched subjects. In this study, it was observed that LV relaxation impairment that comes with aging is not amplified by exercise. While exercise promotes left atrial dilatation in young athletes, the same does not apply for senior athletes. (Donal et al., 2011)

In a small study conducted in 14 master athletes, it was shown that long term training, though beneficial, does not have a significant impact on the age related reduction in left ventricular relaxation. More specifically, transmitral peak E velocity and ratio E/A were significantly higher in master athletes, compared to age matched controls, but these values were lower than in young men. Left ventricular wall motion was the same in sedentary and athletic seniors and lower than young men. These data provide evidence that long-term training does not reduce the age-related decline in LV relaxation properties in humans. (S Nottin et al., 2004)

Standard Doppler echocardiographic data(S Nottin et al., 2004)

	Sedentary young men ($n = 15$)	Sedentary older individuals ($n = 14$)	Master athletes ($n = 14$)
M-Mode and 2D echocardiography			
Septal wall thickness (cm $BSA^{-0.5}$)	0.66 ± 0.09	0.72 ± 0.10	0.71 ± 0.12
Posterior wall thickness (cm $BSA^{-0.5}$)	0.61 ± 0.08	0.66 ± 0.11	0.65 ± 0.06
LV end-diastolic diameter (cm $BSA^{-0.5}$)	3.67 ± 0.24	3.78 ± 0.37	4.04 ± 0.55*,†
LV end-systolic diameter (cm $BSA^{-0.5}$)	2.35 ± 0.21	2.45 ± 0.29	2.49 ± 0.36
LV mass (g BSA^{-1})	82 ± 12	98 ± 22†	104 ± 23††
Ejection fraction (%)	63 ± 5	61 ± 3	62 ± 2
Stroke volume (mL BSA^{-1})	44 ± 9	52 ± 7	66 ± 12*,††
Heart rate (beats min^{-1})	72 ± 11	73 ± 10	63 ± 6**,††
Cardiac output (L BSA^{-1})	3.1 ± 0.7	3.7 ± 0.6	3.8 ± 0.9
Doppler diastolic function			
Peak *E* velocity (cm s^{-1})	80.8 ± 12.7	53.7 ± 9.7†††	68.3 ± 13.1**,††
Peak *A* velocity (cm s^{-1})	51.4 ± 12.3	67.4 ± 12.3†††	66.9 ± 10.6†††
Peak *E/A* ratio	1.60 ± 0.30	0.81 ± 0.18†††	1.04 ± 0.24*,†††
E-wave deceleration time (ms)	109.9 ± 13.1	131.6 ± 13.1††	128.5 ± 20.8††
Isovolumetric relaxation time (ms)	81.6 ± 13.4	97.4 ± 16.4†	99.9 ± 28.7†
E/E_m	4.7 ± 1.0	4.4 ± 1.1	6.1 ± 2.0**,††

A systematic review and metanalysis of 32 studies, demonstrated that athletic older men have larger cardiac dimensions and are favoured by a better cardiac function than healthy, sedentary subjects. Notably, during the course of aging, these effects are maintained. Older athletes have improved global diastolic function which is more independent of late diastolic filling . Greater E/A in aerobic athletes that was derived from this meta analysis is in concurrence with other meta analysis in younger subjects, strongly implying that deviations in diastolic function between aerobic athletes and sedentary controls are induced irrespective of age. Reduced values of A, without concordant reduction in E, has previously been reported in olympic athletes (Caselli, Di Paolo, et al., 2015), proving that continuous exercise throughout the years favors cardiac function.

Older athletes exhibit increased LV wall thickness, LVM, left ventricle end diastolic diameter and Left ventricle end diastolic volume, comparable with younger athletes. RVEDD was similar between older athletes and controls. As previously stated, EF did not differ between younger and older athletes. (A. J. Beaumont et al., 2019)

2.1.3.6 ANABOLIC ANDROGENIC STEROIDS

An emerging factor in left ventricular hypertrophy and function is the excessive use of anabolic androgenic steroids non steroid factors , and since most athletes do not admit their use, the evaluation of its effects can be very challenging. Moreover, left ventricular hypertrophy is a normal adaptation to exercise and hence, the differentiation between the physiologic response and that mediated by anabolic steroid abuse becomes very complicated. Left ventricular hypertrophy induced by anabolic steroids might be associated to the secondary arterial hypertension induced by steroids or to direct effects of steroids on the myocardium, via direct binding of steroids to androgen receptors and tissue up regulation of the renin angiotensin system. Clinical studies have shown that left ventricle hypertrophy in steroid users is different from that of plain exercise alone. Furthermore, visible in changes in the myocardium before the initiation of excessive LVH. (Antonello D'Andrea et al., 2016)

Testosterone and anabolic androgenic steroids have an enhancing effect on both lean muscle mass and athletic performance. Their actions on a cellular level include stimulation of protein synthesis via adrenergic receptors that induce increase of organ mass. The heart is not left out of this process, since myocardial fibrosis can occur. Moreover, although cessation of exercise typically reduces left ventricular hypertrophy, when anabolic substances are used, this effect is subsided. In such cases, it is not uncommon to misdiagnose LVH for hypertrophic cardiomyopathy.

Diastolic function is not typically affected by exercise. Nonetheless, in athletes who misuse anabolic steroids, diastolic function tends to be affected. In a study conducted by (Stéphane Nottin et al., 2006) in male bodybuilders, 6 reported anabolic steroid use and 9 where drug free. E(m) as measured by TDI was smaller in drug-using bodybuilders. The E/E(m) ratio, which indicates LV filling pressures, was similar in both drug free and anabolic steroid users. In drug-using bodybuilders passive filling of the left ventricle did not contribute to LV filling as much as in non drug using bodybuilders and LV relaxation was also impaired.

Systolic function, as assessed by ejection fraction and strain imaging might also be influenced, contrary to athletes who do not use such substances, as was shown on a study conducted in 12 long term anabolic steroid users and 7 non users, of comparable characteristics, by(Baggish et al., 2010) (Galderisi et al., 2015)

Finally, in regard to athletes who abuse anabolic steroids for years, D Andrea et al published an article describing the case of a 35-year old bodybuilder with a history of 15 years of testosterone abuse with severe LVH (IVS 17mm) and subclinical impairment of systolic and diastolic function (EF 50%, E/e' 14). That impairment was correlated with steroid dosage and duration of use.(D'Andrea et al., 2007)

Power of cardiac imaging for suspected diagnosis of performance enhancing substances involvement (Galderisi et al., 2015)

Prohibited substances	Cardiac effect	Demonstration by cardiac imaging
Anabolic androgenic substances	LVH, LV diastolic dysfunction, reduction of EF, reduction of longitudinal strain	+++
Non-steroids anabolic agents (B2 agonists, peptide hormones, growth factors, recombinant human erythropoietin)	LVH, LV diastolic dysfunction	+
Stimulants (amphetamines, methamphetamine and cocaine)	Acute and chronic CAD, Aortic dissection	++

+++, largely demonstrated; ++, well demonstrated; +, poorly demonstrated.

2.2 LEFT VENTRICULAR FUNCTION

2.2.1. SYSTOLIC FUNCTION

Systolic function is evaluated in the standard echocardioraphic study, with current techniques, using mainly ejection fraction. Ejection fraction represents the percentage of blood that is ejected by the left ventricle in every beat. According to Frank Starling's law, the heart can change its force of contraction and therefore stroke volume in response to changes in venous return, in other words, an increase in preload, will lead to an increase in end diastolic pressure of the left ventricle and therefore, an increase in left ventricular contraction and stroke volume. During exercise, there is utilization of the frank starling mechanism, with an elevation in venous return, aka preload, leading to an increase in stroke volume and ejection fraction in athletes. At rest, athletes present with reduction in preload and dilation of the left ventricle which might lead ejection fraction to remain normal or even slightly reduced.(Abergel et al., 2004) Therefore, in order to objectively evaluate ejection fraction in athletes, measurements both at rest and during exercise should be acquired.

Ejection fraction is defined as 100x(EDV-ESV)/EDV. This formula is designed for subjects with normal dimensions of the left ventricle. In athletes, where those dimensions are usually altered, an intrinsic mathematical underestimation of left ventricular function might occur. Moreover, when calculating EF, one estimates left ventricular function, rather than left ventricular contractility. Hence, underestimation of the left ventricle's ability to increase stroke volume during demanding exercise, might also occur. (Galderisi et al., 2015) .

The biplane method of disks (modified Simpson's rule), which was described in the previous chapter, is the currently recommended 2D method to assess ejection fraction by the EACVI guidelines for chamber quantification. According to the same committee, 3D EF measurements are also accurate and reproducible and should be acquired when possible. Both 3D and 2D measurements of ejection fraction and dependent on volume

load, which might be altered in athletes. Therefore, when evaluating EF in athletes by non invasive methods, one should take into account that it might be inconsistent. (Lang et al., 2015)

Normal values for ejection fraction as measured by 2D echocardiography (Lang et al., 2005)

	males		**females**	
parameter	Mean+/-SD	2-SD range	Mean+/-SD	2-SD range
EF(%) biplane	62+/-2	52-72	64+/-5	54-74

Atchley and douglas reviewed that LV systolic function is generally maintained in athletes and pointed out that this feature of the athlete' s heart discriminates it from pathologies of the heart that also lead to left ventricle hypertrophy, such as hypertrophic cardiomyopathy. (Atchley & Douglas, 2007)

In study conducted by Caselli et al in 511 olympic athletes and 159 controls using 3D echocardiography, EF was not reduced to values <50% in athletes and non athletes, suggesting that despite the geometrical changes of the trained left ventricle, systolic function remains untouched. This suggests that in the event of reduced left ventricular ejection function, further examination needs to be done. This study also evaluated possible systolic myocardial dyssynchrony in terms of the enlarged volumes and masses of the athlete 's heart and was calculated as the standard deviation of the time to minimum systolic volume in 16 LV segments, normalized by the RR interval. It concluded that dyssynchrony was not observed, as opposed to myocardial disease where dyssynchrony can be observed. (Caselli et al., 2011)

Claeys et al. examined left ventricle reserve and left ventricular ejection fraction during semi-supine bicycle stress echocardiography of 96 endurance athletes and 48 controls. Left ventricle reserve is an emerging factor in heart failure and cardiovascular disease prognosis and is defined as the difference between peak exercise and resting LVEF. What was obsereved is that Left ventricular ejection fraction at rest was lower in athletes(52.9% ± 5.86) versus non athletes (58.2% ± 6.05, p<0.001), but still within normal range. During exercise LVEF presented a significant increase (ΔLVEF 16.5% ± 8.51), which was more prominent in the athletic group (19% ± 8.53) and when peak exercise was achieved, LVEF was similar in both groups (71.2% ± 6.56), with athletes presenting with a minor lead (72% ± 7.14) versus non athletic controls (69.7% ± 4.94, p=0.086) . Consequently, athletes present a higher LV reserve compared to non athletes. (*Aha_circ138_A10620*, n.d.)

A meta analysis by pluim et al, encompassing The analysis 59 studies and 1451 athletes, used both ejection fraction and fractional fiber shortening in the evaluation of left ventricular systolic function. Functional fiber shortening, calculated by the formula: (LVEDD - LVESD / LVEDD) x 100 gives the percentage of size differences of the left ventricle, suggesting how well the left ventricle contracts and therefore reduces its size during systole. Pluim et al concluded that these two parameters are not significantly different between athletes and non athletic controls and therefore the changes exercise induces on left ventricular geometry are irrelevant to systolic function of the athlete s heart. (Pluim et al., 2000)

2.2.2. DIASTOLIC FUNCTION

In normal LV diastolic function LV pressure decreases during the early phase of diastole and permits a normal-low pressure filling of the LV at rest and at exercise. (Nchimi, 2017) The final result of abnormal LV diastolic function is elevation of LV filling pressure.

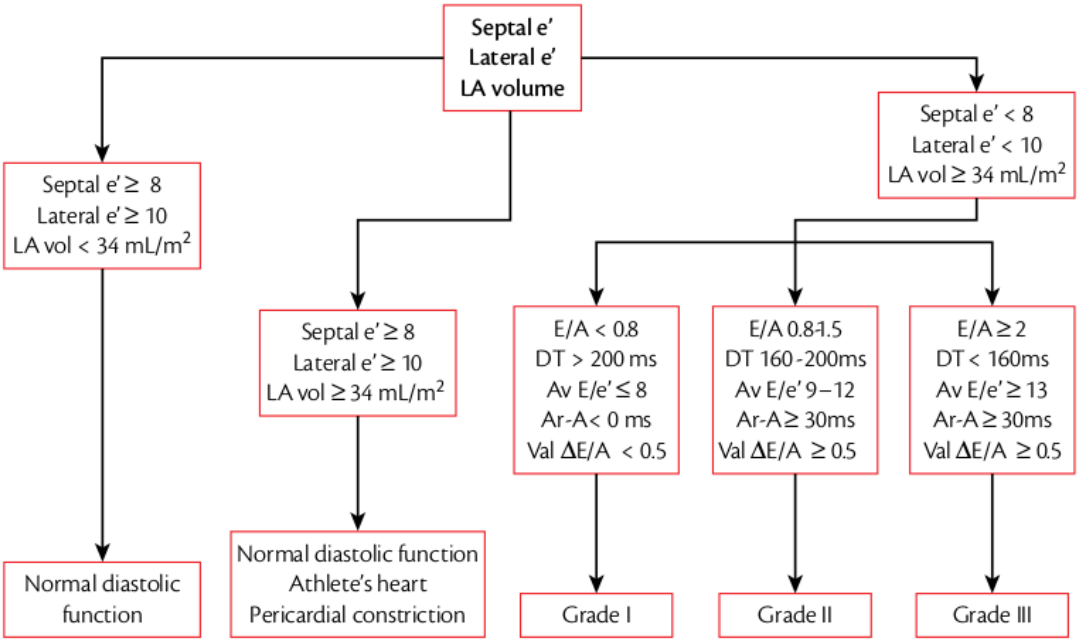
Proper evaluation of diastolic function can be very challenging in the clinical setting, since it is influenced by a variety of factors, such as sinus rhythm dysfunction, myocardial wall thickness, myocardial stiffness, extrinsic compression, increased or decreased preload, mitral regurgitation, tachycardia etc.(Nchimi, 2017). In diastolic function, although both relaxation and compliance can be affected, it should be specified which is the dominant contributing factor by evaluating separately factors influencing compliance and relaxation. More specifically, values to be attained are PW doppler of the mitral annulus peak of early filling (E)wave and peak of late atrial filling (A) wave that represent early diastolic filling and atrial contraction, their ratio (E/A), DMI measurement of lateral and septal e' (early diastolic velocity), that represents relaxation of the myocardium, E/e' which correlates with LV filling pressure or pulmonary capillary wedge pressure, LA volume index, tricuspid valve peak regurgidant velocity with CW Doppler. Apart from these commonly used values, other measurements can aid the assessment of diastolic function if results are inconclusive. These include E wave deceleration time, Isovolumic relaxation time (IVRT), pulmonary venus flow assesement (Peak systolic (S) velocity, Peak anterograde diastolic (D) velocity, The S/D ratio, Peak Ar velocity in late diastole). Reference values of these measurements are provided below.

Presence and severity of diastolic dysfunction (Nchimi, 2017)

Pathophysiology	Normal	Mild	Mild–Moderate	Moderate	Severe
		relaxation ↓	relaxation ↓ LVFP ↑	relaxation↓ compliance↓ LVFP↑	relaxation ↓ compliance ↓↓ LVFP↑↑
E/A	1–2	< 1	< 1	1–2	> 2
e'/a'	1–2	< 1	< 1	< 1	> 1
IVRT (ms)	50–100	> 100	Normal	↓	↓
DT (ms)	150–200	> 200	> 200	150–200	< 150
S/D	≥ 1	S > D	S > D	S < D	S << D
Ar (m/s)	< 0.35	< 0.35	≥ 0.35	≥ 0.35	≥ 0.35
Ar dur–A dur (ms)	< 20	< 20	> 20	> 20	> 20

Correlation between septal E/e ratio and LV filling pressure(Nchimi, 2017)

E/e' < 8	LV filling pressure—normal
E/e' > 15	LV filling pressure—increased
E/e' between 8 and 15	Other echocardiographic indices should be used



Scheme for grading LV diastolic dysfunction. Av: average; LA: left atrium; Val: Valsalva (Nchimi, 2017)

Diastolic function, defines a major component of left ventricular function that gives additional information on the adaptive mechanisms of the heart to exercise. Many studies have evaluated these parameters to conclude that diastolic function remains roughly unchanged in athletes but give interesting and useful information on the function of the athletes heart and discrimination from pathology

In a large study conducted in 1,145 Olympic athletes and 154 controls, E velocities were comparable in athletes and non athletes (87 ± 15 vs 89 ± 16 cm/sec, P = .134) as opposed to A velocities which were considerably lower in athletes (47 ± 10 vs 56 ± 12 cm/sec, P < .001), and consequently E/A ratio were higher. Athletes also exhibited longer isovolumic relaxation(83 ± 13 vs 71 ± 16 msec, P < .001) and deceleration times (203 ± 40 vs 181 ± 36 msec, P < .001) compared to non trained individuals. TDI e' (13.8 ± 2.2 vs 16.2 ± 3.7 cm/sec, P < .001)and a' (7.2 ± 1.8 vs 8.5 ± 2.1 cm/sec, P < .001) were lower in athletes but their ratio did not differ substantially, whereas E/e' were slightly higher in athletes (6.37 ± 1.2 vs 5.72 ± 1.33, P < .001). When type of sport was taken into account, endurance athletes presented with the lower A and a' velocities and the largest E/A ratios. (Caselli, Di Paolo, et al., 2015)

Doppler parameters of diastolic function and reference values (fifth and 95th percentiles) in athletes and untrained controls(Caselli, Di Paolo, et al., 2015)

Variable	Athletes (*n* = 1,145)	Controls (*n* = 154)	*P*
PW E wave (cm/sec)	87 ± 15 (64–112)	89 ± 16 (65–118)	.134
PW A wave (cm/sec)	47 ± 10 (32–65)	56 ± 12 (39–78)	<.001
E/A ratio	1.93 ± 0.50 (1.27–2.85)	1.63 ± 0.35 (1.08–2.27)	<.001
IVRT (msec)	83 ± 13 (60–105)	71 ± 16 (49–100)	<.001
Deceleration time (msec)	203 ± 40 (143–271)	181 ± 36 (137–258)	<.001
DTI e′ wave (cm/sec)	13.8 ± 2.2 (10.3–17.5)	16.2 ± 3.7 (10.6–22.6)	<.001
DTI a′ wave (cm/sec)	7.2 ± 1.8 (4.7–10.0)	8.5 ± 2.1 (5.3–12.3)	<.001
E′/A′ ratio	2.04 ± 0.62 (1.23–3.21)	2.00 ± 0.68 (1.12–3.42)	.494
E/e′ ratio	6.37 ± 1.20 (4.63–8.49)	5.72 ± 1.33 (3.98–8.02)	<.001
PASP (mm Hg)	23 ± 4 (17–29)	22 ± 4 (18–27)	.939

These findings, derived from a large pool of athletes of various sports types would be very interesting to examine a bit more explicitly. In this study alteration in the geometry of the left ventricle in terms of wall thickness was excessive, but left ventricular filling and relaxation remained normal, since E/A ratio was always >1.0, portraying values of below 1.0 as abnormal in athletes. Similarly, an e'/a' ratio < 1.0 was only measured in 1% of athletes, particularly those of more advanced age, increased systolic pressure and LA dimensions. Noticeably, 3% of athletes presented with E/A ratios of 3.0 and more (mainly because of a decrease in A wave values), which should not be considered as a restrictive pattern of diastolic filling. Contributing to this conclusion is the normal DTI e' velocity and E/e' ratio with a normal PASP. Heart rate is highly attributable for these findings, since the lower resting heart rate of athletes results in diastolic filling that is most prominent in early diastole and diastasis. This phenomenon however occurs with normal E velocities since the increased diameters of the left ventricle and the Left atrium and the longer diastolic phase keeps left ventricle inflow velocities normal. Another reason for this is that left ventricle untwists at lower velocities in athletes under resting conditions -and hence causes increased IVRT- and therefore the decrease in left ventricular pressure needed is less, although this phenomenon may alter during exercise. In general, type of sport did not play a profound role in diastolic function, but endurance sports presented with the most prominent reductions reductions in A and a' waves and increases of E/A ratio. As described above, these differences observed in endurance sports were correlated to the larger cavity sizes and lower resting heart rates in this sports category. Similarly, the contained increases in E and A velocities in female athletes compared to their male counterparts, are associated with the mild alterations in left ventricular geometry in female versus male athletes, suggesting that diastolic function modifications are a result of geometrical adaptations to exercise. Moreover, DTI e' velocity was reduced in athletes with excessive left ventricular hypertrophy, irrespective of heart rate, suggesting a correlation between diastolic filling and left ventricular geometry. However values of 8<cm/s where not observed, suggesting that such values should be met with skepstisism in terms of underlying abnormality. Although left atrium diameters were increased in many patients, that finding was not associated with impaired diastolic function.(Caselli, Di Paolo, et al., 2015)

Standard doppler echocardioraphic analysis and pulsed DTI analysis (D'Ascenzi et al., 2011)

Variable	Athletes (n = 23)	Controls (n = 26)	P-Value
Peak E velocity (m/sec)	0.83 ± 0.1	0.71 ± 0.2	<0.01
Peak A velocity (m/sec)	0.42 ± 0.1	0.62 ± 0.2	<0.001
Peak E/A ratio	2.07 ± 0.5	1.19 ± 0.4	<0.0001
Em peak (m/sec)	0.22 ± 0.04	0.12 ± 0.04	<0.001
Am peak (m/sec)	0.08 ± 0.03	0.10 ± 0.04	<0.01
Em/Am ratio	3.13 ± 1.3	1.39 ± 0.8	<0.0001
E/Em ratio	3.91 ± 0.95	6.8 ± 3.1	<0.001
Sm peak (m/sec)	0.12 ± 0.03	0.09 ± 0.04	0.14

Values are expressed as means ± SD.

The previous table is from a study conducted in elite soccer players and controls, showed that athletes have increased lateral Em peak velocity, smaller lateral Am peak velocity, and therefore greater lateral Em/Am ratio than sedentary subjects, and hence a higher than normal diastolic function. More specifically, early and late diastolic periods where enhanced in athletes suggesting that diastolic filling is placed mainly in early rather than late diastole. LA volume index was increased in athletes and that is considered a normal adaptation to increased preload in athletic training. That presumption is enhanced by the fact that left atrial myocardial strain, which was assessed in this study, showed similar values to that of untrained individuals with a trend towards lower values in athletes. In TDI analysis early diastolic myocardial velocity (e) of septal and lateral mitral annulus and e/a lateral velocities were higher in football players than controls and that finding correlates more to endurance training than other training modalities.(D'Ascenzi et al., 2011).

The aforementioned results, can be attributed to the increase in preload during endurance training which, due to the elasticity of the myocardial muscle of athletes(Claessens et al., 2001), leads to a concordant increase in the early relaxation phase, intensifying the application of Frank-Starlings law. The result of these adjustments is an increase in LV stroke volume.

The findings of D' Ascenzi et al. are in accordance to (Tümüklü et al., 2008) who evaluated 28 professional football players and 20 controls. Their team showed that football players exhibit decreased transmitral diastolic late velocity, significantly increased mitral annulus septal (0.22 +/- 0.04 vs. 0.19 +/- 0.04 m/s, $P < 0.05$) and lateral (0.19 +/- 0.03 vs. 0.16 +/- 0.02 m/s, $P < 0.05$) TDI peak early diastolic(e) velocity and lateral TDI e/a ratio(1.96 +/- 0.41 and 1.66 +/- 0.23, $P < 0.05$) .

D' Andrea et al conducted a study upon 370 endurance athletes and 280 power athlete using pulsed-wave tissue Doppler, to assess: systolic peak velocities S(m), early E(m) and late A(m) diastolic velocities, and the E(m)/A(m) ratio. Results supported higher early diastolic peak velocities and Em/Am ratios in endurance trained athletes at the level of lateral and septal wall, while systolic peak velocities did not differ significantly between the two groups. In both endurance and resistance trained athletes, 90% of them had Em> 16 cm/sec and Sm>10 cm/sec, while all of athletes had Em/Am ratios> 1, increased LV end-diastolic dimensions, induced by the increase in preload. Because Em peak velocity and the Em/Am ratio identify with passive diastolic filling, the fact that those measurements were found increased in athletes suggests a increase in myocardial compliance in that poplulation mediated by exercise. (Antonello D'Andrea, Cocchia, Riegler, Scarafile, Salerno, Gravino, Golia, et al., 2010)

Cocchia, Riegler, Scarafile, Salerno, Gravino, Golia, et al., 2010)

Variable	Overall (n = 650)	Endurance (n = 370)	Strength (n = 280)	P
Basal IVS				
S_m peak (m/s)	0.13 ± 0.04 (0.08–0.18)	0.14 ± 0.03 (0.10–0.18)	0.12 ± 0.04 (0.08–0.15)	NS
E_m peak (m/s)	0.14 ± 0.03 (0.10–0.21)	0.16 ± 0.04 (0.12–0.21)	0.12 ± 0.03 (0.10–0.17)	<.001
A_m peak (m/s)	0.11 ± 0.03 (0.07–0.14)	0.12 ± 0.02 (0.09–0.14)	0.11 ± 0.03 (0.07–0.12)	NS
E_m/A_m ratio	1.2 ± 0.3 (1.05–1.6)	1.3 ± 0.3 (1.1–1.7)	1.05 ± 0.3 (1.05–1.4)	<.001
Basal LV lateral wall				
S_m peak (m/s)	0.15 ± 0.04 (0.09–0.20)	0.16 ± 0.02 (0.12–0.20)	0.15 ± 0.03 (0.09–0.18)	NS
E_m peak (m/s)	0.16 ± 0.05 (0.11–0.22)	0.19 ± 0.05 (0.14–0.22)	0.15 ± 0.03 (0.11–0.18)	<.001
A_m peak (m/s)	0.10 ± 0.03 (0.07–0.14)	0.10 ± 0.02 (0.08–0.14)	0.10 ± 0.03 (0.07–0.13)	NS
E_m/A_m ratio	1.62 ± 0.4 (1.2–2)	1.84 ± 0.5 (1.3–2)	1.53 ± 0.4 (1.2–1.8)	<.001

A metanalysis by pluim et al, encompassing 59 studies and 1451 athletes, suggests that diastolic function as assessed by E/A ratio is unaltered or slightly increased in athletes compared to untrained individuals and points out the need to be cautious when evaluating these parameters, since they are highly dependent on heart rate, preload and afterload. For instance, the late diastolic filling component of the left vetricle may be undermined by a slower heart rate that prolongs diastolic filling. These adapations to excercise are considered favourable outcome for left ventricular function, since analogous left ventricular hypertrophy induced by hypertension not only does it not improve, but it decreases diastolic function.(Pluim et al., 2000)

An interesting study, conducted in Berlin marathon runners, younger (22-59 years old), and older (60-72 years old) inspected the possibility of a temporary myocardial impairment after completion of the marathon and differences between the 2 groups. After the marathon, systolic function was unaltered in both groups and measurements of diastolic function showed no alterations in E/E' (7.6 +/- 2.1, 8.7 +/- 3.5, P = .15) After the marathon, deceleration time of E and E' was attenuated in older and younger athletes immediately after the race, as a marker of temporary adaptation of diastole to extensive training and there was not significant difference between the groups. All markers returned to normal in both groups 2 weeks after the race.(Knebel et al., 2009)

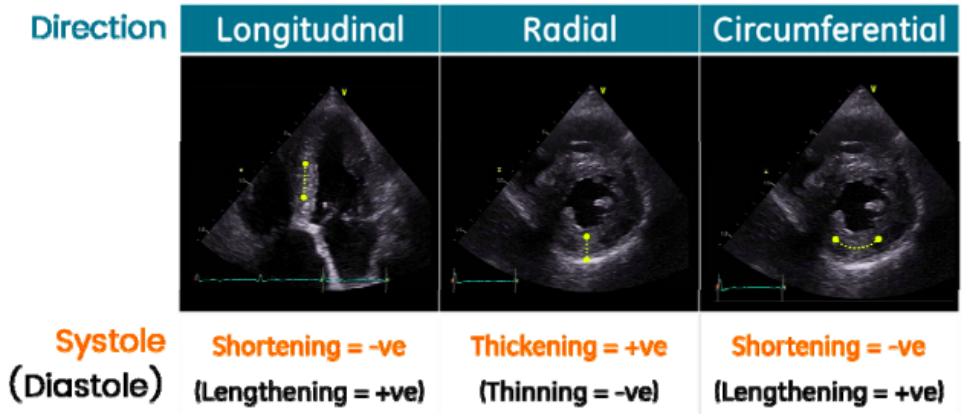
2.2.3. STRAIN AND ROTATIONAL MECHANICS

Strain describes the deformation of an object to its original shape and size(Voigt et al., 2015) and it expresses the deformation of the myocardial wall due to left ventricular contraction. For a one dimensional object such as a very thin line, deformation can occur only in the form of lengthening and shortening. In the case of myocardial deformation, end systole and end diastole can be used as reference time points for these deformations and therefore strain (ε) can be calculated by the difference of systolic to diastolic length divided by diastolic length: (ε) = (L(s)-Ld)/Ld. The amount of deformation (positive or negative strain) is usually expressed in %. This concept applies to all dimensional deformations, and therefore, strain components: longitudinal strain, circumferential strain and radial strain. Positive strain values describe thickening and negative values describe shortening of the myocardial wall, of a given myocardial segment related to its original length. During myocardial contraction, as the wall shortens it also thickens and thus assessment of all parameters, radial thickening (positive strain), circumferential shortening (negative strain) and longitudinal shortening (negative strain), is useful for the evaluation of contractile function. (Dandel et al., 2009)

Using mathematical equations, that are beyond the purposes of this review, strain curves can be produced reflecting strain across the cardiac cycle and different strain values can be obtained at clinically relevant times, such as systole and diastole.

Strain rate expresses the velocity that deformation occurs, and is calculated as the derivative of strain to time ε(t)=dε(t)/d(t). (Voigt et al., 2015) Initially myocardial deformation imaging became possible using tissue Doppler. Myocardial speckle tracking imaging with 2D echocardiography is nowadays a new method for evaluating strain that is gaining more and more attention. Two-dimensional strain uses images from standard two-dimensional

echocardiography by speckle tracking, which is less angle dependent and more reproducible than conventional Doppler-derived strain. (Dandel et al., 2009)



Direction of motion (Anderson,Beginner's guide to strain-2018)

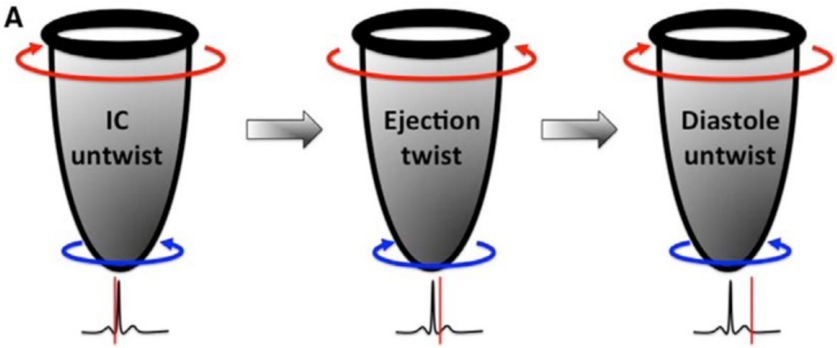
The previous definitions are useful for defining strain and strain rate along a certain myocardial line, during each selected point of the cardiac cycle. Segmental and global strain values offer additional information.(Voigt et al., 2015) The LV myocardium consists of an epicardial layer, an endocardial layer and between the two a mid ventricular layer. Contraction of these layers, results in shortening of the myocadium circumferentially and longitudinally and thickening in the radial direction. Speckle tracking echocardiography offers the means to evaluate these deformations and therefore a better analysis of systolic function than ejection fraction. Speckle tracking echocardiography can be performed offline on two-dimensional echocardiographic data by tracking myocardial 'features' throughout the cardiac cycle. LV GLS is calculated from four-chamber, three-chamber and two-chamber apical views, whereas LV global circumferential strain and LV global radial strain are computed from short-axis images. LV GLS is the most studied measurement since it is more reproducible, given that long axis and four chamber images have not only better resolution, but also include more myocardial tissue than short axis images. Therefore, GLS is the most clinically applicable measurement. (Abou et al., 2020)

Peak GLS describes the relative length change of the LV myocardium between end-diastole and end-systole: GLS(%) = (MLs − MLd)/MLd, where ML is myocardial length at end-systole (MLs) and end-diastole (Mld). Because MLs is smaller than MLd, peak GLS is a negative number.(Rajdeep S.Khattar, n.d.) In a large meta-analysis including more than 2500 healthy subjects aged between 36-58 the normal values of LV GLS was identified between –15.9% to –22.1% (mean 19.7%, 95% CI −20.4% to −18.9%).(Yingchoncharoen et al., 2013) Because GLS is typically influenced by age, sex, and LV loading conditions and heart rate, defining abnormal GLS might be challenging. However, in adults, GLS <16% is abnormal, GLS >18% is normal, and GLS 16% to 18% is borderline, according to American college of cardiology. (GLS is expressed as a negative number.)

The applications of GLS, which is gaining more and more acknowledgement from the scientific community, include identification of left ventricular hypertrophy aetiologies, coronary artery disease, LV systolic dysfunction and heart failure, cardio-oncology and valvular heart disease. Numerous studies are being conducted using strain imaging in the evaluation of the athlete 's heart, most of which suggest that the athletes heart does not induce reduction in longitudinal strain and hence, when observed, it should not be

considered as a normal adaptation. (Lang et al., 2015). Global longitudinal strain is not necessary to complete an echocardiographic study in athletes. However, there are special circumstances where that might prove useful, such as identification of pre-clinical anomalies useful to the differential diagnosis between athlete's heart and early DCM or HCM and characterization of regional wall motion abnormalities of the left and right ventricle.

Other aspects of left ventricular systolic mechanics are also being more and more evaluated to assess left ventricular function. Left ventricular rotation or twist represents a circular movement around the center of the left ventricle in the left ventricular short-axis image and is defined as the peak difference in systolic rotations of the LV apex and base as viewed from the apex. Looking from the apex towards the base, positive values identify counterclockwise rotation and negative values clockwise rotation. For the evaluation of LV rotation, images are obtained from the short axis of the LV at the level of the base, the mitral valve leaflets and the apex.



Temporal Sequence of left ventricular twist (LVT).
Relative rotation of LV base (red curved arrow), and apex (blue curved arrow) during isovolumic contraction, ejection, and isovolumic relaxation and early diastole. (Alaa Mabrouk Salem Omar, MD, PhD, Sharath Vallabhajosyula, MD, MS, n.d.)

These parameters provide with additional data that aid the functional evaluation of the left ventricle. In the athletic population strain and rotational mechanics, are an additional criterion that can be used to differentiate pathologic (hypertrophic cardiomyopathy, hypertension) from physiologic hypertrophy (exercise). Therefore, these methods are gaining more and more attention in the study of the athlete's heart. However, apart from GLS, other parameters are not widely applicable in the ealuation of the athlete's heart in clinical practice, and mostly apply for study purposes.

In a study encompassing 370 endurance athletes and 280 power athletes using speckle tracking echocardiography. Showed that both regional and global myocardial deformation measurements were comparable between the two groups. In particular, 90% of athletes showed LV GLS <- 16%. By multiple linear regression models, LV GLS was independently correlated to the sum of wall thicknesses ($r = 0.65$, $P < .0001$). Therefore, LV hypertrophy, mostly developed in response to pressure overload, results in enhancement of myocardial systolic function, that can manage increases in systolic blood pressure more efficiently.(Antonello D'Andrea, Cocchia, Riegler, Scarafile, Salerno, Gravino, Golia, et al., 2010)

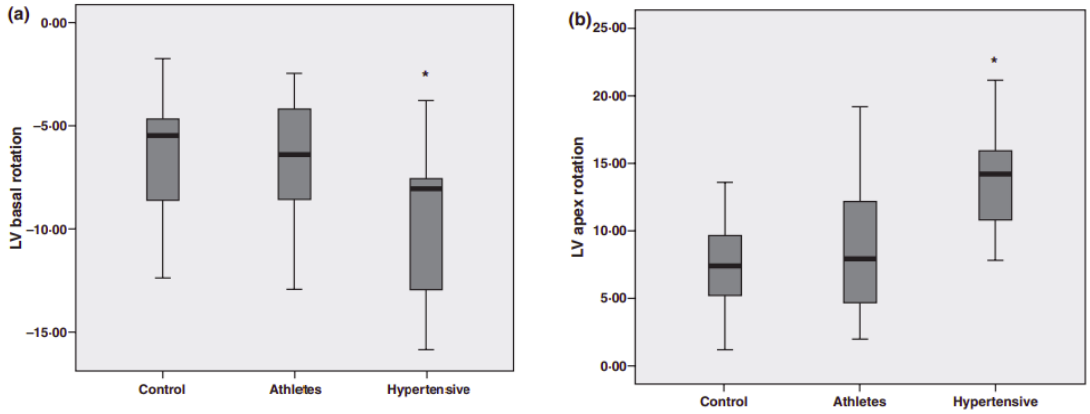
Longitudinal 2DSE assessment of IVS, LV lateral wall, and LV GLS
(Antonello D'Andrea, Cocchia, Riegler, Scarafile, Salerno, Gravino, Golia, et al., 2010)

Variable	Overall (n = 650)	Endurance (n = 370)	Strength (n = 280)	P
Mean 2DSE IVS peak (%)	−17.2 ± 3.3 (13 to 20)	−16.2 ± 3.2 (13 to 18)	−17.8 ± 4.8 (14 to 20)	NS
Mean 2DSE lateral wall peak (%)	−17.5 ± 3.6 (14 to 22)	−16.9 ± 3.4 (14 to 19)	−18.3 ± 3.5 (15 to 22)	NS
LV GLS (%)	−17.5 ± 3.5 (15 to 22)	−17.2 ± 3.1 (15 to 19)	−18.6 ± 3.7 (17 to 22)	NS

Data are expressed as mean ± SD (range).
IVS, Interventricular septum.

2D strain and strain rate analysis was used to differentiate pathological (hypertrophic cardiomyopathy) from physiological (exercise induced) left ventricular hypertrophy, in a study conducted by Butz et al. After studying 15 patients with hypertrophic cardiomyopathy , 20 elite athletes, and a control group of 18 sedentary normal subjects, they concluded that global longitudinal strain and regional peak systolic strain was vastly reduced in pts with hypertrophic cardiomyopathy (GLS: -8.1 ± 3.8%), as opposed to sedentary controls (-16.0 ± 2.8%) and elite athletes (-15.2 ± 3.6%). A value of less than -10% had 80% sensitivity and 95% specificity to detect hypertrophic cardiomyopathy. Therefore, global and regional strain can be used to assess pathology from normal adaptation of the LV in terms of hypertrophy.(Butz et al., 2011)

Similar was the study of Cappelli et al, that tried to differentiate left ventricle hypertrophy as a normal mechanism of adaptation in exercise versus pathological hypertrophy induced by essential hypertension. Hypertensive patients presented with higher apex circumferential strain, higher degree of rotation and torsion and lower LV longitudinal strain. LV basal circumferential strain did not differ considerably. Athletes and sedentary subjects were not different in terms of systolic function. The increase in torsion in hypertensive patients was considered to be a result of subendocardial fibrosis, leading to a slight reduction in subendocardial contractile function. Therefore, the increase in torsion serves as an adaptive mechanism of the heart to compensate for abnormalities in systolic and diastolic function and avoid reduction in left ventricular output.(Cappelli et al., 2010)



LV basal (a) and LV apical (b) rotation in athletes, hypertensives and controls(Cappelli et al., 2010)

Weiner et al conducted a longitudinal study for a 90 day period of training in university rowers and examined left ventricular twist mechanics before and after that period of training. Eccentric hypertrophy of the left ventricle was exhibited by the athletes, who also displayed a noticeable increase in peak systolic apical rotation (8.9 ± 4.2° vs. 12.7 ± 3.9°, p = 0.002), while basal rotation remained unchanged. These findings are in accordance with the findings between athletes and sedentary healthy controls in the previously mentioned study of Cappelli et al. These values also suggested a substantial increase in peak systolic left ventricular torsion (14.1 ± 5.0° vs. 18.0 ± 3.6°, p = 0.002) after the exercise period, that also expands to diastole, since peak early diastolic untwisting rate (-110.6 ± 41.8°/s vs. -148.0 ± 29.8°/s, p = 0.003) and untwisting percentage during isovolumic relaxation (31.2 ± 12.0% vs. 39.9 ± 14.9%, p = 0.04) increased. Therefore, left ventricular torsion and peak early diastolic untwisting rate can be used to assess exercise induced remodeling.(Weiner et al., 2010)

A study conducted in 200 olympic athletes using 2D speckle tracking echocardiography, stated that athletes and sedentary subjects had similar strain results. Global longditunional strain in athletes did not differ much from previous studies in athletes, and it was found comparable but quite lower than sedentary subjects (-18.1 ± 2.2% in athletes vs -19.4 ± 2.3% in controls, P < .001). This finding was irrespective of type of sport practiced. Compared to GLS in patients with abnormal LVH, strain was immensely higher. Systolic strain rate was also lower in athletes (-1.00 ± 0.15 vs -1.11 ± 0.15 sec(-1), P < .001). Normal values for GLS in athletes were -15% to -22% and for systolic strain rate, normal values were -0.8 and -1.2 sec(-1). Athletes exhibit notable geometric left ventricular changes, however, deformation seems to be normal but slightly lower than sedentary subjects, which however does not constitute reduced systolic function in athletes. These results are similar to those of (Kansal et al., 2011) who also portrayed a slight reduction in GLS (negligible at the endocardial level and significant at the epicardial layer) in professional football players. Both of these studies sugest a limit of <15% in global longitudinal strain to depict pathologic hypertrophy (sensitivity, 79% / specificity, 67%). Early diastolic strain rate (SRE) and late diastolic strain rate (SRA)were also calculated. Early diastolic strain rate was similar between groups (1.45 ± 0.32 vs 1.51 ± 0.35 sec(-1), P = .277), although late diastolic strain rate was slihtly lower in athletes (0.67 ± 0.25 vs 0.81 ± 0.20 sec(-1), P < .001). Endurance sport participants presented with the lowest values of Both SRE (1.37 ± 0.30 sec(-1), P < .001) and SRA (0.62 ± 0.23 sec(-1), P < .001).(Caselli, Montesanti, et al., 2015)

Strain and strain rate parameters in controls and trained athletes(Caselli, Montesanti, et al., 2015)

Parameter	Controls	Athletes
GLS (%)	−19.4 ± 2.3 (−16, −23)	−18.1 ± 2.2 (−15, −22)
SRS (sec^{-1})	−1.11 ± 0.15 (−0.9, −1.4)	−1.00 ± 0.15 (−0.8, −1.2)
SRE (sec^{-1})	1.51 ± 0.35 (1.00, 2.10)	1.45 ± 0.32 (1.00, 2.00)
SRA (sec^{-1})	0.81 ± 0.20 (0.50, 1.20)	0.67 ± 0.25 (0.30, 1.20)

p value GLS <0,01, SRS <0,01, SRE 0,277, SRA ,001

A systematic review and meta-analysis by Beaumont et al. evaluated the effect of different kinds of sports on strain and twist mechanics of the LV during the course of ageing of older athletes and controls and concluded that there was no difference in these

aspects between athletes and non athletes. However one can observe subtle differences in twist mechanics when athletes are categorized in respect to the sport discipline they practice. Elite endurance athletes presented with smaller degrees of left ventricular twist and apical rotation than sedentary subjects (d = 0.68, 95% CI 0.19-1.16, p < 0.01; d = 0.64, 95% CI 0.27-1.00, p = 0.001, accordingly), while elite resistance athletes had increased left ventricular twist (d = -0.76, 95% confidence interval [CI] -1.32 to -0.20; p < 0.01)and peak untwisting velocity (d = -0.43, 95% CI -0.84 to -0.03; p < 0.05) than sedentary subjects. Sedentary subjects, also tend to have lower untwisting rates than athletes. Global longitudinal strain was not significantly altered between athletes and controls, hence it is reasonable to assume that it is not affected by training, and can be used as a differentiation criterion between normal and abnormal remodeling in athletes. The fact that GLS remained unchanged in athletes can prove that exercise does not alter GLS, at least at rest. GLS has shown limited augmentation during exercise, in other studies (Balmain et al., 2016) whereas other myocardial STE parameters (i.e., circumferential strain, LV twist mechanics) may be more useful to evaluate myocardial function during effort.(A. Beaumont et al., 2017)

In a study conducted in twenty-two marathon runners, 24 wrestlers, and 20 healthy sedentary individuals using speckle tracking echocardiography with normal ranges of EF in all study groups, LV longitudinal strain (S), LV longitudinal strain rate systolic (SRS), LV longitudinal strain rate diastolic early filling (SRE), and longitudinal strain rate diastolic late filling (SRA) were evaluated by apical two-, three-, and four-chamber gray scale imaging using the global longitudinal strain (GLS) and GLS rate (GLSR). Strain, longitudinal strain rate systolic and GLS, were significantly increased in both the marathon runners and wrestlers compared with controls. (P < 0.05). The normalized GLS values in each group were similar and there was a significant relationship between normalized GLS values and EDVs in marathon runners and wrestlers (r: 0.41 for marathon runners, P < 0.01; r: 0.36 for wrestlers, P < 0.05). In this study, the significant increase in systolic S and SR values in the athletes was attributed to normal adaptations to exercise.(Simsek et al., 2013)

Comparison of longitudinal and global strain and strain rate parameters of the athletes and controls.(Simsek et al., 2013)

Variables	Group I (Marathon Runners)	Group II (Wrestlers)	Group III (Control)	P-Value
S-4C, %	−21.4 ± 2.6*	−21.7 ± 2*	−17.2 ± 2.3	**<0.001**
S-3C, %	−22.2 ± 2.9*	−21.1 ± 2.2*	−19.1 ± 2.1	**<0.001**
S-2C, %	−23.3 ± 2.8*	−22.7 ± 2.6*	−19.4 ± 2.7	**<0.001**
GLS, %	−22.3 ± 2.2*	−21.8 ± 1.7*	−18.5 ± 2.4	**0.001**
Normalized GLS	0.163 ± 0.06	0.173 ± 0.07	0.159 ± 0.06	0.062
SRS-4C, 1/sec	−1.18 ± 0.19*	−1.14 ± 0.18*	−0.99 ± 0.18	**0.005**
SRS-3C, 1/sec	−1.27 ± 0.22*	−1.10 ± 0.15*	−1.10 ± 0.18	**0.004**
SRS-2C, 1/sec	−1.25 ± 0.18*	−1.20 ± 0.19*	−1.04 ± 0.19	**0.001**
GLSRS, 1/sec	−1.22 ± 0.15*	−1.15 ± 0.13*	−1.06 ± 0.13	**0.004**
SRE-4C, 1/sec	1.96 ± 0.53	1.91 ± 0.48	1.84 ± 0.26	0.68
SRE-3C, 1/sec	2.06 ± 0.46	1.84 ± 0.41	1.81 ± 0.19	0.058
SRE-2C, 1/sec	2.05 ± 0.37	1.87 ± 0.38	1.87 ± 0.24	0.136
GLSRE, 1/sec	2.02 ± 0.45	1.87 ± 0.43	1.85 ± 0.23	0.096
SRA-4C, 1/sec	0.66 ± 0.18	0.76 ± 0.18	0.69 ± 0.17	0.085
SRA-3C, 1/sec	0.68 ± 0.15	0.77 ± 0.15	0.76 ± 0.16	0.259
SRA-2C, 1/sec	0.68 ± 0.14	0.77 ± 0.22†	0.77 ± 0.19†	**0.0068**
GLSRA, 1/sec	0.67 ± 0.16	0.77 ± 0.19†	0.74 ± 0.18†	0.055

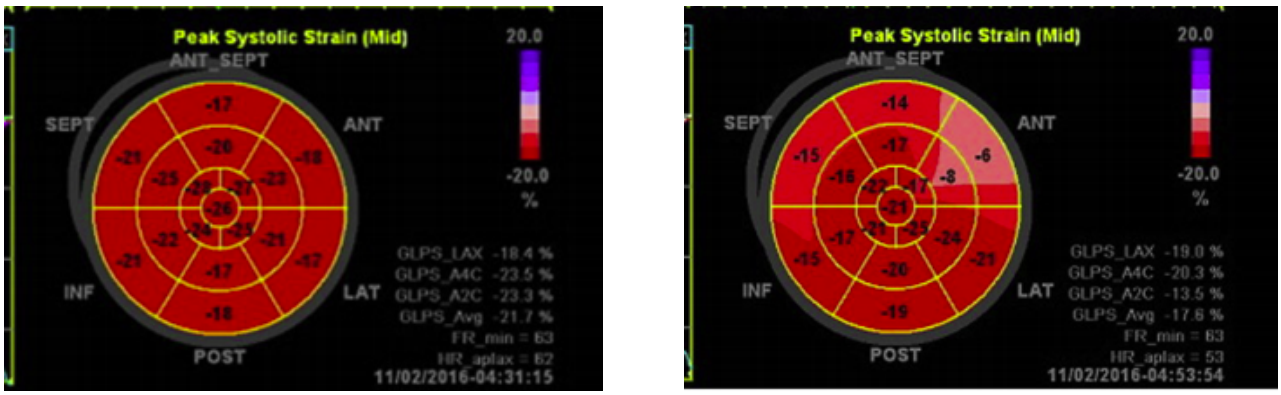
S = longitudinal strain; 4C-3C-2C = apical four-, three-, and two-chamber views; GLS = global longitudinal strain; SRS = systolic longitudinal strain rate; SRE = early diastolic strain rate; SRA = late diastolic strain rate; GLSR = global longitudinal strain rate. Bold indicates statistically significant values.

A recent study evaluated the basal rotation (BR) index, the basal circumferential strain (BCS) index, and the global longitudinal strain (GLS) of the left ventricle in male athletes with physiological cardiac hypertrophy (group A), and athletes (group B) and non-athletes without hypertrophy (control). Athletes with normal LVH exhibited less basal rotation at rest than the two other groups. After physical effort, basal rotation remained unchanged between groups, however left ventricle hypertrophy and physical effort combined had an effect on basal rotation and basal circumferential strain. The group with physiologic left ventricular hypertrophy exhibited increased BCS and decreased GLS after exercise compared to the control group. There was no substantial difference between Left ventricular basal rotation and longitudinal and circumferential strain before and after physical effort in subjects with prominent myocardial hypertrophy. It stands to reason to suggest that basal rotation and circumferential strain might be useful to assess myocardial dysfunction induced by physical effort in individuals with left ventricle hypertrophy, normal or abnormal. (Żebrowska et al., 2019)

Basal rotation absolute value (BR) and relative changes of basal circumferential strain (BCS) and GLS at Rest and Post-Ex and the dynamics of changes (Δ) in the athletes with LVH, athletes without left ventricle hypertrophy (non-LVH) and untrained CG.(Żebrowska et al., 2019)

Indicator	CG			Non-LVH			LVH		
	Rest	Post-Ex	Δ	Rest	Post-Ex	Δ	Rest	Post-Ex	Δ
Basal rotation (BR) (°)	−7.09 (2.86)	−5.63 (2.30)	1.47 (3.96)	−6.84 (2.12)	−6.09 (3.18)	0.76 (1.69)	−2.11 (0.60) *#	−2.02 (0.51) *#	0.69 (2.36)
Basal circumferential strain (BCS) (%)	−19.75 (4.28)	−13.21 (2.82)	6.55 (3.59)	−15.91 (1.96)	−15.24 (5.28)	0.67 (4.47)	−15.47 (3.52)	−15.93 (1.94) *	0.46 (4.60)
Global longitudinal strain (GLS) (%)	−19.54 (5.88)	−20.42 (0.96)	−0.88 (1.72)	−19.45 (2.73)	−17.82 (2.75)	1.64 (0.29)	−14.97 (4.75)	−14.54 (2.64) *#	0.43 (1.57)

Another interesting study evaluated marathon runners pre and post marathon using speckle tracking echocardiography. Pre marathon measurements were taken before the training period and post marathon measurements, into 10 days after the run. Apart from the increase in LV end diastolic volume and LV mass, LV global longitunional strain (-19.3 ± 2.71% before marathon vs -16.5 ± 4.6%, post marathon, p = 0.003) was decreased as well as circumferential strain (-17.2 ± 2.41% pre marathon vs -15.2 ± 2.6% post marathon, p = 0.001).



Peak mid systolic strain pre-marathon (GLS: -21.7%) (left image) and post-marathon (GLS: -17,6%) (right image) (Sengupta et al., 2018)

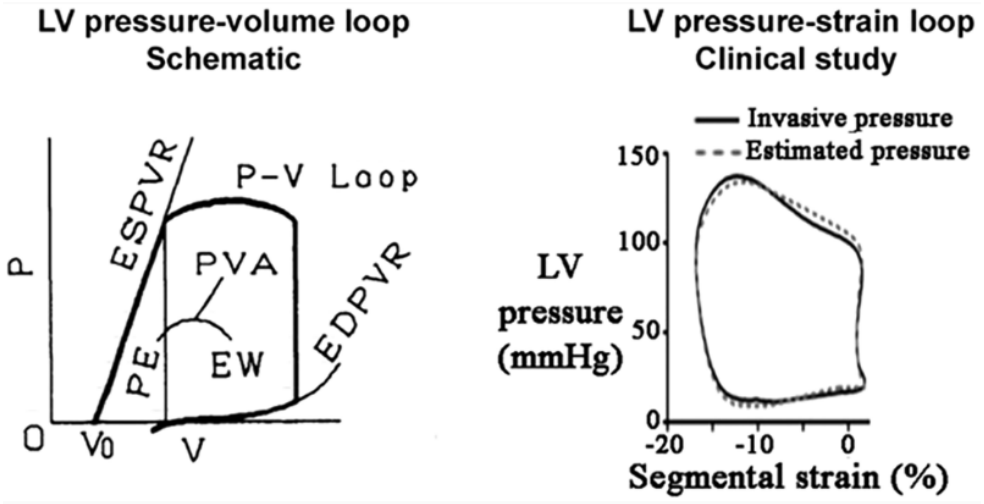
This result is different from the previous study and might be due to the excessive myocardial fatigue experienced with marathon running in recreational runners, which was also accompanied in this study by an increase in NT-proBNP, a value which was not evaluated in the previous study. Radial strain, however, remained unchanged. Moreover a reduction in E transmitral velocity was observed,suggesting a mild impairment in mitral filling which might be correlated to the reduction in circumferential strain, since circumferential relaxation properties play an important role in early diastolic filling.(S. P. Sengupta et al., 2018)

2.2.4 MYOCARDIAL WORK

Assessment of myocardial systolic function has long been evaluated by ejection fraction and due to its many limitations, more recently GLS has been gaining more and more attention, since it gives additional information to EF in terms of subtle systolic dysfunction. However both of these methods share a common disadvantage: they are load dependent. (Boe et al., 2019)

Left ventricular pressure–volume analysis incorporates the load of the left ventricle and as experimental studies have shown, can evaluate left ventricular function in an effective manner. Furthermore, the pressure–volume loop area is an indicator of myocardial O2-consumption. As with pressure–volume curves, LV pressure–strain curves can also be used in the evaluation of regional LV function and segmental work. The following images present how pressure-volume curves can be used to export myocardial work,and how left ventricular systolic function and segmental work can be assessed from pressure-strain curves.(Boe et al., 2019)

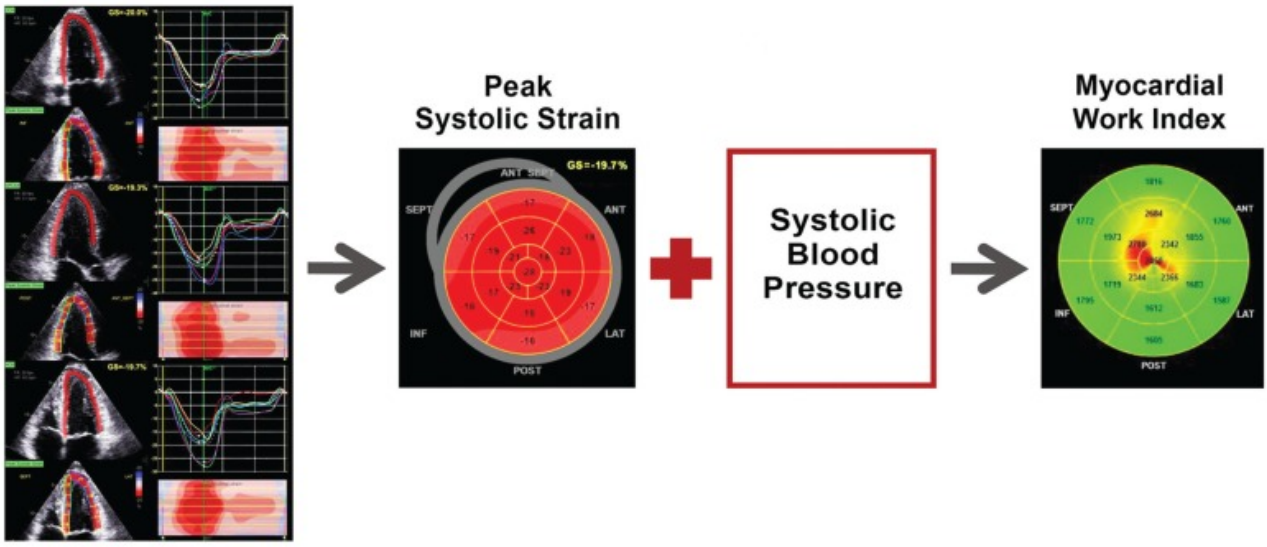
Pressure volume and pressure strain loops
Left panel: the pressure-volume aeria (PVA) defined by end-diastolic and end-systolic pressure-volume relationship curves is the sum of potential energy (PE) and external work (EW). P for pressure; V for volume; V0 for unstressed LV volume. (Suga, 1990)
Right panel: LV pressure–strain loops from a patient with cardiomyopathy. The continuous line shows LV pressure measured by high-fidelity micromanometer and the dotted line represents LV pressure estimated by echocardiography. The area of the LV pressure–strain loop reflects segmental work. (Russell et al., 2012)



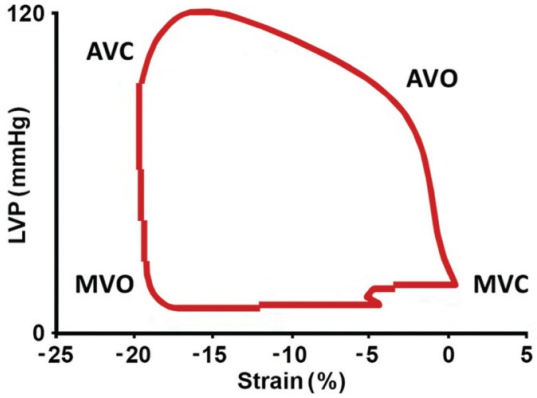
The main feature of myocardial work which transcends it from left ventricular ejection fraction and global longitudinal strain is that it incorporates LV pressure, a factor to which both of these previous methods are dependent on.(Boe et al., 2019)

Normally, all segments of the heart contract and relax in a symmetrical fashion assisting in the creation of a sufficient stroke volume. Each segmental work contribution to systole is called constructive work. However, if there is dyssynchrony in left ventricular contraction, such as in coronary artery disease or bundle branch block, there might be systolic lengthening. In that case, the different segments compensate for this systolic lengthening, and that is ‘wasted work’, since it does not contribute to ejection. Apart from systolic lengthening, myocardial shortening after aortic valve closure, at the isovolumic relaxation time, (post-systolic shortening) is defined as wasted work since it does not contribute to LV ejection either. ‘Myocardial work efficiency’ is calculated as the ratio between constructive work and the sum of wasted and constructive work, reported in percentage or just as the ratio with 1 as the maximum. In the normal heart, wasted work is minimal and as a result efficiency is maximal. (Boe et al., 2019) Left ventricular myocardial work efficiency, is a marker that portrays the capacity of utilizing mechanical energy throughout the cardiac cycle. Global LV myocardial work efficiency is evaluated by using blood pressure measurements and speckle tracking derived strain analysis incorporated in pressure-strain loops. ‘Myocardial work index’ is the area under curve that arises from these data and represents the amount of myocardial work performed by the left ventricle during systole. This novel echocardiographic technique seems very promising in the evaluation of cardiac stress in athletes and is being accepted with more and more enthusiasm in the field of exercise echocardioraphy, however studies are yet limited.

Creation of myocardial work bull’s-eye plot. Peak global longitudinal strain is derived from 3 high-quality apical views of the myocardium.



The bull’s-eye plot of peak systolic strain is sensitive to afterload. Using noninvasive systolic blood pressure from cuff measurements,to compensate for the invasively calculated systemic left ventricular pressure, a second bull’s-eye plot of myocardial work is created (right panel). Myocardial work based on blood pressure and global longitudinal strain is calculated from a complex algorithm within ultrasound machine software, which is beyond the purposes of this review(S. Sengupta et al., 2020)



Creation of myocardial work pressure strain loops. Peak global longditutional strain and after load (systolic blood pressure) are used to generate a pressure strain loop similar to a pressure volume loop of the left ventricle. The area under the curve represents total myocardial work. (S. Sengupta et al., 2020)

A study encompassing myocardial work that was performed by Antonello D' Andrea et al. in 350 endurance athletes and 150 sedentary healthy controls is the largest study so far using myocardial work. Ejection fraction measurements were comparable between the two groups, as previous studies have demonstrated and left ventricular global longditutional strain at rest was lower in endurance athletes [-21- (-15.8)% versus -25.7-(-19.1)% in controls; $p < 0.01$]. Myocardial work efficiency was comparable among athletes and non athletes. When multivariable analysis was performed on myocardial work efficiency at rest, there was statistically significant relation between MWE and maximal watts reached ($p < 0.0001$), peak VO2, ($p < 0.0001$), left ventricular E/e' ($p < 0.001$) at peak effort. Myocardial work efficiency is less dependent on preload and afterload conditions than global longitudinal strain, since an increase in preload or afterload can lead to lower strain but MWE remains unaltered or even increased. The fact that myocardial work presents normal values at rest in endurance athletes deflects a normal type of remodeling and an increased exercise capacity. Moreover, myocardial work efficiency is an independent factor to predict considerable cardiac reserve during exercise. Global work index was calculated during follow up of patients and quantified global function according to systolic blood pressure, a useful measurement that can be applied to athletes with different blood pressure measurements or load conditions from visit to visit. Therefore, myocardial work can be used to evaluate whether remodeling is physiological at an early stage during baseline echocardiographic evaluation. (Antonello D'Andrea et al., 2020)

Another even more recent study in asian athletes of non competitive level, used echocardiography to evaluate cardiac structure and function 48 hours before, 2 and 72 hours after completing the marathon. Results showed that although global longditutional strain was reduced post marathon in all athletes, global work index was unchanged in 11 athletes and increased in 13 athletes. The athletes who showed increased GWI also presented with increased heart rate, lower left ventricular volumes and increased BNP levels implying that the difference observed in myocardial work expresses a difference in myocardial stress. Later on, both groups returned to normal values, however there is implication of myocardial fatigue in patients with increased work, but further studies need to be performed to evaluate its long term clinical significance (S. Sengupta et al., 2020)

A very recent study encompassing 30 elite swimmers and 23 healthy sedentary controls evaluated Global MW index (GMWI) and constructive MW index (CMWI) using a

vendor-specific module of evaluation of GLS by speckle-tracking echocardiography and LV pressure curves estimated from brachial cuff systolic pressure. A concomitant 18-rat model with induced LV hypertrophy by swim training was also used with evaluation of GLS and LV pressure curves derived from invasive analysis compaired to 17 untrained rat controls. The results showed decreased GLS in human athletes (athletes vs. controls: −18±2 vs. −19±1, $p<0.05$)with higher values of CMWI (2097±293 vs. 1943±213 mmHg%, $p<0.05$), and preserved GMWI compared to controls (1850±299 vs. 1755±189 mmHg%, p=NS). The trained group of rats was characterized by unchanged GLS (−22±3 vs. −20±4, p=NS), however, end systolic pressure-volume relationship, GMWI, and CMWI were increased (3.64±0.70 vs. 2.55±0.38 mmHg/μL, $p<0.001$; 3002±488 vs. 2554±375 mmHg %, $p<0.05$; 3200±532 vs. 2780±591 mmHg%, $p<0.05$) compared to control rats. Myocardial work indexes were related to cardiac contractility, as was evaluated by Pressure-Volume analysis (ESPVR vs. GMWI $r=0.38$, $p<0.05$; vs. CMWI $r=0.39$, $p<0.05$). Despite the reduction in GLS in trained humans global myocardial work index was sustained and constructive myocardial work index was increased. The experimental model of rats confirmed that these alterations were related to left venticular contractility, therefore, myocardial work seems to transcend GLS in the evaluation of systolic function in athletes. .(Tokodi et al., 2020)

2.3 THE LEFT ATRIUM

The left atrium is affected by excessive exercise in terms of geometry and function in the same manner as the left ventricle does. Increase in LA dimensions and volumes is considered to be a feature of diastolic function in the general population since it enlarges as a compensatory mechanism to reduced LV compliance. In fact, LAVi>34ml/m2 is considered to be one of the diagnostic features of diastolic dysfunction. LA enlargement in highly trained athletes, however, is perceived as a normal adaptation to exercise due to elevated preload and not a consequence of increased LV filling pressures secondary to diastolic dysfunction, and this feature has been shown in a variety of studies. (Cesare Cuspidi et al., 2019)

Evaluation of the left atrium involves LA linear dimensions and LA volume. LA size should be measured during its largest possible dimension, at end- systole. In terms of linear measurements, the most widely used dimension is the LA anteroposterior (AP) measurement in the parasternal long-axis view. For more objective measurements of size and remodeling of the left atrium, LA volume measurements are needed, since it gives information of alterations of LA volume in all directions. The biplane method of discs, or the area-length technique are the currently 2D methods for acquiring those measurements. The upper normal limit for 2D echocardiographic LA volume is 34 mL/m2 for both genders. (Lang et al., 2015)

A study that included 1777 competitive athletes detected an antero-posterior diameter above ≥40 mm in 18% of participants and >45 mm) in 2%, and these findings

were in accordance with dilation of the left ventricle in those athletes, suggesting a physiological phenomenon, and establishing the upper limit of left atrial measurements in female athletes at 45mm and 50mm in male athletes(linear method). (Antonio Pelliccia et al., 2005) In this study, AF and other supraventricular tachyarrhythmias were uncommon (prevalence <1%), similar to that of the general population. As far as the LAVi dimension measurements are concerned, which is widely accepted as a more objective measurement, a recent study by D' Andrea and Riegler (Antonello D'Andrea, Riegler, et al., 2010) found mild enlargement of 29-33ml/m2 in 24% and moderate enlargement >34ml/m2 in 3,2% of 615 trained athletes. Enlarged atriums were all found in male athletes. The upper limit of LA enlargement was 36 ml/m2.

Training modality and duration of training are the dominant independent predictive factors of LAVi, with endurance athletes presenting with the highest LA indexes, a finding which is in accordance with left ventricular enlargement. Moreover, LAVi measurements were highest in endurance athletes, suggesting that the enlargement of the LA comes along with enlargement of all cardiac chambers. Nistri et al. conducted a study in which LA dimensions were compared between athletes and non athletes, and concluded that 67% of athletes had a LAVi >34ml/m2, in whom LV end diastolic volume index and LV mass were also enlarged accordingly whereas in sedentary subjects increased LA indexes were determined by their body mass index and their E/A ratio.(Nistri et al., 2011)

As far as LA function is concerned, a study conducted by D'Andrea and collegues (A D'Andrea et al., 2008), comparing LA strain in athletes, non athletes and hypertensives, found that strain, and therefore function, is normal in athletes. Atrial longitudinal strain was performed from the apical four and two chamber views for the basal segment of LA septum, lateral wall and roof. In patients with pathological LV hypertrophy (hypertensives) LA peak systolic strain was markedly reduced compared to athletes and sedentary subjects, and the major determinants for this was LV end diastolic volume and LV mass, same as for LAVi in the Nistri et al study. However, in hypertensives, later wall peak systolic strain was adversely correlated with LV mass and circumferential end-systolic stress. In patients with LVH (athletes and hypertensives) LA diameter and maximum volume were increased in a comparable manner. LA active emptying volume and fraction were both higher in patients with hypertension. LA lateral wall systolic strain was an independent predictor of maximum workload during exercise in all subjects with LVH. ($p<0.0001$).(A D'Andrea et al., 2008). All in all, it is safe to suggest that as with other adaptations of cardiac chambers to exercise, LA enlargement is normal in athletes compared to sedentary subjects and hypertensive patients of the same age.

In another study, conducted in 114 international-level rowers, who underwent a cardio-pulmonary exercise test and resting transthoracic echocardiography, including two dimensional speckle tracking, mild, moderate and severe left atrial enlargement was present in 27.2°%, 11.4% and 4.4% athletes, accordingly. Left atrial volume index and maximal aerobic capacity were strongly related ($R > 0.3$; $p < 0.001$). Atrial diameters, left ventricle hypertrophy and left ventricle filling pressure were not related to left atrial strain measurements. Hence, the study concludes, that left atrial enlargement is an a normal adaptation to endurance sports athletes, and should be considered as another aspect of the athlete;s heart.(Król et al., 2016)

Atrial size parameters and cardiopulmonary test results in the examined group of rowers (Król et al., 2016)

	All (N = 114) Mean ± SD	Women (n = 53) Mean ± SD	Men (n = 61) Mean ± SD	*p*
LA (cm)	3.65 ± 0.40	3.50 ± 0.3	3.77 ± 0.44	<0.001
LAA (cm^2)	22.6 ±3.4	20.1 ±2.6	24.0 ± 3.4	<0.001
RAA (cm^2)	18.0 ± 3.1	16.6 ± 2.7	19.3 ± 2.8	<0.001
LA/BSA (cm/m^2)	1.90 ± 0.20	1.95 ± 0.17	1.86 ± 0.22	0.02
RAA/BSA (cm^2/m^2)	9.35 ± 1.4	9.20 ±1.53	9.48 ± 1.27	NS
LAA/BSA (cm^2/m^2)	11.7 ± 1.6	11.7 ± 1.5	11.8 ±1.6	NS
LAV (cm^3)	66.3 ± 15.3	57.5 ± 11	73.9 ± 14.5	<0.001
LAVI (cm^3/m^2)	34.3 ± 6.9	31.9 ±6.1	36.3 ± 6.9	<0.001
VO_{2max} (l/min)	4.20 ± 0.9	3.36 ± 0.4	4.94 ± 0.6	<0,001
VO_{2max} (ml/kg/min)	56.4 ±8.2	49.9 ± 5.1	62,1 ± 5.8	<0,001
HR_{max} (/min)	195 ±8.2	194 ± 7.6	195 ± 8.7	NS

In a systematic review and metanalysis by Cuspidi et al.(Cesare Cuspidi et al., 2019) including 16 studies LA dimensions were calculated between 2425 elite athletes and 720 controls average LAV indexed to BSA (LAVI) was 37% higher in athletes than in nonathletic controls (31.0 ± 1.4 mL/m2 vs 22.2 ± 0.9 mL/m2) the standard means difference (SMD) being 1.12 ± 0.13 (CI: 0.86-1.89, P < 0.0001). SMD in high-dynamic/high-static trained athletes was increased (1.78 ± 0.24, CI: 1.30-2.20, P < 0.001) than in high-dynamic/low-static trained athletes 1.00 ± 0.16, CI: 0.70-1.30, P < 0.001).Highly trained individuals present with increased left atrial volume index, while increase in dimensions (antero posterior diameter) of the left atrium alone is a more prominent finding in high dynamic and high static training modalities.

Increased atrial dimensions are generally related to increased incidence of atrial fibrillation. This correlation in athletes seems to be controversial. Pelicia et al,(Antonio Pelliccia et al., 2005) did not find an increased incidence of AF in athletes. On the other hand, a recent meta-analysis with a total of 9113 subjects showed that AF had an increased prevalence among athletes, which was more pronounced with age.(OR = 1.64; CI: 1.10-2.43)(Ayinde et al., 2018) All in all, in the athlete's heart increased dimensions of the left atrium are a result of increased functional performance at exercise. All in all, in the athlete's heart, increased dimensions of the left atrium are a result of increased functional performance at exercise, however, association with increased risk of development of pathology, such as AF, cannot be excluded.

2.4. AORTIC ROOT

When discussing the adaptations of the heart to exercise training, the aortic root should be included. Increase in aortic root diameter due to chronic exercise can be expected as a result of chronic haemodynamic overload implied upon the left ventricle. The normal upper limit of aortic root in the general population is 40mm. Factors affecting aortic root dimensions include predominantly height and body size, but also age, sex, and blood pressure.(Antonio Pelliccia et al., 2012)

Aortic root dimensions in normal adults(Lang et al., 2015)

Aortic Root	Absolute values (cm)		Indexed values (cm/m^2)	
	Men	Women	Men	Women
Annulus	2.6 ± 0.3	2.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.1
Sinuses of Valsalva	3.4 ± 0.3	3.0 ± 0.3	1.7 ± 0.2	1.8 ± 0.2
Sinotubular junction	2.9 ± 0.3	2.6 ± 0.3	1.5 ± 0.2	1.5 ± 0.2
Proximal ascending aorta	3.0 ± 0.4	2.7 ± 0.4	1.5 ± 0.2	1.6 ± 0.3

With echocardiography, measurements of the aortic annulus should be made in the zoom mode in midsystole, when the annulus is slightly larger and rounder than in diastole, between the hinge points of the aortic valve leaflets from inner edge to inner edge. All other aortic measurements should be made at end-diastole, in a strictly perpendicular plane to that of the long axis of the aorta.(Lang et al., 2015)

Static and dynamic exercise have different pathophysiologic mechanisms which determine different effects upon the aortic root. Endurance exercise leads to increase in stroke volume and systolic blood pressure during training, while in strength exercise short periods of high intensity training leads to short periods of elevated cardiac output with increased activity of the sympathetic nervous system, leading to increases in blood pressure of up to 480/350mmHg.(MacDougall et al., 1992) Comparable with the pathophysiology of arterial hypertension, volume overload during prolonged endurance training and pressure overload during static training, can lead to aortic root dilatation.

In a review performed by (Antonio Pelliccia et al., 2012) the 99th percentile value of aortic root diameter (acquired form parasternal long-axis view) was 40 mm in males and 34 mm in females, correlating to the upper limits of accepted as physiologic aortic root dilatation in enlargement in athletes. 1,3% of men and 0,9% of women presented with values above these limits, which is a very small percentage. In these athletes with aortic root diameter >40mm, increased height and body surface area were also identified but none of these athletes met the criteria for the diagnosis of marfan syndrome and only one male had bicuspid aortic valve. Of interest is the fact that the most noteworthy increases in aortic dimensions in athletes are more prevalent in midlife, rather than younger age, where training is maximal, and that affects males to a grater degree than females, who might need serial follow up of aortic root.

A study by (Antonello D'Andrea, 2010) measured the aortic root dimensions of 615 elite athletes (370 endurance-trained athletes, 245 strengthtrained athletes) by echocardiography at end diastole. Measurements were taken at the level of the aortic annulus, the sinuses of Valsalva, the sinotubular junction, and the maximum diameter of the proximal ascending aorta.

Variable	Overall (n = 615)	Endurance (n = 370)	Strength (n = 245)
Aortic annulus (cm)	2.3 (1.8–2.8)	2.1 (1.8–2.4)	2.5 (2.2–2.8)
Sinuses of Valsalva (cm)	3.3 (2.8–4.2)	3.1 (2.8–3.6)	3.6 (3.2–4.2)
Supra-aortic ridge (cm)	3.1 (2.6–3.7)	2.9 (2.6–3.2)	3.3 (2.9–3.7)
Proximal ascending aorta (cm)	3.3 (2.8–3.9)	3.1 (2.8–3.4)	3.5 (3.1–3.9)

Echocardiographic aortic root diameters in athletes. P value <0.05 (D'Andrea, 2010)

Strength trained athletes presented with increased aortic root diameters, and this difference was more pronounced in men than women. However, when indexed to BSA,

these differences were extinguished. Male strength trained athletes who showed ascending aorta dilatation were only (1%). 21 athletes (3.4%) presented with mild aortic regurgitation. Body surface area ($p < 0.0001$), type ($p < 0.001$) and duration ($p < 0.01$) of training, and LV circumferential end-systolic stress ($p < 0.01$) were the only independent predictors of the aortic root diameter at all levels.

Although aortic root dilatation was more pronounced in strength trained athletes, due to the innate features of static exercise, it was unocommon in this study. Athletes with borderline values should undergo periodic assessment to exclude anuloartic ectasia in these young subjects.

A large meta-analysis of 23 observational studies (Iskandar & Thompson, 2013) found that weighted mean aortic root dimensions in men were 31.6 mm (95% confidence interval, 30.2–33.1) at the sinuses of Valsalva and 30.8 mm (95% confidence interval, 29.9–31.8) at the aortic valve annulus. Weighted mean aortic root dimension in elite female athletes at the sinuses of Valsalva was 25.1 mm. Using meta-regression analysis, pooled mean aortic root diameter at the sinuses of Valsalva was increased in athletes versus controls by 3.2 mm ($P=0.02$), whereas aortic root size at the aortic valve annulus was 1.6 mm ($P=0.04$) greater in athletes than in controls. Therefore, athletes present with increased aortic root diameters than sedentary subjects, but this increase, though statistically significant, is minor.

The presence of bicuspid aortic valve, is a known risk factor that can lead to aortic dilatation in the general population. In athletes with BAV, training does not seem to alter the rate of increase of aortic size. A study of 88 athletes with BAV who were assessed annually with echocardiography for a 5-year interval, suggested that the proximal ascending aorta increase rate was 0.98 mm/y,(Galanti et al., 2010) which is comparable to the general population with BAV (0.2–1.9 mm/year).(Tadros et al., 2009). Therefore, aortic root dilatation in athletes above the limit of 40mm is rare, and when encountered, it should be evaluated carefully since it is very unlikely that it is attributed to exercise alone. In patients with a tendency to pathology of the aortic root and a higher probability of rupture, such as Merfan’s syndrome, should avoid excessive exercise, of either static or dynamic components, since there might be an exacerbation of dilatation with exercise. (Antonello D’Andrea et al., 2017)

3.HYPERTENSIVE CARDIOMYOPATHY

3.1. PARAMETERS OF THE HYPERTENSIVE HEART

Before comparing the athlete's heart to hypertensive heart disease, a brief reminder of the parameters of the hypertensive heart is in order. Distinguishing the two entities might be challenging, however if the clinician is familiar with their aspects, their discrimination becomes clearer. Therefore, in the following chapter, the echocardiographic findings of hypertensive caridomyopathy will be reexamined, in order to aid its comparison with the althete's heart.

Systemic hypertension leads to haemodynamic overload resulting in left ventricular remodelling, as an adaptive mechanism of the heart. The Laplace law, T = ¼ P r/2h, where tension or stress in the LV wall (T) is directly related to LV pressure (P) and radius (r) and is inversely related to LV wall thickness (h) , can help explain these alterations. (Frohlich & Susic, 2012) Increased blood pressure over a sustained period of time impels stress upon the left ventricular wall and therefore increases the demand of the left ventricle for oxygen, resulting in an increase in LV wall stress, wall thickness and LV mass, by stimulating myocyte hypertrophy, collagen formation and fibroblasts, and thus remodeling of the myocardium with a disproportionate increase in fibrous tissue. Sooner or later, left ventricular compliance will be reduced, resulting in diastolic dysfunction. Apart from the above impacts of hypertension on LV structure and mass, other factors such as ethnicity, gender, neurohumoral, environmental and genetic factors also tend to affect the left ventricle in terms of hypertrophy.

Neurohumoral mechanisms include the expression of catecholamines, angiotensin II, and growth factors from cardiac nonmyocytes. In clinical trials, an imbalance of adaptive immunity and elevated levels of pro -inflammatory markers induces end -organ damage, including left ventricle hypertrophy, in hypertensive patients. Up-regulation of the central nervous system is also an important determinant of left ventricular hypertrophy, as shown by reversion of HTN and LV mass by adrenalectomy in rats models in clinical trials. (Devereux et al., 1987)

The severity of hypertension is an important factor on the prevalence of left ventricular hypertrophy. 20% of patients with mild hypertension tend to exibit LVH, wild the percentage goes as high as 100% in severe or complicated hypertension.(Ruilope & Schmieder, 2008) A review of 30 studies and the review's subsequent studies(C Cuspidi et al., 2012) showed that the pattern of hypertrophy also varies between hypertensives since concentric remodeling is not the most frequent form, accounting for 18% of remodeling patterns, eccentric remodeling accounts for 25% and normal geometry takes up to 57% of hypertensive patients. Therefore, in a significant number of hypertensive patients volume load is the dominant mechanism for left ventricular hypertrophy. (W Nadruz, 2015)

3.2 LEFT VENTRICULAR HYPERTROPHY

3.2.1 QUANTIFICATION

Evaluation of left ventricular hypertrophy is predominantly done by transthoracic echocardiography. As it has been defined in previous chapters, left ventricular hypertrophy can be classified into 4 types:
-normal LV geometry (normal LV mass and lower value of relative wall thickness),
-eccentric LV hypertrophy (increased LV mass and lower value of relative wall thickness),
-concentric LV hypertrophy (increased LV mass and relative wall thickness) and
-concentric LV remodeling (normal LV mass and increased relative wall thickness)(Nadruz, 2015)

As mentioned in the first chapter, numeric values concerning LVH are: concentric hypertrophy (RWT> 0,42 and LVMi> 95gm/m2 for women or >115gm/m2 for men) or eccentric hypertrophy (RWT< 0,42 and LVMi> 95gm/m2 for women or >115gm/m2 for men), concentric remodeling (RWT> 0,42 and LVMi<95gm/m2 for women or <115gm/m2 for men) and normal geometry (RWT< 0,42 and LVMi<95gm/m2 for women or <115gm/m2 for men), (Williams et al., 2018)

Concentric left ventricular hypertrophy is one of the most known patterns of LV remodeling due to hypertension. LVH is a result of pressure overload on the left ventricle due to increased systemic pressure over a sustained period of time, while eccentric LV Hypertrophy is linked to volume overload. Eccentric hypertrophy is characterised by increased LV cavity size, normal LV wall thickness, and increased LVM (2 × LV posterior wall thickness relative to LV end-diastolic dimension ≤ 0.42). Both eccentric and concentric hypertrophy affect diastolic function and strain properties. Concentric Remodeling is a result of long standing hypertension (and coronary artery disease) due to either pressure or volume overload and correlates with impaired systolic function of the left ventricle. It is characterized by normal or small LV cavity size, usually increased LV wall thickness and normal LVM, accompanied by a rounder shape of the left ventricle as compared to its normal bullet-shape.

In long standing hypertension, pressure overload inflicted upon the left ventricle results firstly in diastolic dysfunction, and later on when filling pressures have increased substantially, left ventricular hypertrophy prevails. Diastolic filling becomes even more impaired, and systolic function deteriorates. (Marwick et al., 2015)

Pressure overload of the hypertensive heart is not equally distributed among left Ventricular wall, due to the left ventricle's unsymmetrical shape (bullet like). Its largest diameter is located at the basal part of the left ventricle, mainly the basal septum, where wall stress is highest, and correspondingly, the basal septum develops a systolic bulge, which is most prominent at the early stages of hypertension, due to normal wall thickness of the rest of the myocardial wall. (Büchi et al., 1990).

The progression of left ventricular hypertrophy in hypertensive patients towards concentricity or eccentricity, is affected by a variety of factors including:
(I) the severity, duration, and rapidity of onset of the increased pressure load;(Subjects with concentric versus eccentric hypertrophy have been shown to have higher systolic blood pressures and total peripheral resistance)
(II) the volume load;

(III) age, race/ethnicity, and sex;(blacks with hypertension are more likely than whites with hypertension to develop concentric LVH, gender; women with hypertension are more likely than men with hypertension to develop concentric LVH)
(IV) co morbidities such as coronary artery disease, diabetes mellitus, obesity, and valvular heart disease;(Diabetes mellitus; in patients with hypertension is associated with concentric LVH, whereas obesity and coronary artery disease in patients with hypertension are more likely to be associated with eccentric LVH.)
(V) the neurohormonal milieu; (high- versus low-renin blood values are correlated with concentric versus eccentric hypertrophy, accordingly. However, the Framingham Offspring Study, using a large sample stated that increased aldosterone-to-renin ratio was associated with both concentric and eccentric hypertrophy in multivariable models. (Velagaleti et al., 2008))
(VI) alterations of the extracellular matrix; Those with dilated cardiac failure had a lower amount of collagen surrounding the cardiomyocytes, a higher amount of perivascular and scar-related collagen, and a higher ratio of matrix metalloproteinase-1 to tissue inhibitor of matrix metalloproteinase-1, highlighting the importance of alterations of the extracellular matrix in leading to LV dilation(López et al., 2006)
(VII) genetic factors (as data from studies on canine(Koide et al., 1997) and rat models have shown)(Drazner, 2011)

2013 ESH/ESC Guidelines for the management of arterial hypertension(Williams et al., 2018)

Parameter	Abnormal if
LV mass index (g/m^2)	>95 (women) >115 (men)
Relative wall thickness (RWT)	>0.42
Diastolic function: Septal e' velocity (cm/sec) Lateral e' velocity (cm/sec) LA volume index (mL/m^2)	 <8 <10 ≥34
LV Filling pressures : E / e' (averaged) ratio	 ≥13

3.1.2.2 LVH AND CARDIOVASCULAR RISK

The importance of identifying left ventricular hypertrophy in hypertension lies upon risk stratification for the hypertensive patient, as is widely known since the Framingham Heart study and numerous following studies.(Franklin & Wong, 2013) (Manyari, 1990) (Krzesinski, 2003)

Elevated blood pressure is related to increased incidence of several CV events such as stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease, end-stage renal disease and this applies to all age and ethnic groups. The relationship with BP extends from high BP levels to relatively low values of 110–115 mmHg for SBP and 70– 75 mmHg for diastolic BP (DBP). SBP appears to be a better

predictor of events than DBP after the age of 50 years. Blood pressure values and cardiovascular morbidity and mortality are amplified by the concomitant presence of other cardiovascular risk factors. (Williams et al., 2018)

The SCORE system, is based on numerous data and is a widely accepted system for the evaluation of 10 year risk of a first fatal atherosclerotic event, taking into account age, sex, smoking habits, total cholesterol level, and SBP. The SCORE system also takes into account CV risk levels across numerous European countries. Recently it has been updated for inclusion not only of age groups of 40-65years, but also, for over 65 years old patients. (Williams et al., 2018) According to the latest guidelines for the management of hypertension, estimation of 10 year CV risk using the SCORE system is recommended. In the 10year risk categories for the SCORE system, echocardiographic left ventricular hypertrophy automatically classifies patients as high risk, thus pointing out the impact of left entricular hypertrophy in cardiovascular risk.

Left ventricular hypertrophy in hypertension is defined as LV mass index>50 g/m for men and>47 g/m for women or LV mass/BSA g/m2>115 (men) and >95 (women). Along with microalbuminuria(30–300 mg/24 h), increased pulse pressure >60mmHg, carotid femoral PWV>10m/s, ECG documented LVH (Sokolow–Lyon index >35 mm, or R in aVL ≥11mm; Cornell voltage duration product >2440 mm.ms, or Cornell voltage >28 mm in men or >20 mm in women), chronic kidney disease (GFR<60 mL/min/1.73 m2 (BSA), ankle−brachial index <0.9 and advanced retinopathy (haemorrhages or exudates, papilloedema), LVH classifies as asymptomatic hypertension mediated end organ damage and determines cardiovascular risk independently of SCORE stratification system.

Ten year cardiovascular risk categories Systemic Coronary Risk Evaluation system (SCORE)

Very high risk	**People with any of the following:**
	Documented CVD, either clinical or unequivocal on imaging. • **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD • **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥50% stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness • **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR <30 mL/min/1.73 m^2) • **A calculated 10 year SCORE of ≥10%**
High risk	**People with any of the following:** • **Marked elevation of a single risk factor**, particularly cholesterol >8 mmol/L (>310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP ≥180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk)
	Hypertensive LVH
	Moderate CKD eGFR 30-59 mL/min/1.73 m^2)
	A calculated 10 year SCORE of 5-10%
Moderate risk	**People with:** • **A calculated 10 year SCORE of ≥1 to <5%** • **Grade 2 hypertension** • **Many middle-aged people belong to this category**
Low risk	**People with:** • **A calculated 10 year SCORE of <1%**

3.1.2.3. REGRESSION OF LVH

A very important factor of hypertension induced LVH is its regression with medication and control of hypertension, resulting in improvement of risk of cardiovascular events. A prospective cohort sub-study of 941 patients aged 55 to 80 years old in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial with hypertension and electrocardiographic LVH had left ventricular mass measured by echocardiography . (Palmieri et al., 2001) At 4.8-year follow-up, reduction in echocardiographic left ventricular mass index by antihypertensive drug treatment reduced the incidence of cardiovascular mortality by 38%, stroke by 24%, myocardial infarction by 15%, and all-cause mortality by 28%, independent of systolic blood pressure and assigned treatment. At 4-year follow-up of 9,193 persons aged 55 to 80 years old with hypertension and electrocardiographic LVH diagnosed by Cornell criteria or by Sokolow-Lyon voltage criteria in the LIFE trial, less severe electrocardiographic LVH by the Cornell criteria and by the Sokolow-Lyon voltage criteria, were associated with a 14% and 17%, respectively, decrease in the composite endpoint of cardiovascular death, myocardial infarction or stroke (Okin et al., 2004).

Change in echocardiographic LV mass from baseline to year-1 according to the presence or absence of regression of electrocardiographic LVH by the Cornell voltage–duration product (Okin et al., 2004)

Variable	*Change in Cornell product*			
	Progression (increase, n = 143)	*No significant decrease (<25% decrease, n = 286)*	*Regression (⩾25% decrease, n = 155)*	*Overall P-value*
Gender-adjusted				
LV mass (g)	−16±33	−29±37[b]	−32±41[b,c]	<0.001
LV mass (%)	−5.7±14.6	−11.3±13.6b	−12.3±15.6[b,c]	<0.001
Multivariate[a]				
LV mass (g)	−17±37	−28±38[b]	−31±38[b,c]	0.002
LV mass (%)	−6.0±14.3	−11.2±15.2[b]	−12.4±14.9[b,c]	<0.001

[a]Adjusted for age, sex, baseline DBP, and change in SBP and DBP from baseline to year 1.
[b]$P<0.05$ *vs* progression group.
[c]$P<0.05$ *vs* no significant decrease group.
Data are expressed as mean±s.d.

In an outpatient clinic, at 67-month follow-up of patients with hypertension and echocardiographic LVH, clear-cut regression of LVH was documented in 14% of patients (13±8% reduction of initial LVMi) or 23% when also considering those with a reduction of LVMi ≥5 g/m. Greater age, longer duration of hypertension, poor blood pressure control, larger body mass index, LV mass, and carotid intima-media thickness were realated to persistent LVH. Number and class of antihypertensive drugs during follow-up did not differ between groups.(Lønnebakken et al., 2017)

3.1.3 LEFT VENTRICULAR FUNCTION

3.1.3.1 DIASTOLIC FUNCTION

Hypertension induces alterations in the diastolic and systolic function of the left ventricle. Diastolic dysfunction of the left ventricle is associated with symptoms and signs of heart failure even with preserved ejection fraction. Parameters most often used to quantify diastolic filling are Doppler transmitral inflow pattern as well as pulsed Tissue Doppler of the mitral annulus and they have been more extensively analyzed in previous chapters.

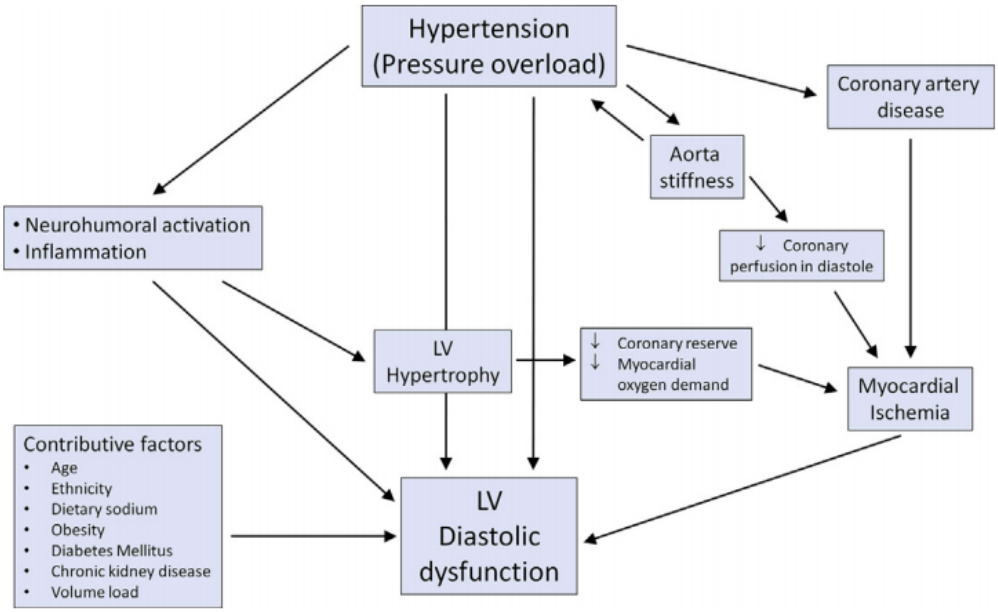
Normal doppler values for diastolic function measurements(Nagueh et al., 2016)

Measurement	Age group (years)			
	16–20	21–40	41–60	>60
IVRT (ms)	<32, >68	<51, >83	<60, >88	<73, >101
E/A ratio	<0.98, >2.78	<0.73, >2.33	<0.78, >1.78	<0.6, >1.32
DT (ms)	<104, >180	<138, >194	<143, >219	<142, >258
Septal *e′* (cm/s)	<10.1	<10.1	<7.6	<6.2
Lateral *e′* (cm/s)	<13	<14	<11.5	<5.9

For septal *E/e′*, values of <8 can be considered normal and >15 are elevated, with 8–15 being ambiguous.

The mechanisms of diastolic dysfunction in hypertension are multiple and include the following(Wilson Nadruz et al., 2017):

- Pressure overload induced upon the left ventricle, which as studies have shown, is closely related to diastolic dysfunction
- stiffening of the larger arteries and consequent increased afterload during systole and decreased coronary perfusion during diastole
- myocardial ischaemia, since hypertension is closely related to coronaryatheroomatosis. Patients with hypertension, and especially left ventricular hypertrophy present with reduced coronary reserve and increased myocardial oxygen demand, contributing to impaired LV relaxation and increased LV filling pressures, or in other words, diastolic dysfunction.
- Neurohumoral activation and inflammation and activation of the renin-angiotensin-aldosterone system.
- Other factors such as age, diabetes mellitus, ethnicity, dietary sodium intake, obesity, chronic kidney disease



Pathways of left ventricular (LV) diastolic dysfunction secondary to hypertension.
(Wilson Nadruz et al., 2017)

Typically, in hypertensive heart disease Tissue Doppler-derived early diastolic velocity (e') -septal or lateral is reduced and, often, the septal e' is reduced more than the lateral e'. Diagnosis and grading of diastolic dysfunction is based on e' (average of septal and lateral mitral annulus) and additional measurements including the ratio between transmitral E and e' (E/e' ratio) and left atrial size (using left atrial volume index) Quantifying those parameters can predict all cause mortallity (Bella et al., 2002) .The values of e' velocity and of E/e' ratio are mainly affected by age and less by gender. (De Sutter et al., 2005) Increase in LV filling pressures is depicted by E/e' ratio . In the hypertensive heart, e' velocity holds a prognostic value and, moreover, E/e' ratio ≥ 13 is associated with increased cardiac risk, independent of LVM and relative wall thickness in hypertensive patients.(Sharp et al., 2010) An other aspect of diastolic dysfunction is increased left atrial volume index. LAVi ≥34 mL/m2 is an independent predictor of death, heart failure, atrial fibrillation and ischaemic stroke. (Abhayaratna et al., 2006) . (Williams et al., 2018)

In a study conducted between 250 hypertensive patients with (i) normal LV geometry; (ii) concentric LV remodelling; (iii) eccentric LVH; (iv) concentric LVH, suggested that LVMI, E/A and e' were comparable between the two groups, E/e' was significantly increased in patients with concentric LVH (13.4 ± 5.4) than in those with eccentric LVH (11.1 ± 3.6), suggesting worse diastolic function in that group, even with similar LVMIs in those groups. EF was normal and comparable between the groups. As opposed to the group with normal left ventricular geometry, the eccentric and concentric LVH groups had significantly lower values for E/A and e' parameters, implying impaired diastolic function in LVH. No significant differences in E/A or e′ were observed, however, between the eccentric and concentric LVH groups. All in all, concentric LVH in hypertensive patients results in more severe LV diastolic dysfunction than eccentric LVH in

a given LVMi. Therefore, the pattern of left ventricular hypertrophy is an important determinant of the severity of dsiastolic function. (Masugata et al., 2011)

Echocardiographic parameters in the four groups of hypertensive patients with normal and abnormal left ventricular geometry(Masugata et al., 2011)

Parameter	Left ventricular geometry			
	Normal (n = 69)	CR (n = 55)	EH (n = 58)	CH (n = 68)
LV systolic function				
LVEF, %	72 ± 6	71 ± 6	72 ± 8	71 ± 8
LV diastolic function				
E/A	0.87 ± 0.23	0.75 ± 0.21	0.72 ± 0.17***	0.76 ± 0.20*
e′, cm/s	6.3 ± 1.7	5.6 ± 1.7	5.2 ± 1.5**	5.1 ± 1.5***
E/e′	10.2 ± 3.0	10.5 ± 3.5	11.1 ± 3.6	13.4 ± 5.4***

In a study conducted upon 980 participants in the Anglo-Scandinavian Cardiac Outcomes Trial, where all participants had Hypertension, but not known cardiac disease, showed that in patients with well-controlled hypertension and three cardiac risk factors, the E/E' ratio of transmitral flow to mitral annular velocity is a strong, independent predictor of cardiac outcomes. For each unit rise in the E/E' ratio, there was a 15% increase in first cardiac events. Those with an E/E' in the uppermost quartile of this population had a hazard ratio of 2.4 times that of patients in the lowest quartile. This was the first study to demonstrate the ability of the E/E' ratio to predict primary cardiac events in a hypertensive population without established cardiac disease and suggested that even values of E/E' within the normal range can be associated with an increased risk of cardiac events. Elevated E/E' is related to prediction of death following myocardial infarction, more than other echocardiographic features.(Sharp et al., 2010)

An interesting study showed that diastolic dysfunction is present even before the establishment of hypertension. It is known that prehypertension is associated with increased risk of progression to hypertension and that the relationship between blood pressure levels and cardiovascular eents starts with values of 115 and 75mmHg. In this study, patients were devided into 3 groups: optimal blood pressure (BP <120mm Hg and <80mm Hg), pre-hypertension (blood pressure (BP) of 120–139mm Hg systolic and/or 80–89mm Hg diastolic) and hypertension and evaluated in terms of diastolic function. Results showed that parameters of diastolic function (E/A, E′, and E/E′) were deteriorating from optimal blood pressure to prehypertension and to hypertension. The same applied for the prevelance of mild and moderate to severe diastolic dysfunction, since in optimal blood pressure diastolic function occurred in 44% of participants, 59% of subjects with prehypertension and 67% of patients with hypertension. (Santos et al., 2016)

3.1.3.2 SYSTOLIC FUNCTION

With the progression of diastolic dysfunction in hypertension and the persistence of volume and pressure overload some patients will present with symptoms of heart failure

and eventually deterioration of systolic function. However, before that becomes imminent, subclinical systolic dysfunctioncan be detected with speckle tracking echocardiography can quantify longitudinal contractile function (longitudinal strain) and aid to reveal early subclinical systolic dysfunction even without LVH.

A study conducted upon 98 hypertensive patients and controls devided subjects into three categories according to the presence of LVH: normal geometry, eccentric hypertrophy and conctentric hypertrophy. Ejection fraction was preserved in all three groups. The mean peak systolic longitudinal, circumferential, and radial strains in the concentric LVH group were lower compared to the control and other 2 HT groups. The mean peak systolic strain rates in longitudinal and radial directions were lower in all hypertensive groups compared to controls. Moreover, the mean peak systolic circumferential strain rate was reduced in the concentric LVH group than in the other 2 HT groups. There were no differences in the LV torsion and torsional rate between the control and 3 HT groups. The mean peak systolic circumferential strain was an independent predictor related to LV ejection fraction in all patients.(Mizuguchi et al., 2010)

In a study conducted in 22 top-level rowers, and 18 young newly diagnosed, never-treated patients with hypertension, GLS was lower in patients with hypertension (-17.5 ± 2.8%) than in rowers (-22.2 ± 2.7%) (P < .0001). Global circumferential strain, global radial strain, and torsion were similar between athletes and hypertensives. In the pooled population, GLS was an independent contributor to E/e' ratio (P < .0001) after balancing for age, heart rate, meridional end-systolic stress, LV mass index and left atrial volume index. Both GLS and E/e' ratio were accurate values for the differentiation of patients with hypertension and healthy subjects. E/e’ was a more sensitive indicator of pathology (77.8%) and GLS a more specific one (89.5%).The severity of GLS is strongly associated with LV diastolic function, independently of afterload changes and the degree of LV hypertrophy(Galderisi et al., 2010)

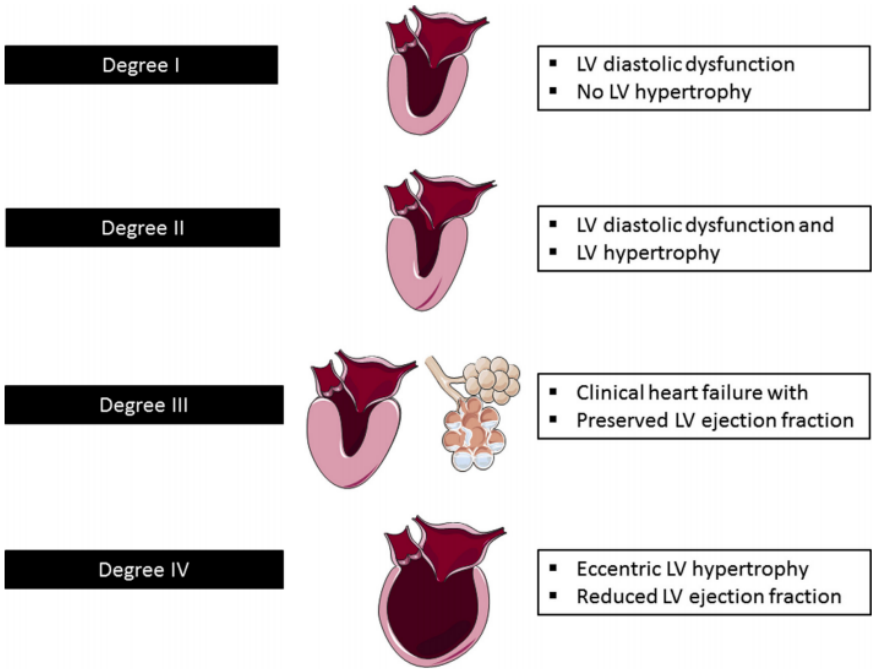
In an aforementioned study of hypertensives, prehypertensives and subjects with optical blood pressure measurements, GLS and circumferential strain were calculated. Results are shown in the following table and suggest that reduction in GLS occurs in hypertensive patients, however prehypertensie patients maintain their GLS. Circumferential strain did not show considerable differences between the 3 groups. (Santos et al., 2016)

Different parameters of systolic function in patients with optimal BP, prehypertension and hypertension (Santos et al., 2016)

Characteristic	Optimal BP (*n* = 402)	Prehypertension (*n* = 537)	Hypertension (*n* = 3,932)
LV ejection fraction (%)	66±5	66±5	66±6
Longitudinal strain (%)	−18.6±2.2	−18.5±2.3	−17.9±2.5*,†
Circumferential strain (%)	−27.6±3.7	−28.0±3.6	−27.9±3.9

In long standing hypertension, the risk of heart failure increases, whether this is HfpEF or HfrEF, even when other risk factors such as age, gender, blood pressure,

myocardial infarction, and diabetes are controlled. In a study by de Simone and colleagues (de Simone et al., 2008), each 1% increase in left ventricular mass, evaluated by echocardioraphy, above the normal range relates to 1% increased incidence of heart failure after controlling for risk factors, such as prior myocardial infarction. However, In a review article, Levy and colleagues(Vasan & Levy, 1996) suggest that myocardial infarction is an obligatory pathway towards systolic heart failure and this is likely to be true to the majority, but not all of hypertensive patients, since in large observational studies, nearly half of patients with hypertensive heart disease tend to exhibit systolic dysfunction without coronary artery disease. (Levy et al., 1996) Other mechanisms, such as toxins, genetic factors, or environmental exposures, may be responsible for accelerated myocyte loss leading to HFrEF. (Slivnick & Lampert, 2019)

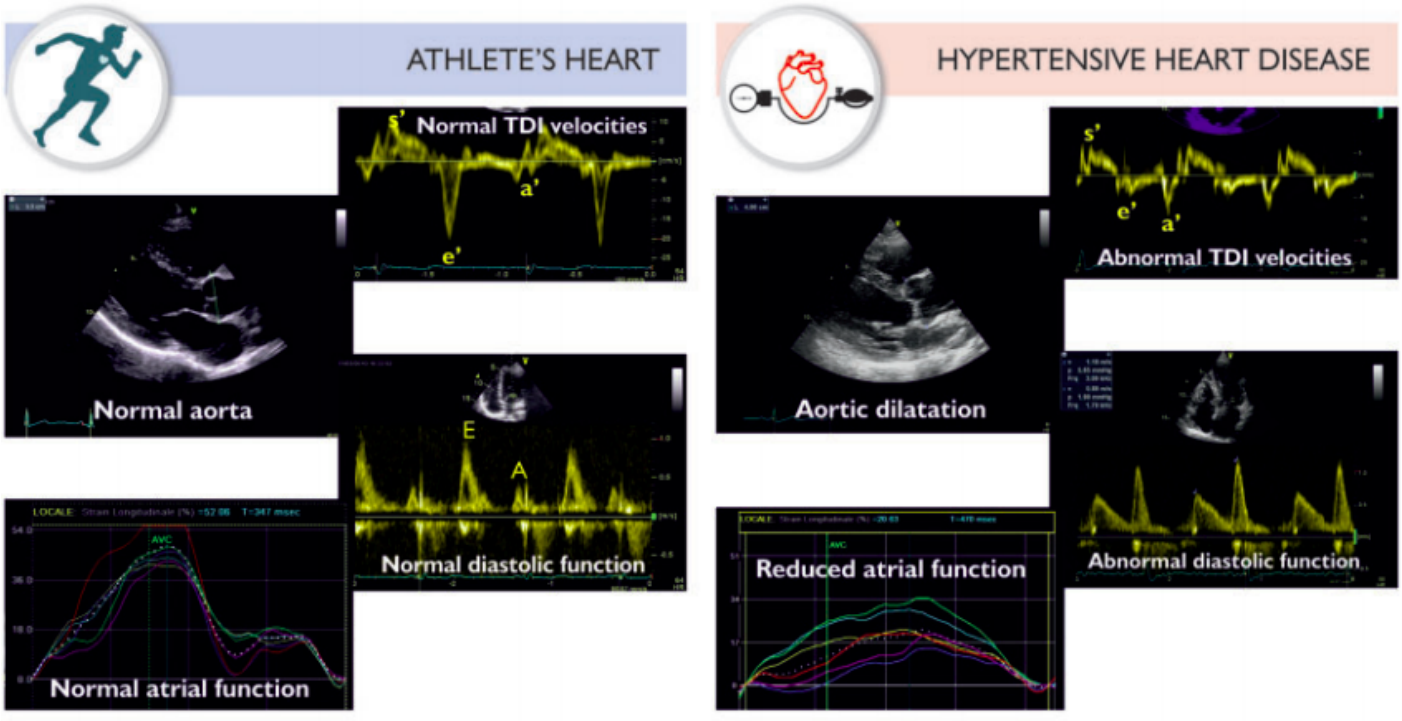


Stages of hypertensive heart disease (Messerli et al., 2017)

Eventually, in long standing hypertension, a portion of patients will develop systolic dysfunction leading to symptomatic HFrEF. Contrary to hypertensives who develop HfpEF, patients with HFrEF appear with more prominent myocyte loss than hypertrophy. Moreover, patients with eccentric hypertrophy have a higher tendency towards HFrEF (hazard ratio [HR] 1.89, 95% confidence interval [CI] 1.41 to 2.54), than those with concentric hypertrophy (HR 2.23, 95% CI 1.48 to 3.37), but these patients are more likely to develop HfpEF, as was shown in a study by (Velagaleti et al., 2014). Interestingly, when HFrEF of end stage develops in hypertensive patients,blood pressure might be low. In a review performed by Messerli and colleagues, the term “decapitated hypertension” was used to depict this phenomenon. The decrease in SBP derives from the reduced ability of the heart to pump blood to the periferal tissues and the resultant reduction in cardiac output, despite peripheral vasoconstriction that develops as a compensatory mechanism. (Messerli et al., 2017) Low blood pressure may mask the diagnosis of predesposing hypertensive heart disease in those patients. The increase in blood pressure after optimal medical treatment may aid the identification if preexisting hypertensive heart disease.

4. DIFFERENTIATING THE ATHLETE'S HEART FROM HYPERTENSIVE CARDIOMYOPATHY

In previous chapters, the aspects of left ventricular adaptation to exercise and hypertension, have been discussed extensively. However, differentiating one from the other in daily practice can be really challenging, let alone clinically significant. For instance, athletes with hypertrophy should be given instructions for their training program and similarly, hypertensive patients who exercise regularly will need to be classified as hypertensives with end organ damage or hypertensives with athlete's heart syndrome. The differentiation is crucial, as hypertensives with hypertension mediated end organ damage are in increased cardiovascular risk and need aggressive anti-hypertensive treatment, as opposed to alterations included in the spectrum of the athlete's heart. Moreover, it should be taken into account that athletes may also present with hypertension, although the prevalence of hypertension in the athletic population is still debated. Caselli et al. after studying 2040 high level athletes, between the ages of 18–40 years, found that the prevelance of hypertension was lower (3%) than in the general population of comparable age(11% in 493 subjects, aged 18–35 years). (Caselli et al., 2017) D'Ascenzi et al. found that 3,8% of 1058 olympic athletes were hypertensives. (D'Ascenzi et al., 2019) However, these percentages might be altered, if abuse of anabolic androenic steroids is taken into account. All of the above, contribute to the fact that hypertension and the athlete's heart can be intertwined, coexist or appear consecutively in some subjects or become a diaforodiagnostic hazard when deciding which of the two is the cause of left ventricular geometrical and functional abnormalities.



(D'Ascenzi et al., 2020)

4.1 LEFT VENTRICULAR GEOMETRY

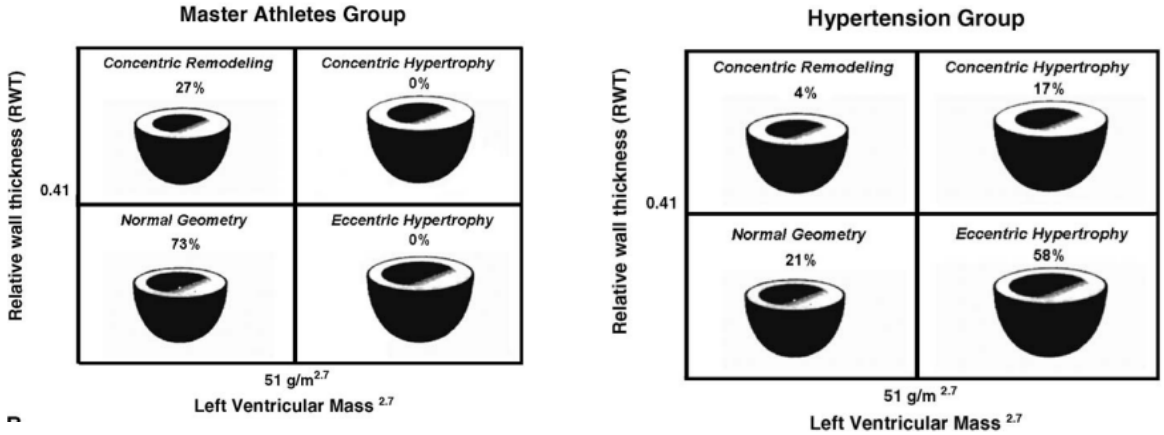
As mentioned in previous chapters, both hypertension and athletic activity can induce alterations in the geometrical features of the left ventricle, that correspond to hypertrophy and increase of internal dimensions. Exercise induces left ventricular remodeling and hypertrophy which is highly dependent on the type of sport discipline practiced. Endurance training induces eccentric remodeling, strength training induces concentric remodeling, sports that include strength and endurance components induce a mixed type of remodeling and skill sports do not cause significant left ventricular alterations. These correlations have been debated over the years, suggesting that other factors, such as gender, height and BSA also play a role in the morphology of the athlete's heart, however, the model of concentric hypertrophy in resistance exercise and eccentric hypertrophy in dynamic exercise, is still widely accepted. On the other hand, although hypertension has been correlated with both concentric and eccentric hypertrophy, the concentric type of hypertrophy is most often encountered. In the athlete's heart, hypertrophy, is considered a physiologic adaptive mechanism due to increased cardiac output with reduced systemic vascular resistance, in the case of endurance sports, or due to increased systemic vascular resistance, systolic blood pressure and volume overload, in strength sports. Both sports types are characterized by normal myocyte structure and function. In hypertension however, hypertrophy is a result of chronic pressure overload, accompanied by activation of neurohormonal cascades including sympathetic nervous system and renin-angiotensin aldosterone axis activation, foetal gene activation, apoptosis and fibrosis.(D'Ascenzi et al., 2020) Moreover, there are differences in the structure of the myocardium between hypertensives and athletes. The myocardium of patients with hypertension is characterized by fibrosis, which might precede the development of left ventricular hypertrophy, while in athletes there is an increase of active muscular mass. (Tsioufis, 2018)

Typical echocardiographic features of the left ventricle in different hypertrophic hearts

Disease	Maximal end-diastolic wall thickness (mm)	Ejection fraction	Systolic strain rate in the region of interest	Diastolic function	LVOT gradient	Special feature
Athlete's heart	14	Normal	Normal/supranormal	Normal	No	Slightly increased LV dimension
Obstructive HCM	>20	Normal	Markedly reduced	Impaired relaxation	Yes	Asymmetric hypertrophy
Hypertension	15	Normal	Slightly reduced	Impaired relaxation	No	Basal septal bulge
Amyloidosis	14	Normal	Markedly reduced	Pseudonormal/ restriction	No	Sparkling texture
Friedreich's ataxia	15	Normal	Slightly reduced	Normal	No	Sparkling texture
Fabry disease	16	Normal	Moderately reduced	Impaired relaxation	No	Prominent papillary muscle
Noncompaction	25	Reduced	Moderately/markedly reduced	Impaired relaxation	No	Trabecularization

However, those pathophysiological mechanisms are not applicable in every-day practice and physicians will eventually have to differentiate the two entities. Concentric or eccentric remodeling or hypertrophy might appear in any of the two- hypertension and the

athlete's heart. The study of (Galderisi et al., 2010) in competitive rowers and young hypertensives, found that left ventricle mass index was significantly increased in both rowers and in patients with hypertension than in controls, with the prevelance of left ventricular hypertrophy as defined by LVMi > 44 g/m2.7 in women and LVMi > 48 g/m2.7 in men was found to be 20.3% (12 of 59) in the pooled population and more specifically, 36.4% (8 of 22) in rowers and 22.2% (4 of 18) in hypertensives (c2 test, P = .53). Moreover, in a study performed upon 30 soccer players, 24 hypertensives and 20 individuals with hypertrophic cardiomyopathy, showed that LVM/BSA (which is abnormal wat values above 125 g/m2) was elevated in 10% of master athletes, in 54% of hypertensives and in 60% of patients with hypertrophic cardiomyopathy. LV geometry was normal in 22 athletes (73%), and 27% of them were found to have concentric remodeling. 79% of the hypertensive population had left ventricular remodeling in the form of concentric remodeling in one patient (4%), concentric hypertrophy in 4 patients (17%) and eccentric hypertrophy in 14 patients (58%). (Limongelli et al., 2006). Therefore, although more prevalent in hypertensive patients, remodeling of the left ventricle can occur in both entities.



Left ventricular geometry in master athletes and hypertension group(Limongelli et al., 2006)

The most effective way to discriminate hypertensive heart disease from LVH of the athlete's heart is to refrain from exercise for a sustained period of time of about three to four months. Septal thickness decreases about 15-33% in the case of exercise induced hypertrophy.(D'Ascenzi et al., 2020)This phenomenon has been observed in several studies, the largest of which, was a longitudinal study performed by peliccia et al. conducted upon 40 top level athletes with LV dilation of more than 60mm or with left ventricular hypertrophy of more than 13mm. Athletes were evaluated by echocardioraphy for 5.6 years after discontinuation of training. In all of the participants, return of wall thickness to normality and reduction of internal dimensions was observed. 9 athletes, which accounts for 22% of participants, had end diastolic dimension above 6cm persistently, and that could be attributed to continuous exercise or increase in BSA, however no relation was found with long term cardiovascular effects (Antonio Pelliccia et al., 2002)

4.2 DIASTOLIC FUNCTION

Another important diaforodiagnostic tool to distinguish between the athlete's heart and hypertensive cardiomyopathy is diastolic function. The evaluation of diastolic function has a lot of different parameters to take under consideration and numerous limitations, however according to recent guidelines diastolic function is present when at least 50% of the following criteria: septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, average E/e >14, tricuspid regurgitation velocity>2.8 m/s and LA volume index>34mL/m2. (Galderisi et al., 2015) In hypertensives diastolic function is a characteristic finding and might even preexist before left ventricular hypertrophy. Diastolic function in the hypertensive patient might vary between impaired relaxation to restrictive filling depending on the duration and severity of hypertension. In the hypertensive patient left ventricular hypertrophy is always accompanied by diastolic dysfunction and if uncontrolled, it will eventually result in deterioration of systolic function as well. However, in the athlete's heart of endurance exercise, diastolic dysfunction not only remains normal but is enhanced in order to keep up with the high heart rate that develops in endurance training. (Nagueh et al., 2016) More specifically endurance athlete's present with increased transmitral E-wave as well as mitral-annular LV tissue velocities. As mentioned in previous chapters, E/A ratio might reach values of greater than 2, similar to those of restrictive filling. However, septal and lateral e remain normal (>8 and >10cm/s respectively). However in strength athletes, diastolic function can be normal or slighlty reduced with E' basal lateral LV values of 8,8-11,6 cm/s according to the findings of (Tsioufis, 2018) An interesting study by Vineareanu et al compared hypertensive patients, patients with hypertrophic cardiomyopathy, athletes and controls, using peak velocities of mitral annular motion at 4 sites by tissue Doppler echocardiography. Hypertensives and patients with hypertrophic cardiomyopathy had lower long-axis systolic and early diastolic velocities than the athletes ($p < 0.01$) for all 4 sites. The most effective way to diagnose pathologic from physiologic hypertrophy was by using a cut off value of mean systolic annular velocity <9 cm/s (sensitivity 87%, specificity 97%). Long-axis systolic and early diastolic velocities are decreased in patients with pathologic hypertrophy, such as hypertension and hypertrophic cardiomyopathy, as opposed to athletes, where these values were preserved.(Vinereanu et al., 2001)

Saghir et al., in the study of 108 subjects, 30 patients with hypertension, 30 strength-trained athletes with LVH and 48 controls, concluded that there were notable differences in E/e' among the 3 groups, with hypertensive patients having the highest values (hypertensive patients: 12.71 +/-4.4; athletes: 5.85 +/-0.82; controls: 7.23+/- 2.01, $p < 0.05$), supporting the theory of supranormal diastolic function in athletes(Saghir et al., 2007).

General echocardiographic characteristics(Saghir et al., 2007)

	athletes	controls	hypertensives
E/A	1.73 ± 0.42	1.52 ± 0.53	1.19 ± 0.40*
Sm, m/s	0.09 ± 0.01	0.09 ± 0.02	0.08 ± 0.01*
Em, m/s	0.13 ± 0.02*	0.12 ± 0.03	0.07 ± 0.02*
Am, m/s	0.08 ± 0.02	0.09 ± 0.03	0.09 ± 0.02
E/Em	5.85 ± 0.82*	7.23 ± 2.01	12.71 ± 4.40*
LVM, g	288 ± 52*	179 ± 44	340 ± 73*
LVMI, g/m^2	154 ± 21*	94 ± 18	165 ± 38*
IVRT, ms	98 ± 12	100 ± 20	131 ± 29*

Similarly to the previously mentioned study, Galderisi et al. in their study of 22 top-level rowers, and 18 young hypertensives, showed that hypertensives had lower s' velocity and e' velocity and higher E/e' ratio compared to athletes ($p < 0.001$ for all the parameters). In the study population, E/e' was related to age ($r = 0.31$, $P < .01$), body mass index ($r = 0.32$, $P < .01$), systolic BP ($r = 0.45$, $P < .0001$), diastolic BP ($r = 0.51$, $P < .0001$), mean BP ($r = 0.52$, $P < .0001$), LVMi ($r = 0.30$, $P < .01$) and GLS ($r = 0.47$, $P < .0001$). Interestingly, E/e' ratio was irrelevant to relative wall thickness ($r = 0.12$), midwall fractional shortening ($r = 0.20$), or LAVi ($r = 0.10$). Increased E/e' ratio comes along with reduced GLS which appears to be accurate in differentiating patients with hypertension from healthy controls. This correlation will be further analyzed in this chapter (Galderisi et al., 2010)

Doppler echocardiographic features of the study population (Galderisi et al., 2010)

Variable	Healthy controls	Rowers	Patients with hypertension	P
IVSTd (mm)	8.4 ± 1.2	9.9 ± 1.0¶	9.1 ± 2.0§	<.01
PWTd (mm)	7.7 ± 1.1	9.0 ± 1.0**	8.3 ± 1.1§	<.001
LVEDV (mL)	133.9 ± 33.0	161.3 ± 33.3¶	131.4 ± 44.0*	<.02
LVESV (mL)	49.8 ± 18.0	60.3 ± 21.5	52.3 ± 33.9	NS
LVMi ($g/m^{2.7}$)	30.8 ± 5.6	41.1 ± 8.1#	37.0 ± 11.2§	<.0001
RWTd	0.30 ± 0.06	0.32 ± 0.04	0.33 ± 0.07	NS
EF (%)	61.7 ± 6.8	66.3 ± 6.9	61.6 ± 5.9	NS
Midwall FS (%)	18.9 ± 2.5	18.3 ± 2.0	17.6 ± 3.4	NS
ESSm (g/cm^2)	43.8 ± 14.3	40.0 ± 9.9	50.4 ± 17.1*§	<.05
ESSc (g/cm^2)	82.4 ± 24.0	78.8 ± 16.8	96.9 ± 30.9*§	<.05
SV (mL)	84.2 ± 19.3	101.0 ± 16.1¶	79.1 ± 20.0†	<.001
LAVi (mL/m^2)	26.7 ± 7.3	36.6 ± 8.7**	29.4 ± 6.3*	<.0001
E peak velocity (m/s)	0.78 ± 0.12	0.80 ± 0.13	0.78 ± 0.16	NS
A peak velocity (m/s)	0.52 ± 0.12	0.44 ± 0.10	0.62 ± 0.13‡§	<.0001
E/A ratio	1.61 ± 0.48	1.92 ± 0.53#	1.31 ± 0.40†	<.001
DT (ms)	172.8 ± 23.3	184.1 ± 33.7	185.0 ± 32.8	NS
IVRT (ms)	80.1 ± 17.2	79.4 ± 15.8	80.4 ± 17.8	NS
Sa average (cm/s)	9.3 ± 1.7	10.6 ± 2.0	8.1 ± 1.7‡	<.001
Ea average (cm/s)	13.9 ± 2.7	15.5 ± 3.0	10.8 ± 3.7‡§	<.0001
E/Ea ratio	5.8 ± 1.1	5.2 ± 7.4	7.9 ± 3.0‡‖	<.0001

4.3 SYSTOLIC FUNCTION

Systolic function also offers interesting information in differentiating hypertensive cardiomyopathy from the athlete's heart. Assessing ejection fraction reliably in athletes might be a challenge with conventional techniques, such as simpson's , especially in those with elevated left ventricular volumes, in which case, it might be underestimated. The formula used to calculate EF (100 × SV/LV end-diastolic volume) is mathematically designed for left ventricles with normal dimensions, whereas athletes generally have increased end diastolic volumes, producing an intrinsic error in the formula. Moreover, EF estimates left ventricular function but not contractility, which is increased in athletes during demanding physical activity, in order to increase stroke volume. Accordingly, in order to fully assess systolic function in athletes, one should evaluate it both at rest and at exercise. (Saghir et al., 2007) Nonetheless, endurance athletes might rarely present with mildly reduced ejection fraction. However, values bellow 50% require further evaluation to

detect underlying pathology, not attributable to exercise alone. As mentioned before, deterioration of ejection fraction in hypertensive patients is not an uncommon finding, especially if left untreated. The natural history of hypertension involves diastolic dysfunction as a first sign of hypertensive cardiomyopathy, which might later on deteriorate to systolic dysfunction and reduction in ejection fraction. This reduction might be attributable to hypertension alone or to other contributing factors, such as coronary artery disease, that often coexist. However even without reduction of ejection fraction diastolic dysfunction might present with symptoms of heart failure due to diastolic dysfunction, also known as heart failure with preserved ejection fraction. On the other hand, this does not apply for the athlete's heart, since ejection fraction is maintained, stroke volume becomes supernormal and peak s' velocity is typically found above 9cm/s (Pluim et al., 2000)suggesting normal systolic and diastolic function. Indeed , a cut-off value of 9 cm/s of systolic peak velocity (s') demonstrated 87% sensitivity and 97% specificity in distinguishing pathological LVH (arterial hypertension or HCM) from athlete's LVH. Even when mild reductions in ejection fraction are present, symptoms of heart failure are unlikely to prevail.

4.4 STRAIN AND SPECKLE TRACKING ECHOCARDIORAPHY

Nonetheless, mild reductions in ejection fraction in athletes compared to hypertensives have an important diaforodiagnostic feature, which is no other than global longitudinal strain. Speckle tracking echocardiography, can therefore seem very useful in this case, since GLS is often impaired in hypertensives, with or without left ventricular hypertrophy, whereas in athletes this is not the case. Before jumping to conclusions however, clinicians should take into account that the experience with STE is still preliminary and can not be routinely used for diaforodiagnostic purposes. A study by Saghir et al, compared strength trained athletes with Left ventricular hypertrophy and hypertensive patients with left ventricular hypertrophy in terms of strain, peak systolic strain rate and peak early and late diastolic strain rate and concluded that individuals with hypertensive LVH had significantly decreased strain, peak systolic strain rate(SR(S)), and peak early diastolic strain rate (SR(E))(-16.8 +/- 3.2%, -0.99 +/- 0.15 s(-1), and 1.54 +/- 0.40 s(-1), respectively) compared with control subjects (-21.7 +/- 3.5%, -1.31 +/- 0.27 s(-1), and 2.35 +/- 0.57 s(-1), respectively; all $P < .0001$), whereas athletes had no significant differences in strain, SR(S), SR(E), or peak late diastolic strain rate compared with control subjects ($P = 0.11$, 0.99, 0.85, and 0.09, respectively). Basal strain values in the athletic population was increased compared to the hypertensive population. More explicitly, in the athletes as well as the sedentary controls, the basal septum had increased strain and strain rates when compared to the mid and apical septum. On the other hand, hypertensives presented with lower strain values of the basal septum. These findings imply the presence of subendocardial damage in hypertensives, contrary to athletes, where left ventricular hypertrophy is a normal adaptation and these findings could differentiate the athlete's heart from hypertensive cardiomyopathy. (Saghir et al., 2007) .

Performance of echocardiographic criteria in differentiating between pathologic left ventricular hypertrophy and control(Saghir et al., 2007)

	Sensitivity	Specificity
Longitudinal strain cutoff $< -20.3\%$	93%	73%
Longitudinal SR_S cutoff $< -1.17 s^{-1}$	97%	61%
Early diastolic annular velocity < 9 cm/s	85%	78%
Systolic annular velocity < 9 cm/s	66%	69%

Strain and strain rate characteristics (mean SD)(Saghir et al., 2007)

	AT (n = 30)	CT (n = 48)	HT (n = 30)
Basal septum			
Strain	−26.3 ± 4.7%	−22.5 ± 5.7%	−14.2 ± 4.1%
SR_S, s^{-1}	−1.45 ± 0.39	−1.31 ± 0.43	−0.88 ± 0.23
SR_E, s^{-1}	2.63 ± 0.91	2.48 ± 0.95	1.39 ± 0.51
SR_A, s^{-1}	1.66 ± 0.65	1.53 ± 0.64	1.37 ± 0.45
Midseptum			
Strain	−21.6 ± 3.6%	−21.7 ± 4.6%	−16.9 ± 4.4%
SR_S, s^{-1}	−1.34 ± 0.31	−1.36 ± 0.36	−1.04 ± 0.30
SR_E, s^{-1}	2.05 ± 0.50	2.13 ± 0.75	1.39 ± 0.56
SR_A, s^{-1}	0.97 ± 0.36*	1.30 ± 0.64	1.34 ± 0.47

	AT (n = 30)	CT (n = 48)	HT (n = 30)
Apical septum			
Strain	−20.8 ± 4.8%	−21.0 ± 6.3%	−18.6 ± 4.5%
SR_S, s^{-1}	−1.13 ± 0.36	−1.21 ± 0.37	−1.03 ± 0.21*
SR_E, s^{-1}	2.43 ± 0.54	2.45 ± 0.72	1.79 ± 0.60
SR_A, s^{-1}	0.73 ± 0.27*	0.99 ± 0.59	1.39 ± 0.47
Average septum			
Strain	−22.9 ± 2.4%	−21.7 ± 3.5%	−16.8 ± 3.2%
SR_S, s^{-1}	−1.31 ± 0.19	−1.31 ± 0.27	−0.99 ± 0.15
SR_E, s^{-1}	2.37 ± 0.40	2.35 ± 0.57	1.54 ± 0.40
SR_A, s^{-1}	1.12 ± 0.25	1.28 ± 0.46	1.38 ± 0.37

In the aforementioned study by Galderisi et al. of 19 sedentary controls, 22 top-level rowers, and 18 young newly diagnosed, never-treated patients with hypertension, showed that GLS was lower hypertensive patients (−17.5 ± 2.8%) than in rowers (−22.2 ± 2.7%) and in controls (−21.1 ± 2.0%) ($P < 0.0001$). Global circumferential strain, global radial strain, and torsion were similar among the three groups, although there was a tendency towards higher values of LV torsion in hypertensive patients .Basal, middle and apical circumferential and radial strain were not significantly different among the three groups. In hypertensive patients longitudinal strain was greater at the basal and middle levels, as opposed to the apical level. GLS was related to age (r = 0.40, P < .001), mean BP (r = 0.50, P < .0001), ESSm (meridional fractional shortening) (r = 0.39, P < .001), and average Sa (r = 0.33, P < .01). In the hypertensive population, reduced e' velocity and increased E/e' ratio was correlated with reduced annular systolic velocity or GLS, or in other words, reduced longitudinal systolic function of subendocardial fibers. Circumferential strain of midwall fibers was not reduced in this study, compatible with The early stages of hypertensive disease where LV geometry is still unaltered. GLS was positively related to LV active muscle mass in rowers, and on the other hand, GLS and GRS had a negative relation to LV mass in the patients with hypertension. In other words, myocardial composition, for instance myocardial fibrosis of hypertension, plays an important role on systolic strain. The most interesting finding is the relation between E/e' to GLS, and the absence of relation of E/e' with GCS and GRS. This can be interpreted by the fact that in the longitudinal motion of the heart LV systolic and diastolic function are correlated, and even though diastolic function might be the only apparent impairment, systolic function is in fact sub-clinically affected. All in all, in differentiating patients with

hypertension from subjects with athlete's heart, a GLS cutoff point < 19% and E/e' ratio cutoff point =/< 6.16 appeared to be accurate, with E/e' ratio being more sensitive (77.8%) and GLS more specific (89.5%) (Galderisi et al., 2010)

Average values of longitudinal, circumferential, and radial strain at the basal, middle, and apical level of the left ventricle. p value was significant only in longitudinal strain(Galderisi et al., 2010)

Variable	Healthy controls	Rowers	Patients with hypertension
Basal longitudinal strain (%)	−20.9 ± 2.3	−22.0 ± 2.9	−17.5 ± 2.8†‡
Middle longitudinal strain (%)	−20.9 ± 1.9	−22.1 ± 2.8	−17.4 ± 2.8†§
Apical longitudinal strain (%)	−21.2 ± 2.1	−22.4 ± 2.6	−17.6 ± 3.1*‡
Basal circumferential strain (%)	−16.7 ± 2.7	−16.8 ± 2.4	−13.5 ± 8.6
Middle circumferential strain (%)	−18.2 ± 3.3	−18.8 ± 2.6	−17.3 ± 3.2
Apical circumferential strain (%)	−17.8 ± 2.9	−17.8 ± 2.6	−16.7 ± 3.3
Basal radial strain (%)	46.7 ± 13.6	48.1 ± 17.0	49.6 ± 19.4
Middle radial strain (%)	44.9 ± 13.9	45.8 ± 17.0	46.8 ± 19.1
Apical radial strain (%)	44.0 ± 12.2	44.0 ± 16.9	46.9 ± 19.0

Another important factor that should be taken into account when differentiating the athlete's hear from hypertensive cardiomyopathy, is the use of anabolic substances. It is not uncommon that athletes in order to enhance their performance in sports, use agents such as testosterone, anabolic androgenic steroids, corticosteroids, peptide hormones, growth factors and erythropoietin, β-2 agonists, hormone and metabolic modulators, diuretics and masking agents, stimulants (amphetamine, cocaine), and cannabinoids. Most of these drugs induce adrenergic hyperactivation to a degree higher than the one caused by mere exercise, leading to arrhythmias, coronary artery disease, myocarditis, pericarditis, heart failure, and sudden cardiac death. Moreover, these drugs may induce hypertension and left ventricular hypertrophy, sometimes accompanied by deterioration in systolic function, reduction of myocardial strain and diastolic function. These results alter the benign phenotype of the athlete's heart, making it hard to differentiate from pathology. Hypertension tends to cause similar alterations in left ventricular geometry and function and hence the identification of the aetiology behind these findings, and correspondigly the requiered therapy become shady. Many of these patients will be erroneously diagnosed with hypertrophic cardiomyopathy since these drugs exacerbate exercise induced hypertrophy to pathologic degrees, which does not decondition with cessation of exercise. In these cases, echocardiography alone might not be able to provide with a clear answer and more advanced imaging techniques, such as magnetic resonance, might be necessary.(Tsioufis, 2018)

Differences between the athlete's heart and hypertensive heart (Galderisi et al., 2015)

	Hypertensive heart	Athlete's heart
LV wall thickness	Increased	Increased
LV diastolic dimension	Decreased, normal, or increased	Increased
LV systolic dimension	Decreased, normal, or increased	Increased
Stroke volume	Increased	Increased
Fractional shortening	High, preserved, or depressed	Preserved
Diastolic dysfunction	Often present	Absent
LV wall strain	Present	Absent
Heart rate	Not affected	Bradycardia

4.5 THE LEFT ATRIUM

Appart from the left ventricle, the left atrium can also aid to the differentiation of pathology to normal adaptation. Hypertension results in dilation of the left atrium due to elevated filling pressures and diastolic dysfunction and is associated to LVM irrespective of type of hypertrophy.(Nagueh et al., 2016) In athletes, LA dilatation has been observed in numerous studies and is considered a normal adaptation to volume load during exercise , which follows left ventricular adaptations and regresses with detraining. Indeed, Peliccia et al. detected an antero-posterior diameter above ≥40 mm in 18% of athletes, and these findings were in accordance with dilation of the left ventricle in those athletes. (Antonio Pelliccia et al., 2005) As far as the LAVi dimension measurements are concerned, D' Andrea and Riegler (Antonello D'Andrea, Riegler, et al., 2010) found mild enlargement of 29-33ml/m2 in 24% and moderate enlargement >34ml/m2 in 3,2% of 615 trained athletes. The upper limit of LA enlargement was 36 ml/m2. Another study showed that 67% of athletes had a LAVi >34ml/m2, with LV end diastolic volume index and LV mass being enlarged accordingly, while in sedentary subjects increased LA indexes were determined by their body mass index and their E/A ratio. (Nistri et al., 2011)

Hypertensive patients may also present with LA dilatation and this is an early sign of hypertensive heart disease and diastolic dysfunction. During diastole, the pressures of the left ventricle are directly inflicted upon the left atrium, and these pressures increase with decrease in LV compliance. As a result, LA pressure increases to maintain adequate filling, And this increased pressure leads to the dilatation of the left atrium. Indeed, in a study of 341 hypertensive patients, LA enlargement was noted in 195 hypertensive patients (57.2%)(Ikejder et al., 2020) In hypertensive heart disease, LA dilatation is a risk factor for adverse outcome with correlation to cardiovascular disease, atrial fibrillation and disease burden.

Differential diagnosis between athlete's heart and hypertensive heart disease. (++) usually observed; (+/-)can be observed; (--) usually not observed.(D'Ascenzi et al., 2014)

Athlete's heart	Findings	Hypertensive Heart Disease
ECG		
--	Intrinsicoid deflection; P-wave terminal force in V1; P-wave dispersion	++
+-	Left ventricular hypertrophy	+-
--	Left axis deviation	+-
--	LBBB	+-
--	TWI in the infero-lateral leads	+-
--	St-T segment "strain"	+-
Echocardiography & Cardiac magnetic resonance		
+-	LV hypertrophy	++
++	Regression of LV hypertrophy after detraining*	--
--	Aortic dilatation (more than mild)	+-
--	Reduction of LV function	+-
--	Diastolic dysfunction	++
--	Increased intracardiac filling pressures	++
--	Reduced LV e' velocity	++
+-	Atrial dilatation	+-
--	Reduction of atrial function	+-
--	Reduced LV and LA deformation indexes	++
++	Balanced biventricular remodelling	--
++	Balanced biatrial remodelling	--

All in all, both entities, hypertensive heart disease and the athlete's heart result in LA dilatation, and once more, functional investigation can aid in the differentiation of the two. LA functional analysis provides information on the adaptation of the LA to the three phases of the cardiac cycle: reservoir (maximal filling), conduit (passive emptying) and boost pump (active emptying).(D'Ascenzi et al., 2020)LA strain seems to be influenced in hypertensive patients even with normal LA size, as was shown in a study of 155 patients with diabetes or hypertension (Mondillo et al., 2011)where peak atrial longitudinal strain was reduced in hypertensive patients (29.0 ± 6.5%) compared to controls (39.6 7.8%) ($p < 0.0001$).Tadic et al. evaluated 49 normotensive subjects, 50 masked hypertensive subjects and 70 untreated patients with hypertension and concluded that conduit and reservoir LA functions were significantly reduced in both hypertensive and masked hypertensive patients. Non invasive evaluation of LA stiffness was performed in the aforementioned study and the results showed that LA stiffness significantly and progressively increased from normotensive controls to sustained hypertensive patients. (Tadic et al., 2017) Despite the elevated LA dimensions, there is no increase in the left atrial stiffness in athletes, confirming the model of physiological adaptation to exercise, according to LA stiffness is normal in athletes, supporting the hypothesis of a physiological remodeling induced by exercise

4.6 AORTIC ROOT

Another parameter that should be evaluated when differentiating the athlete's heart from hypertensive heart disease, is the aortic root. Hypertension induces stress upon the aortic wall due to pressure overload which, if left untreated can even lead to the development of aortic aneurysm. Indeed aortic root dilatation in hypertensive patients has been found in a study of 1076 untreated and treated essential hypertensive patients, to have a prevalence of 9.1% (with a difference between men and women: 12.7 vs 4.5%, odds ratio 3.15; 95% CI 2.68–3.71) to 22% of patients.(Milan et al., 2013) Moreover in a systematic review and metanalysis of 10 791 hypertensive patients, aortic root dilatation was found in 9.1% of hypertensives, which was correlated with increased age and left ventricular mass (0.52 SDs, 95% confidence interval 0.41-0.63).(Covella et al., 2014)

On the contrary, in athletes, although aortic root dilatation could be anticipated as a result of haemodynamic overload inflicted upon the aorta due to exercise, this does not seem to be supported by current literature. Indeed, Pelliccia et al. studied 2317 Olympic athletes and identified the 99th percentile value of aortic root diameter to be 40 mm in males and 34 mm in females, which could be considered as the physiological upper limits aortic root enlargement in athletes. Aortic root dimensions above these values were identified in 1.3%, male athletes and 0.9% female athletes, raising the suspicion of pathology (Antonio Pelliccia et al., 2012) This finding is supported by other studies. D'Andrea et al., in a study of 615 athletes, found aortic root dimensions aboe normal in 1% of athletes..(Antonello D'Andrea, Cocchia, Riegler, Scarafile, Salerno, Gravino, Vriz, et al., 2010) Gati et al. confirm the former findings in a study of 3781 athletes in whom aortic root dilatation was observed in 0,3% of patients. In a longitudinal follow up of 3,5-6,6

years, aortic root was not increased progressively, as would be expected in pathological aortic dilatation.(Gati et al., 2019) (D'Ascenzi et al., 2020)

5. DISCUSSION

A large pool of studies was incorporated in the present thesis, and their results, although in some cases mildly contradictory, are summarized in the following chapter.

Increased wall thickness can be found in athletes, however values above 13mm are very rare (of about 1-3%) and therefore when encountered, they should raise suspicion for further testing. Left ventricular internal dimensions are also increased, and are a more common finding than increased wall thickness. End diastolic dimensions >60mm, however are extremely rare and should therefore be looked upon with suspicion. As a result of increased wall thickness and internal dimensions, LVM is also increased in athletes.

These findings are highly correlated to certain factors. Type of sport is major contributing factor, with a general appraisal of the Morganroth hypothesis that endurance sports inflicts eccentric LVH (LV mass increase with increased LV cavity dimension) and strength sports inflict concentric LVH (increased wall thickness with no change in cavity size). Some studies doubt this dichotomous view, either by failing to prove the concentric hypertrophy model of strength training or by supporting a third, mixed type of sport that incorporates features of strength and endurance training. Gender differences are also significant, with males presenting with increased internal dimensions and wall thickness compared to women, but for many studies, those differences were insignificant when adjusted for BSA. Others conclude that both men and women have increased dimensions and wall thickness induced by exercise, but the degree to which this extends, is more profound in men. Therefore, BSA, is a contributing factor affecting left ventricular geometry, along with other somatometric features such as fat free mass. In fact, in some studies, BSA was found to be an independent predictor of cardiac dimensions. Age also plays a role in the phenotype of athletes, showing a more favorable profile of cardiac function in older patient compared to controls, without however completely normalizing the effects of aging on the left ventricle. Last but not least, abuse of anabolic androgenic steroids affects left ventricular remodeling, by setting a turning point from physiologic adaptation to pathology. Studies support that those substances are correlated with increase in wall thickness and reductions in systolic function, not normally encountered in the spectrum of physiologic adaptations of the athlete's heart.

As for left ventricular function, most studies coincide that ejection fraction is generally preserved in athletes and values below 50% should promote further evaluation. GLS offers additional information in this manner, since it is generally maintained in athletic training, compared to pathologic forms of hypertrophy, such as hypertension. Myocardial work, a novel echocardiographic technique, is also normal in athletes, and can aid in the differentiation from pathology, in even earlier stages than GLS, but results are still preliminary.

Diastolic function seems to present in a supranormal fashion in athletes. The transmitral E/A ratio is typically above 2 in athletes, and this is an interesting diaforodiagnostic tool from hyperetensive patients were E/A ratio is mainly below 1 and E

velocity deceleration time is prolonged. Moreover, pulsed tissue Doppler-derived early-diastolic myocardial velocity e′ and e′ /a′ ratio are usually increased in athletes.

The left atrium follows the alterations of the left ventricle during intense athletic activity. In most studies, the dimensions of the left atrium could be increased in athletes compared to controls, with the upper limits found to be 45mm in female and 50mm in male athletes, while LAVi measurements above 36ml/m2 could not be attributed to exercise alone. Strain imaging of the left atrium proves that those alterations are of benign nature and differentiates them from the pathologic remodeling of hypertensive heart disease.

Last but not least, the aortic root, can also be found dilated in elite athletes, associated with physiologic adaptation as well. This dilatation does not increase over time in the same manner as pathological aortic root dilatation. A cutoff value of 40mm in men and 34mm in women has been proposed, beyond which further testing is suggested.

Key echocardioraphic measurements to be obtained in athletes (Galderisi et al., 2015)

Left ventricle	**Right ventricle**
LV mass index (g/m^2)	RV free wall (mm)
LV end-diastolic volume (mL)	RV basal diameter (mm)
Septal wall thickness (mm)	RV base to apex diameter (mm)
LV EF (%)	TAPSE (mm)
LV SV (mL)	IVC size (mm)
LV CO (L/min)	IVC respiratory reactivity (%)
Transmitral E/A ratio	
E velocity deceleration time (ms)	
Annular s′ velocity (ms)	
Annular e′ velocity (cm/s)	
E/e′ ratio	
e′/a′ ratio	

The above characteristics of athletic training are not specialized only for clinicians implicated in sports cardiology. Nowadays, more and more individuals are taking up exercise and intensive training, and the athlete’s heart syndrome can be anticipated not only in the elite level of competitive athleticism, but also in recreational athletes of all ages interested in good physical condition. Therefore, the clinician should be acquainted with the above findings, even though only a small percentage of athletes and trained individuals will develop them, and even a smaller percentage of them will raise to values indicative of pathology. However, echocardiography is a mere exam and careful history, clinical examination and individual characteristics should be evaluated in clinical practice and a holistic approach towards the patient should always be applied.

6.FURTHER STUDY

In the process of this review a vast bibliography on the athlete's heart has been revisited, since authors have been studying the subject for decades, leading up to the most recent publication of guidelines on Sports Cardiology, by the European Society of Cardiology. Still, though, there are parameters that need further study and longitudinal follow up, which has not been achieved so far. Moreover, newer imaging techniques such as magnetic resonance and 3D echocardiography are gaining ground in the study of the athlete's heart and will provide further and more spheric information on the topic. The right ventricle, although it was not evaluated in the present thesis, is an inseparable part of an echocardioraphic study, even though its fundamental role in the adaptation to athletic activity was appreciated more recently. Apart from hypertensive heart disease, other pathologies can be misdiagnosed when evaluating an athletic heart. These include hypertrophic cardiomyopathy, dilated cardiomyopathy and non compaction cardiomyopathy. Although they were not incorporated in this review, it should be noted that echocardioraphy alone might not be able to provide all the necessary information for their differentiation and more advanced techniques might be necessary.

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