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EVALUATION OF SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION DURING EXERCISE IN ATHLETES

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VÄRDERING AV SYSTOLISK OCH DIASTOLISK VÄNSTERKAMMARFUNKTION UNDER ANSTRÄNGNING HOS IDROTTARE

DEJAN BILAL

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Idrottshjärta är ett kardiovaskulärt tillstånd som uppträder under längre perioder av intensiv träning som orsakar strukturella, funktionella och elektriska förändringar hos hjärtat och är en fysiologisk anpassning som svar på ett ökat hemodynamiskt behov under fysisk ansträngning. De fysiologiska anpassningarna har dock blivit ett diagnostiskt dilemma att urskilja från de patologiska förändringarna såsom hypertrofisk kardiomyopati. Det finns därför ett behov av standardisering av kardiovaskulär screening hos idrottare för att upptäcka underliggande eller dolda kardiomyopatier som kan leda till allvarliga konsekvenser under fysisk ansträngning. Studiens ändamål var att undersöka den systoliska och diastoliska vänsterkammarfunktionen under ansträngning hos idrottare och öka förståelsen om vad som händer med de olika variablerna under arbete. Nio friska idrottare genomförde stressekokardiografi där cardiac index, ejektionsfraktion, fyllnadstryck, mitralisklaffplanets longitudinella rörelse (MAPSE), mitralisinflöde, vävnadsdoppler (e´ och s´) och veninflöde undersöktes före, under och efter ett ansträngningstest på ergometercykel. Variablerna under och efter cykeltestet jämfördes sedan med värdena i vila. Resultaten visade en signifikant ökning av cardiac index, MAPSE och vävnadsdoppler under ansträngning. Sammanfattningsvis visade studien att flera av variablerna förbättrades under ansträngning och en del av de visade sig vara relativt okänsliga för störningar och artefakter vilket kan vara användbart för framtida studie protokoll som avser utföra en hjärtstudie under arbete.

Nyckelord: Idrottshjärta, kardiomyopati, screening, stressekokardiografi, vänsterkammarfunktion

EVALUATION OF SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION DURING EXERCISE IN ATHLETES

DEJAN BILAL

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Athlete’s heart is a cardiovascular condition that occurs during extended periods of intense exercise that causes structural, functional and electrical changes of the heart and is a physiological adaptation in response to increased hemodynamic needs during physical exertion. However, the physiological adaptations have become a diagnostic dilemma to distinguish from the pathological changes such as hypertrophic cardiomyopathy. Therefore, there is a need for standardization of cardiovascular screening in athletes to detect underlying or hidden cardiomyopathies that can lead to severe consequences during physical exercise. The aim of the present study was to investigate the systolic and diastolic left ventricular function during exercise in athletes and to increase the understanding of what happens to the various variables during exertion. Nine healthy athletes conducted stress echocardiography where cardiac index, ejection fraction, filling pressure, mitral annular plane systolic excursion (MAPSE), mitral inflow, tissue Doppler imaging (e 'and s') and pulmonary venous inflow were examined before, during and after a cycle ergometer test. The variables during and after the cycle test were then compared to baseline. The results showed a significant increase in cardiac index, MAPSE, and tissue Doppler imaging during exertion. In conclusion, the study showed that several of the variables improved during exertion and some of them proved to be quite insensitive to disturbances and artifacts, which may be useful in future study protocols that consider carrying out a cardiac study during work.

Keywords: Athlete’s heart, cardiomyopathy, left ventricular function, screening, stress echocardiography

PREFACE

I would like to express my sincere gratitude to my supervisor and biomedical scientist, Andreas Malmgren, who gave me the opportunity to carry out this project but also his assistance with collecting ultrasound images and expertise throughout the study. In addition, I would like to thank biomedical scientist, Haris Zilic, for his assistance with the image collection, and chief physician Karin Åström-Olsson who, besides being the medically responsible physician, also contributed great expertise throughout the study. Finally, I would like to thank the unit manager Sanela Halak at Clinical Physiology at Skåne University Hospital in Malmö for the opportunity to conduct the study in her department.

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ABBREVIATIONS

A = Late filling phase
B-mode = Brightness mode
CI = Cardiac index
Dia. BP = Diastolic blood pressure
E´ = Peak mitral annular diastolic velocity
E = Early filling phase
E/A = Mitral inflow ratio
E/E´ = Left ventricular filling pressure
ECG = Electrocardiogram
EDV = End-diastolic volume
EF = Ejection fraction
ESV = End-systolic volume
GLS = Global longitudinal strain
HR = Heart rate
LV = Left ventricle
M-mode = Motion mode
MAPSE = Mitral annular plane systolic excursion
MRI = Magnetic Resonance Imaging
S´ = Peak mitral annular systolic velocity
Sys. BP = Systolic blood pressure
SV = Stroke volume
TDI = Tissue Doppler Imaging
TTE = Transthoracic Echocardiography
W = Watt

BACKGROUND

Athlete's heart is a cardiovascular condition that develops when extended periods of intense exercise is exerted which causes structural, functional and electrical changes of the heart and is a physiological adaptation in response to an increased hemodynamic need during physical exertion [1-2]. The heart adapts in such a way that it becomes vigorous while maintaining its compliance and contractility, which in turn promotes a more effective heart filling and pumping capacity of larger blood volumes [2]. However, the ability of the heart to adapt to the hemodynamic needs has become a diagnostic dilemma to distinguish the physiological changes from the pathological conditions such as left ventricular hypertrophy caused by hypertension and hypertrophic cardiomyopathy [3]. At the same time, some studies have found that the physiological changes are not necessarily beneficial but may be associated with increased risk of cardiac arrhythmias and cardiac arrest [4-5]. Thus, there is a need for standardization of cardiovascular screening in athletes to detect underlying or masked cardiomyopathies that can lead to severe consequences during physical exercise [1,6–8].

Morphological and physiological adaptations of the left ventricle

The way of how the cardiovascular system is structured entails that the left ventricle work against a significantly higher arterial load than the right ventricle. This is due to the enormous vascular branches that penetrate every organ and vary the metabolic need depending on the demand, of which the skeletal muscle during work requires the greatest perfusion. The size of the left ventricle is relative to its load and has about three times greater mass compared to the right ventricle and generates up to five times higher pressure to maintain sufficient blood pressure that can supply the tissues [2]. Morphologically there are two types of athlete's heart, both of which were identified by Morganroth in 1975, and these develop depending on the type of exercise being practiced [9]. Dynamic exercise or isotonic activity such as running, skiing, and swimming utilize aerobic processes, which results in increased oxygen consumption and the need for increased cardiac output. The initial physiological response is that the arterial resistance decreases and the venous return increase [6,9]. The blood volume returning to the heart gives rise to volume overload and causes the left ventricle to dilate as a response to the larger end-diastolic volume (EDV). Dilatation of the left ventricle stretches the myocardial fibers more than usual and produce a greater pressure which leads to an increased stroke volume with subsequent cardiac output. Furthermore, a moderate increase in blood pressure is seen in response to the volume overload. Dynamic exercise thus contributes to an eccentric hypertrophic heart [6-7,10]. The second type is developed by static exercise or isometric activity that mainly characterizes strength training which involves anaerobic processes and with a significant increase in intra-abdominal and intrapleural pressure. This pressure increase propagates through the lung vessels to the heart and contributes to increased systolic and diastolic blood pressure [11-12]. The pressure overload causes stress to the myocardium and to maintain this the left ventricle, as well as rest of the heart, adjusts by increasing the muscle mass which is termed concentric hypertrophy. Stroke volume remains the same since the course of events does not cause any change in the venous return, whereas the heart rate increases due to breathing and with this, a slightly increased cardiac output is seen [9-10,13].

Figure 1. Illustration of a normal heart to the left. In the middle is a dilated and to the right is a hypertrophic heart. The illustration is made by Dejan Bilal.

However, there are very few sports today that only utilizes one form of activity, most of them combine both dynamic and static training. In addition to the type of training, factors such as ethnicity, age, body size, gender, and genes also contribute to physiological changes in the heart [1,6].

Echocardiography

The principle of echocardiography is based on an ultrasonic transducer containing a piezoelectric material that converts electrical signals into pressure variations (ultrasonic waves) during transmission. When the ultrasound wave reaches an interface, such as musculature or skeletal tissue, a portion of the wave is transmitted to the next interface while some are absorbed or reflected. The property of the piezoelectric material is that the proportion of ultrasonic waves that are reflected back to the ultrasonic transducer, which now functions as a receiver, is again converted to electrical signals. The time from the transmission of the ultrasonic signal to the reception of the first echo is measured while echoes from deep-lying structures return gradually. The making of a two-dimensional ultrasound image is obtained by allowing the echo signal to control the light intensity on a display called *Brightness mode* (B-mode). B-mode gives a line of dots at a distance corresponding to the boundary layer where reflection took place. Higher density media such as bone tissue reflect more and thus emit a stronger echo which is seen on the display as a dot of high intensity. Correspondingly, lower density media such as muscles give a lower intensity. Compilation of hundreds of lines with dots of different light intensities eventually builds up an ultrasound image that reflects a structure in grayscale [14]. Due to the method's non-invasive trait and commercial availability, transthoracic echocardiography (TTE) is the primary choice for evaluation of heart filling, contractility, wall thickness, and ventricle dimensions as well as morphological and physiological abnormalities [15–17].

Variables of the left ventricular function

When the pressure during the isovolumetric contraction phase exceeds the pressure on the arterial side, the aortic valve opens, and the ejection phase begins. During the ejection phase a simultaneous longitudinal contraction, circumferential twisting and radial reduction of the ventricle diameter occur, resulting in the diastolic blood volume being ejected into the aorta [18,19]. The ejection fraction is a systolic parameter that describes how much of the diastolic volume (stroke volume) is pumped out during the ejection phase. This is calculated quantitatively with Simpson's biplane method, whose principle is that the left ventricle is divided into a number of discs in the four-chamber view and the two-chamber view. The volume of each disc is calculated by the product of the disc's length and area and the sum of all discs constitutes the total volume of the left ventricle. The end-diastolic volume is obtained as the name suggests in end diastole and end-systolic volume (ESV) during end systole. The ejection fraction is then obtained according to the following equation [20]:

$$\text{Ejection fraction \%} = \frac{(\text{EDV} - \text{ESV})}{\text{EDV}}$$

Mitral annular plane systolic excursion

Motion mode (M-mode) is an alternative to B-mode where the transducer transmits and receives sound waves at very high frequencies, enabling image reconstruction of moving structures [21]. M-mode is used in assessing the longitudinal movement of the mitral plane or MAPSE (mitral annular plane systolic excursion) which is a measurement of the left ventricular pumping capability and refers to how much the mitral plane in diastole is displaced towards the cardiac apex during systole. The displacement is examined both from the septal and lateral mitral annulus wall in the four-chamber view and from the inferior and anterior mitral annulus wall in the two-chamber view. However, more well-developed techniques such as strain and tissue Doppler (see below) have more or less replaced MAPSE [21-22]. One advantage of MAPSE is that the quality of the ultrasound image does not need to be optimal in order to obtain assessable results, unlike the other techniques whose good image quality is a prerequisite for reliable results [21].

Cardiac Index

Cardiac output is the product of heart rate and stroke volume and these variables change during physical activity. However, exercise is not the only contributing factor, also age, sex, and body size have a direct impact on cardiac output both at rest and during exercise [23-24]. Cardiac Index (CI) is a systolic parameter that takes consideration to the cardiac output in relation to the individual's body size and indicates how much blood volume is pumped out per minute per square meter according to the equation [24]:

$$\text{CI liter/minute/m}^2 = \frac{\text{Cardiac output}}{\text{Body surface area}}$$

Strain – a systolic measurement of deformation

Strain (ε) is another systolic parameter that describes the degree of longitudinal, radial and circumferential deformation, that is, shortening, elongation, and thickening of the myocardium. The principle is that the myocardium is divided into segment lengths (L) which are deformed over time (t) during systole and diastole, and with knowledge of the original length (L0) strain can be acquired according to the equation [25]:

$$\varepsilon(\text{t}) = \frac{(\text{L}(\text{t}) - \text{L}_0)}{\text{L}_0}$$

A positive strain value means prolongation of the myocardium while a negative value means shortening [25]. On the grayscale of the two-dimensional ultrasound image, small irregular structures of different intensity are seen which interfere with each other (speckles). Speckle tracking is a method that follows these speckles between two consecutive images during the cardiac cycle. By comparing the movement of speckles over time between two dots, strain can be calculated [25].

Tissue Doppler – systolic contraction and diastolic relaxation
During ventricular contraction and relaxation, the movement of blood flow and the myocardium emit different frequencies which can be differentiated by tissue Doppler imaging (TDI). Blood flow gives rise to signals of high frequency and low amplitude, while the movement of the myocardium produces signals of low frequency and high amplitude. Adding a low-frequency filter will filter out the blood flow signals. This enables evaluation of the myocardial contraction and relaxation velocity in the longitudinal plane during the cardiac cycle [26]. The spectral Doppler shows partly a predominantly positive wave representing the systolic contraction (s') and partly two predominantly negative waves, the diastolic relaxation (e 'and a'). e´ and a´ corresponds to the E wave and the A wave of the mitral inflow (see below) [26].

Mitral inflow – the diastolic filling
After the systolic phase, the intraventricular pressure is lower than the arterial side and the aortic valve closes which initiates the isovolumetric relaxation phase. During this time the myocardium relaxes, and the intraventricular pressure decreases. When the intraventricular pressure is lower than the atrial pressure, the mitral valve opens and the stored blood volume in the left atrium enters the left ventricle. On the pulsed spectral Doppler, two positive waves E and A are seen which represent the early filling phase and the late filling phase (atrial contraction) respectively [17,27].

Left ventricular filling pressure
For an efficient filling of the left ventricle, the left atrium needs to have adequate pressure and the myocardium must have at least a moderate ability to relax. The E/e´ ratio is a diastolic estimation of left ventricular filling pressure [28-29].

Pulmonary vein inflow
During systole (S) the left atrium is continuously filled from the pulmonary vein and when diastole (D) commence, a negative pressure occurs in the left ventricle, which causes the blood volume in the pulmonary vein to be sucked into the left ventricle through the left atrium without intermission. When the atrial contraction occurs, a slight reversal of the blood volume to the pulmonary vein can be seen on the spectral Doppler [30-31].

Previous studies
The dilemma with hypertrophic cardiomyopathy and idiopathic dilated cardiomyopathy has led to a great demand for finding adequate variables that can be used to distinguish the physiological conditions from the pathologies. Previous clinical studies have in many cases focused on wall and ventricle dimensions and compared these to reference values in normal individuals [32–36]. Others have in addition to the wall and ventricle dimensions also examined the diastolic filling and discovered significant differences in, among other things, the mitral inflow [36–38]. While a recent study conducted on athletes and sedentary individuals measuring myocardial performance index showed no significant difference

between the two groups [39]. One aspect to consider is that several of these studies have been carried out either at rest or after exertion, which causes a loss of information during the exertion test which can possibly be valuable.

Aim

The aim of this study is to evaluate and increase the understanding of the systolic and diastolic left ventricular function during physical exertion, by comparing left ventricular variables during and after exertion to rest in athletes.

METHOD AND MATERIAL

The recruitment process focused on healthy volunteering athletes with a relatively high training activity and who were continuously active for at least one year in their respective sports, and that the sports they practiced combined dynamic and static activity. Contact was made with football and handball clubs in Malmö and Lund, and the athletes were recruited on site at their sports facilities. The selection criteria for participation were that all athletes, without exception, would be over 18 years and did not have any known cardiovascular disease. Based on these conditions, the study included nine men and one woman. The age of the athletes was between 18 and 36 years.

Ethical permission

In conjunction with the planning and preparation of the study, an application for ethical review was submitted to Malmö University's ethics committee at the Faculty of Health and Society. An approved statement was received 2019–02–01 (HS2019 serial number 31).

During the recruitment, all interested athletes were informed verbally and in writing with an information letter (Appendix 1) about the study. Before the examination, the athletes were informed again and had to give a written consent that they had understood the contents and purpose of the study (Appendix 2). All participants were given the opportunity to ask any questions prior to and after the examination. Participation was completely voluntary, and everyone was entitled to cancel or withdraw from the study at any time without having to give any reason.

Stress echocardiography

The examination protocol was explained to the participants and their length and weight were documented for calculation of their body area surface. The two-dimensional echocardiographic examinations were performed by a licensed biomedical scientist who used Philips EPIQ 7G (Philips Medical Systems, Bothell, WA, USA) ultrasound apparatus equipped with a Philips X5-1 xMATRIX transducer and an accessory device with the purpose of holding the transducer in place on the chest. The exertion test was performed on a Marquette Holy Medical Systems ERG 900 ergometer cycle. Heart rate was visualized with GE MAC 5500 and blood pressure was measured auscultatory. A medically responsible physician participated throughout the study. All measurements were digitally stored and analysed offline by a student after completing the examination with the IntelliSpace Cardiovascular software (Version 2.3, Philips Medical Systems, Veenpluis, Netherlands). The echocardiographic measurements were performed according to the current guidelines of the American Society of

Echocardiography and the European Association of Cardiovascular Imaging [40,41].

The participant was in a left lateral decubitus position with the left arm under the head and the right arm along the body and a unipolar electrocardiogram (ECG) was used to follow the heart cycle. In the parasternal view, the diameter of the left ventricular outflow tract was measured between the inner walls of the aorta cusps. The apical window was then located for the attachment of the device which was intended to hold the ultrasonic transducer in place during the exercise test.

The participant moved to the cycle ergometer and the blood pressure was registered in the right arm. Another ECG was used for visualization of the heart rate used to calculate the cardiac output. The transducer was attached to the chest and all measurements were initially performed at rest in an upright sitting position.

The four-chamber view was visualized apically (figure 2 and 3) where the end diastolic and end systolic left ventricular volumes were recorded for calculating the ejection fraction, along with the left ventricular volume in the two-chamber view, according to the Simpsons biplane method. The longitudinal movement of the mitral plane was recorded with M-mode across the septal and lateral mitral annulus. The longitudinal displacement of the mitral plane was measured from diastole to systole. Likewise, the longitudinal velocity of the myocardium was registered with pulsed tissue Doppler (figure 4 and 5) along the septal and lateral ventricle wall with the sample volume at the mitral annulus for measurement of contraction (s') and relaxation (e 'and a') velocities. With pulsed wave Doppler, the mitral and pulmonary vein inflows were measured, where the sample volume was placed at the tip of the mitral cusps to record the early filling phase (E) and the atrial contraction (A) and inside the pulmonary vein to register the systolic (S) and diastolic (D) inflow. Based on these variables, the E/A and S/D ratios were calculated. In addition, the filling pressure (E/e ') was estimated based on the variables obtained.

The apical two- and three chamber view was obtained by adjusting the degrees of the ultrasound beam. In the two-chamber view, the end diastolic and end systolic left ventricular volumes were registered as before. MAPSE was similarly measured inferior and anterior of the mitral annulus. In the three-chamber view, pulsed wave Doppler was used in the left ventricular outflow tract to calculate the stroke volume along with the diameter obtained from the parasternal view.

Starting workload on the cycle ergometer was set to 75 watts (W) with an incremental increase of 15 W every minute for both men and women and lasted until the athletes could no longer continue. During cycling, the echocardiographic process, blood pressure measurement, and heart rate monitoring were repeated after two minutes of exertion, at 85% of maximum heart rate (220 minus age multiplied by the percentage) and finally four minutes after completed exertion.

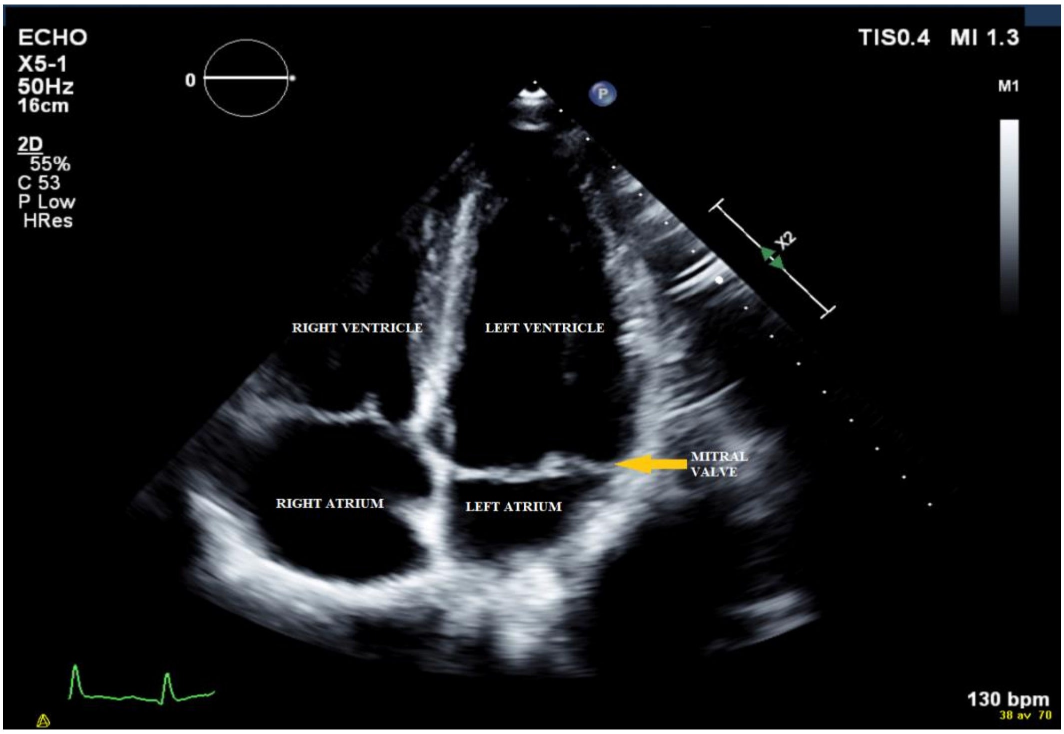

Figure 2. Apical four-chamber view at rest. The apex of the left ventricle is obscured (top of the ultrasound image), the right chamber is partly outside the image, the right atrium is noticeably larger than the left atrium, which is due to the fixation of the transducer. The high heart rate is due to the nervousness of the participant. The ultrasound image is produced and approved for publication by Andreas Malmgren, licensed biomedical scientist, Skåne University Hospital Malmö, Clinical Physiology and Nuclear Medicine.

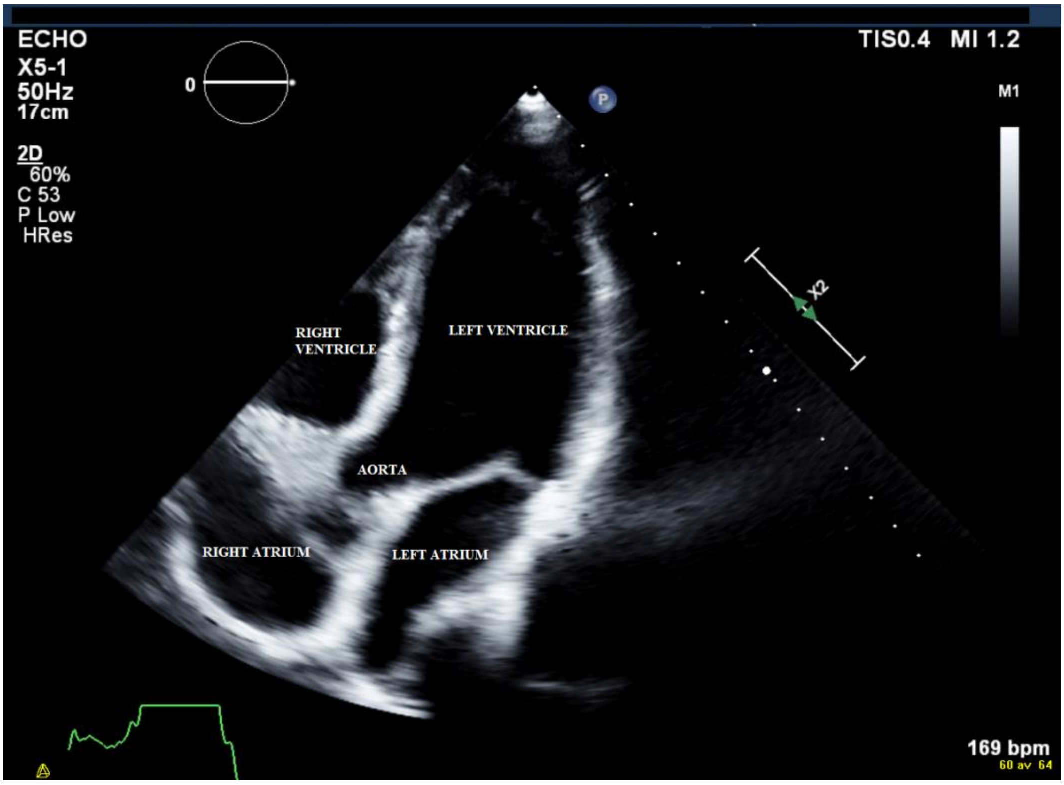

Figure 3. The apical five-chamber view at 85 % of maximal heart rate. A different shape of the right and left atrium is seen, respectively. Additionally, the aorta is shown which is due to the participant's movement which moved the device and thus the transducer, this caused the five-chamber view to appear instead of the desired four-chamber view. The electrocardiogram also shows disturbances due to movement. The ultrasound image is produced and approved for publication by Andreas Malmgren, licensed biomedical scientist, Skånes University Hospital Malmö, Clinical Physiology and Nuclear Medicine.

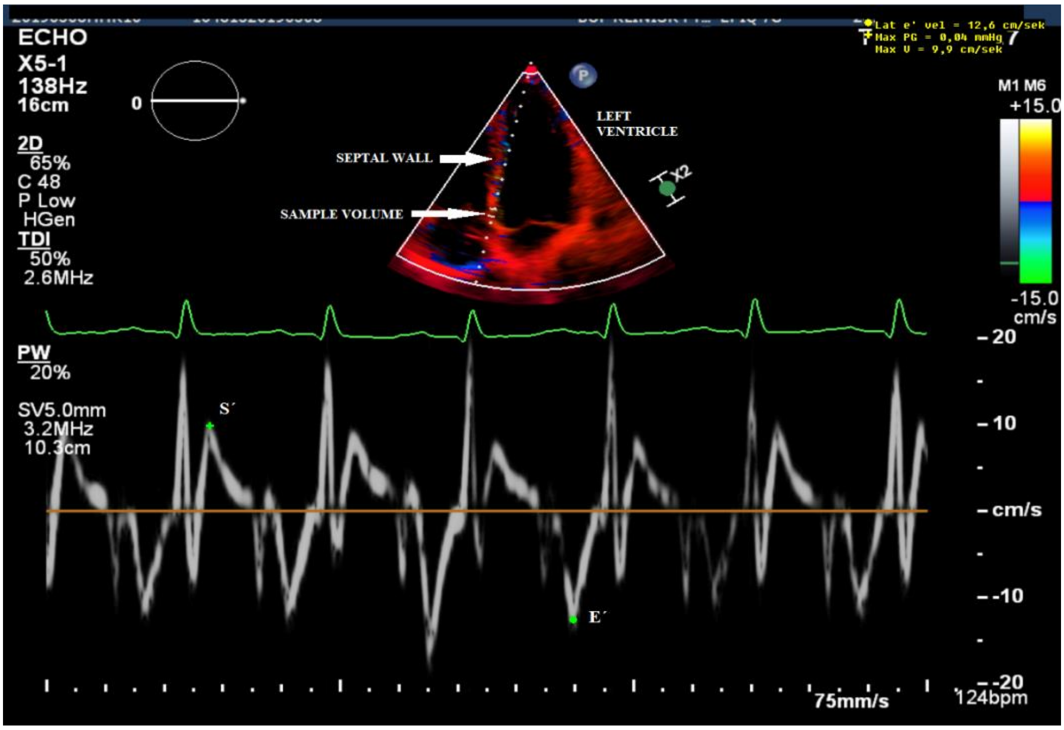

Figure 4. Registration with tissue Doppler imaging, TDI, (top of the illustration) is seen along the septal ventricle wall and sample volume placed adjacent to the mitral annulus at rest. When the annulus moves toward the apex in systole, it appears above the baseline. s´ (systolic contraction) velocity is registered at the maximum velocity. When the ventricle relaxes, the annulus moves to its original position, which appears below the baseline on the spectral Doppler. e´ (diastolic relaxation) velocity is registered as previously. The ultrasound image is produced and approved for publication by Andreas Malmgren, licensed biomedical scientist, Skåne University Hospital Malmö, Clinical Physiology and Nuclear Medicine.

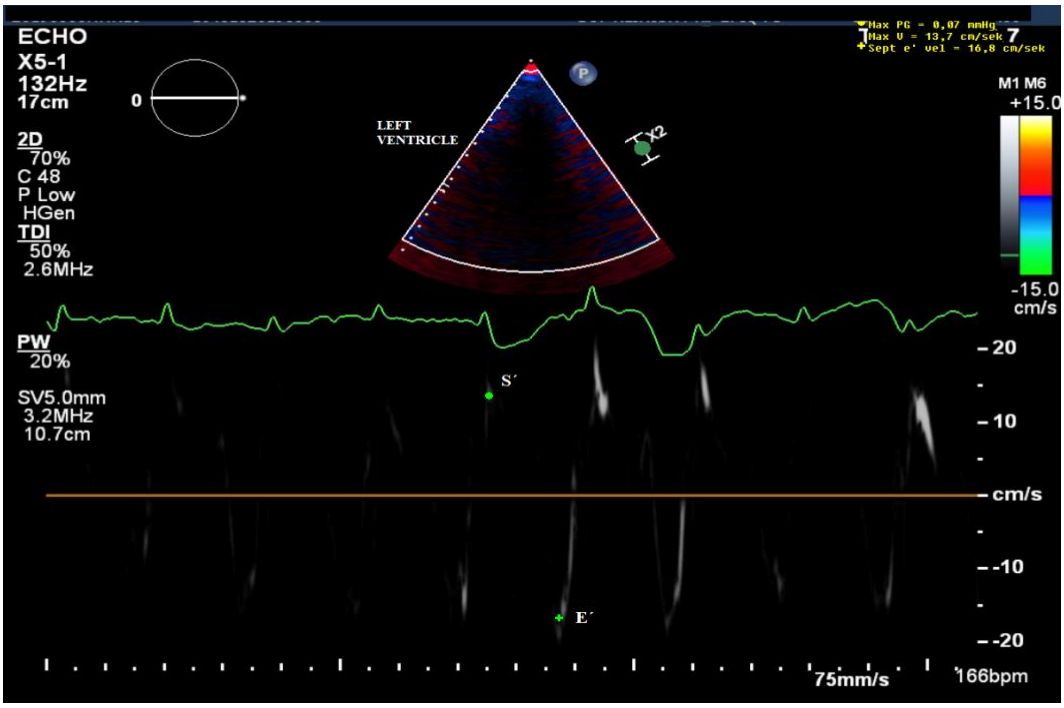

Figure 5. Registration with tissue Doppler imaging, TDI, at the septal ventricle wall in the four-chamber view (not visualized at the top of the illustration) at 85% of maximum heart rate. s´ and e´ in the spectral Doppler is not as clearly defined as in rest, which is partly due to where the sample volume is placed and how well the left ventricle is visualized. The ultrasound image is produced and approved for publication by Andreas Malmgren, licensed biomedical scientist, Skåne University Hospital Malmö, Clinical Physiology and Nuclear Medicine.

Statistics

All collected data were processed and compiled in Microsoft Excel (Version 2016, Microsoft) and presented in the form of mean values and standard deviation.

For the inferential statistical analysis, this study used Wilcoxon's signed-rank test which is a non-parametric method for comparing the same variable at two different times [41-42]. The analysis was conducted in the IBM SPSS Statistics software (Version 25.0, IBM Corporation). Non-parametric methods do not require that the data being analysed meet specific statistical requirements, for example, if the data is normally distributed or not [42-43]. The results stated on the ordinal scale were ranked and with the Wilcoxon signed-rank test, a confidence interval of 95% was calculated around the median difference and a *p*-value was obtained [44]. All variables were compared to baseline (two minutes - baseline, 85% of maximum heart rate - baseline and four minutes - baseline). A *p*-value <0.05 indicates that there is a statistical significance, which means a systematic difference of the variable at two different times. A *p*-value >0.05 indicates correspondingly that there is no statistical difference of the variable at two different times [42,45].

RESULTS

Out of the ten athletes, everyone except one completed the examination. The mean age of the athletes was 24 ± 6 years and the average time for the exertion test was 13 ± 2 minutes. The mean body weight was 82 ± 13 kg and the maximum workload the athletes achieved on average was 255 ± 44 W. Table 1 presents general data from all nine athletes. Heart rate and systolic blood pressure increased with increasing workload and almost returned to baseline four minutes after exertion. Diastolic blood pressure could not be auscultated under exertion. EDV in the left ventricle showed a volume increase after two minutes which then decreased with higher heart rate. The ESV remained the same until the heart rate was about 85%. However, both EDV and ESV reduced below baseline after exertion.

Table 1. Mean ± standard deviation of general data. *Sys. BP*, Systolic Blood Pressure; *Dia. BP*, Diastolic Blood Pressure; *LV EDV*, left ventricular end-diastolic volume; *LV ESV*, left ventricular end-systolic volume.

	Baseline	**2 minutes exertion**	**85 % max. heart rate**	**4 minutes postexertion**
Watt (W)	75 ± 0	105 ± 0	220 ± 31	-
Heart rate (bpm)	75 ± 20	108 ± 12	154 ± 9	101 ± 18
Sys. BP (mm Hg)	121 ± 18	157 ± 22	202 ± 20	129 ± 19
Dia. BP (mm Hg)	80 ± 11	-	-	68 ± 14
LV EDV (mL/m^2)	56,2 ± 10,0	62,6 ± 10,3	58,5 ± 5,4	51,2 ± 7,2
LV ESV (mL/m^2)	27,1 ± 7,4	27,0 ± 10,6	24,3 ± 7,0	24,9 ± 6,6

Table 2 presents data of the left ventricular systolic function expressed in mean ± standard deviation. Among the nine athletes, the ejection fraction improved during exercise and almost returned to baseline after exertion. Significant improvement also appeared with MAPSE and TDI s´. CI takes into consideration of every individual's body area surface and showed in many cases a double increase. Stroke volume showed a great variation as opposed to the other variables, however, this variable is missing in one-third of the athletes.

Table 2. Mean ± standard deviation of the systolic left ventricular function. The number of values is shown as (^{n}) when less than nine and $\overline{x}$ is the mean of the mitral plane in the left ventricle. *EF,* Ejection fraction; *SV,* Stroke volume; *CI,* Cardiac index; *MAPSE,* Mitral annular plane systolic excursion; *TDI,* tissue Doppler imaging; *GLS,* Global longitudinal strain.

	Baseline	**2 minutes exertion**	**85 % max. heart rate**	**4 minutes postexertion**
EF (%)	51,2 ± 9,4	57,4 ± 10,5	55,6 ± 10,1	49,8 ± 7,5
SV (ml)	53,3 ± 13,8	82,5 ± 12,4	68,2 ± 22,0$^{(6)}$	53,6 ± 12,4$^{(8)}$
CI (L/min/m^2)	2,0 ± 0,5	4,5 ± 1,2	5,2 ± 1,7$^{(6)}$	2,7 ± 0,8$^{(8)}$
MAPSE $\overline{x}$ (mm)	12,1 ± 1,9	17,7 ± 1,6	21,0 ± 1,5$^{(8)}$	13,4 ± 1,8
TDI s´ (cm/s)	9,6 ± 1,5	13,3 ± 2,6$^{(8)}$	17,9 ± 5,7	12,0 ± 1,0
GLS (-%)	14,0 ± 1,9	14,6 ± 4,2	13,4 ± 3,2$^{(8)}$	13,3 ± 1,7

Data on the diastolic left ventricular function is presented in Table 3. In most athletes, no E/A ratio could be obtained during exertion. After the test, a majority of the athletes showed a reduced mitral inflow compared to rest. On the contrary, the filling pressure in the left ventricle improved at the beginning of the test which later on decreased with increasing heart rate. The pulmonary vein inflow remained the same throughout the test. TDI e' show in a similar way as TDI s´ an increase during the test, which then regresses to baseline after completion.

Table 3. Mean ± standard deviation of the left ventricular diastolic function. The number of values is shown as (^{n}) when less than nine. *E/A,* mitral inflow ratio; *S/D,* pulmonary vein inflow ratio; *TDI,* tissue Doppler imaging; *E/e´,* filling pressure.

	Baseline	**2 minutes exertion**	**85 % max heart rate**	**4 minutes postexertion**
E/A	1,9 ± 0,5	1,3 ± 0$^{(2)}$	-	1,4 ± 0,5$^{(5)}$
S/D	>1 ± 0	>1 ± 0	>1 ± 0$^{(7)}$	>1 ± 0
TDI e´ (cm/s)	9,9 ± 2,2	15,0 ± 3,0	23,1 ± 4,7$^{(8)}$	10,4 ± 3,3
E/e´	6,9 ± 1,3	7,2 ± 1,3	6,3 ± 1,4$^{(8)}$	8,1 ± 2,5

Statistical results

Results from Wilcoxon's signed-rank test are presented in the tables below. Each variable is compared against itself, that is, the moments during and after the exertion test are compared to the baseline. Tables 4, 5 and 6 show whether a variable has increased, decreased or remained the same during and after exertion, respectively. The number of positive values indicates that an increase has occurred, the number of negative values indicates that a reduction has occurred while the number of ties indicates that no difference has occurred. The greater the median difference is between the positive, negative and ties values, the lower the *p*-value is. The confidence interval is 95% around the median difference, which means that p-value <0.05 shows a statistically significant difference of the variable during or after the exertion test.

The volume in the left ventricle at the end of diastole and systole in Table 4 does not show any significant difference either during or after the exertion test.

Table 4. Median difference of the left ventricular volume compared to baseline. Number (n) of positive, negative or ties indicate whether an increase, reduction or no difference has occurred during or after the exertion test. A *p*-value <0.05 indicates that the variable shows a statistical difference during a given time. *LV EDV*, left ventricular end-diastolic volume; *LV ESV*, left ventricular end-systolic volume.

Variable	Time	n positive	n negative	n ties	*p* value
	2 minutes	3	6	0	0,21
LV EDV	85 % max	5	4	0	0,52
	4 minutes	3	6	0	0,21
	2 minutes	3	6	0	0,37
LV ESV	85 % max	3	6	0	0,44
	4 minutes	5	4	0	0,52

In table 5, cardiac index, MAPSE and TDI s´ show that a statistically significant difference exists throughout the exertion test while ejection fraction and stroke volume only show a difference two minutes after the test. Global longitudinal strain, on the other hand, shows no significant difference throughout the test.

Table 5. Median difference of the left ventricular systolic variables compared to baseline. Number (n) of positive, negative or ties indicate whether an increase, reduction or no difference has occurred during or after the exertion test. A *p*-value <0.05 indicates that the variable shows a statistical difference during a given time. *EF*, Ejection fraction; *SV*, Stroke volume; *CI*, Cardiac index; *MAPSE*, Mitral annular plane systolic excursion; *TDI*, Tissue Doppler Imaging; *GLS*, Global longitudinal strain.

Variable	Time	n positive	n negative	n ties	*p* value
	2 minutes	7	2	0	0,028
EF	85 % max	5	4	0	0,55
	4 minutes	4	5	0	0,86
	2 minutes	9	0	0	0,008
SV	85 % max	4	2	0	0,25
	4 minutes	2	6	0	0,58
	2 minutes	9	0	0	0,008
CI	85 % max	6	0	0	0,028
	4 minutes	8	0	0	0,012
	2 minutes	9	0	0	0,008
MAPSE	85 % max	8	0	0	0,012
	4 minutes	9	0	0	0,007
	2 minutes	8	0	0	0,012
TDI s´	85 % max	8	1	0	0,011
	4 minutes	8	1	0	0,011
	2 minutes	5	3	1	0,48
GLS	85 % max	3	5	0	0,26
	4 minutes	3	6	0	0,31

Only a few results of the E / A ratio were obtained after two minutes, which did not meet the criteria (n <4) for calculation with Wilcoxon's signed-rank test, the p-value is thus 1.0. After the test, the E/A ratio does not show any significant difference. Likewise, the filling pressure also shows no difference throughout the test, whereas TDI e´ shows an evident significant difference during the test.

Table 6. Median difference of the left ventricular diastolic variables compared to baseline. Number (n) of positive, negative or ties indicate whether an increase, reduction or no difference has occurred during or after the exertion test. A *p*-value <0.05 indicates that the variable shows a statistical difference during a given time. *E/A*, mitral inflow ratio; *TDI*, Tissue Doppler Imaging; *E/e´*, filling pressure. The star (*) reports a small number of results.

Variable	Time	n positive	n negative	n ties	*p* value
	2 minutes*	1	2	0	1,0
E/A	85 % max	-	-	-	-
	4 minutes	2	4	0	0,46
	2 minutes	9	0	0	0,008
TDI e´	85 % max	8	0	0	0,012
	4 minutes	5	4	0	0,86
	2 minutes	7	2	0	0,29
E/e´	85 % max	3	4	1	0,18
	4 minutes	6	3	0	0,07

DISCUSSION

The lack of standardized screening among athletes poses a risk of missing cardiomyopathies or other subtle pathologies. Therefore, there is a need to find suitable methods and parameters that can be used to distinguish physiological adaptations from pathological changes [1,6–8]. With current guidelines in echocardiography, normal values are based on data from both healthy sedentary and healthy athletes. But in an athlete, the morphological and physiological adaptations in the heart often mean that larger heart mass, higher blood flow rates, heart volumes and larger blood volumes pumped out will be the new norm [9]. A variable that has decreased a few percent’s may still be considered normal since it is within the normal limits. While in a sedentary individual, it might have dropped below the normal limits and thus considered to be of a pathological cause. Therefore, this study evaluated the systolic and diastolic left ventricular function during exertion to see the changes in the physiology. Furthermore, some of the variables examined may possibly be used for future screening of athletes and new specific reference values may perhaps be compiled to better determine whether a change in the athlete is a normal phenomenon or pathological.

Selection discussion

During the selection process, even gender distribution was sought in the study and initially included ten men and ten women who trained football or handball. Unfortunately, unforeseen events occurred such as illness and dropouts which drastically reduced the number of participants. Among the respondents, the participation interest was four times greater in men than in women. Economic reasons and limited time in the hospital contributed to the maximum number of twenty participants, and these were prioritized to athletes. This meant that a control group of untrained or sedentary individuals was not included. Otherwise, a control group is necessary to determine if changes that occur in the athletes also occur in untrained individuals and to what degree, and how much it differs between the two groups.

The criteria for the physical activity are based on physical regression (detraining) when the body is no longer stimulated to the same degree as before, which causes the physiological adaptations such as hypertrophy, increased cardiac output and so forth to regress in some degree. This regression begins to develop after about three weeks of detraining [45-46]. Considering this, athletes included in the present study trained continuously and with relatively high activity, which for this group of athletes corresponded between eight to sixteen hours a week. They should have trained their sport for a longer period of time in order for the physiological and morphological changes to appear. Some of the athletes had not previously performed a cardiac examination while others had in conjunction with the transition to a new sports club made a health check of various kinds. There was, therefore, no history of cardiovascular disease, instead their prosperous was based on their own statement. For the study, this meant that there was a potential risk of detecting abnormalities in conjunction with the ultrasound examination or that something unexpected could occur during the exertion test [47-48]. For this reason, a medically responsible physician participated throughout the study.

Method discussion

In Europe, cycle ergometer tests are routinely used for evaluation of the physical capacity such as fitness and oxygen consumption, but also for the evaluation of cardiovascular disease and the effect of various treatments [50]. At the department in the hospital where the study was conducted, both treadmill and ergometer bikes were available. One advantage of cycling is that fewer artifacts occur in the electrocardiogram compared to treadmill [50]. Athletes whose performance is to be evaluated with a cycle ergometer test is the recommended starting workload 40 W with an incremental increase of 10 W per minute [50]. In this study, the starting workload was instead 75 W with an incremental increase of 15 W per minute for both men and women for standardization purposes. Differences in physical capacity between men and women regarding muscle mass, strength and fitness may possibly affect the achieved workload [51]. Such differences did however not occur in this study, all athletes performed similarly to each other. However, the female athlete does not represent how other women would have performed under the same conditions. A larger number of female athletes were needed to get a better representation. A healthy individual between the ages of 18 and 35 is 85% of the maximum heart rate between 157 and 175 beats per minute. With this protocol, it meant that the athletes after ten minutes have reached a workload of 225 W which corresponds to a heart rate of about 170 beats per minute [50]. Considering the limited time that was one hour for each athlete, this study protocol was the most appropriate choice.

Cycle ergometry is a form of dynamic activity which means that the arterial resistance decreases and the venous return increase during work [6]. As mentioned earlier this results in volume overload. Volume overload, in turn, contributes to increased cardiac output and subsequent increase in systolic blood pressure [6,49]. From a safety perspective measurement of the systolic blood pressure was thus an important factor to measure so it increased with increasing workload. A systolic blood pressure that does not increase significantly with increasing effort indicates an underlying disease [52]. The diastolic blood pressure either remained the same or decreased slightly due to the vasodilation of the blood vessels and is therefore not of equal importance [49].

The reason why two ECGs were used (ECG in the ultrasound device and the portable ECG device) was that the electrodes belonging to the ultrasound device were incredibly sensitive, and during motion, interference occurred which caused misleading heart rhythm and heart rate. A secondary ECG device that was significantly more durable was therefore used to monitoring the heart rhythm and heart rate. Visualization of the heart rate was of great importance for the knowledge of when the athlete achieved 85% of the maximum heart rate.

The ultrasound examination was only performed apically because the device being used to fixate the transducer was basically fixed in place when attached on the chest. Thus, in order to obtain parasternal or subcostal projections, the device had to be removed and reattached which was not possible during the test. However, a parasternal image of the left ventricular outflow tract was obtained prior to attaching the device where the diameter was used to calculate the stroke volume. The study protocol proved to be effective. The systematic structure meant that the cursor and sample volume did not need to be moved to a greater extent except for angular adjustment as in the transition of M-mode of MAPSE to pulsed tissue Doppler along the ventricle wall. Likewise, for the registration of the mitral inflow and the pulmonary inflow, the cursor was only angularly adjusted, and the sample volume was moved in the longitudinal direction. The layout of the protocol saved potential time and effort than if the measurements had been made randomly.

Limitations

During the attachment of the device, concerns were discovered with the product which came to affect the examination. The device that was intended to hold the transducer in place was very bothersome. When an optimal apical view was obtained the device had to be fixed in place with straps around the chest and over the neck which at times would release, causing the transducer to move from its location and the apical view disappeared. Realignment did not always give the same image as before; the ventricle was either obscured by artifacts or the transducer was misplaced. The attachment procedure was often experienced as very uncomfortable for the athlete due to the continuous pressure on the ribs produced by the device. This meant that some changed their posture to reduce discomfort or pain, and this, in turn, caused the ultrasound image to disappear. Likewise, the athlete's physique affected how well the device was in place. The breast tissue from the female athlete had a tendency to push it down, while for men there was often a gap between the transducer and the skin. Men with narrow body gave the best ultrasound images at the expense of more pain to the ribs. During the entire procedure, the examiner held the transducer in place and manually adjusted the angle that vanished when the transducer was released. The device was not user-independent as it was expected of.

During cycling the ultrasound image would often improve, that is the entire ventricle appeared well without any major artifacts and may possibly be because the body movement favoured the positioning of the device and the transducer. The main concern was that there was no adequate angular correction, but also that some of the obtained ultrasound images showed deformed ventricles (round or rectangular). The lack of angular correction contributed to the fact that several measurements both at rest and during exertion, but mainly during exertion, gave misleading values. However, it was not just the angular correction that contributed to misleading values. With increasing heart rate, breathing also increased causing the lungs and other artifacts to obscure the heart and thus both the cursor and sample volume could not be properly positioned for measurement. This was found to be most difficult at about 85% of maximum heart rate.

A physical obstacle that every athlete encountered was early fatigue. At about 180 W the majority of athletes began to feel fatigued even though they thought they still had a lot of energy left to give. Factors such as ergonomics, revolutions per minute (RPM) and the number of muscles that are activated, the technique, during cycling have an impact on how fast muscle fatigue occurs [52-53]. Energy consumption increases for example if the RPM is constantly varied during increasing workload. On a cycle ergometer, the maximum performance is ten percent less compared to running due to the fewer muscles being activated [50].

In some places, a semi-supine cycle ergometer is used instead of an upright sitting cycle ergometer because the upper body is mostly stationary and in an angled position. The angled posture widens the space between the ribs and thus enables ultrasound examination during exertion [54-55]. Even with a semi-supine cycle ergometer, one cannot overlook that the breathing that increases with the workload will be a continuing concern. Likewise, the problem of fatigue will persist, even arising earlier than an upright sitting cycle ergometer because it is more difficult to generate the same amount of force required as when being upright [50].

The heart's morphology and physiology can also be evaluated using Magnetic Resonance Imaging (MRI). Unlike echocardiography that uses ultrasound waves, MRI uses radio waves to excite the hydrogen nuclei in the body which in turn induces a radio signal in a receiver. After data processing, a visual image with different light intensities is obtained which depends on the concentration of hydrogen nuclei in the tissue [14]. The images are much more resolved compared to echocardiography, which gives more detailed information. However, studies have shown that heart volumes and the ejection fraction calculated from the Simpsons biplane method are somewhat similar between the methods. The disadvantage of MRI is that it requires the individual to be still because movement gives rise to artifacts, which is why these studies have been carried out either at rest or after exertion [56-57].

Result discussion

One athlete did not complete the study because the image quality was too poor during the test and no variables could be measured. For this reason, this athlete was excluded from the results. The rest of the athletes completed the exertion test within ten to twenty minutes. According to Löllgen & Leyk study [50] healthy individuals, based on this study's age group, body weight, and gender, should achieve a maximum workload between 210 to 260 W, which everyone did. With the single female athlete, a conclusion cannot be drawn about the maximum workload for a larger population of women because the number of participants in this study is too small. However, this athlete performed more than the average for women and even better than some men [50]. The systolic blood pressure was essential to check for any underlying heart disease. If that would be the case, the systolic blood pressure had either remained unchanged or would have suddenly dropped during exertion [52]. Systolic blood pressure exceeding >250 mm Hg during an exercise test may pose a potential risk to develop left ventricular hypertrophy and elevated blood pressure in the future [49,59]. However, nothing suggests that there is any heart disease present in these athletes based on these parameters since the systolic blood pressure never exceeded >250 mm Hg neither did it drop. After the test, the systolic blood pressure regressed to baseline. Since the diastolic blood pressure could not be measured during the test, no results are available that can be compared to reference values. Nonetheless, the diastolic pressure was about the same at the beginning as at the end [49].

The results of the echocardiographic measurements must be taken with caution due to the lack of angular correction that occurred during the study. At rest, the EDV of the LV corresponds to the current normal values [36,60]. During the exertion test, EDV increased just as previous studies have also shown [36,61]. The assessment of the ESV varies depending on the reference values used. In the *NORRE* study [60] were 865 healthy individuals conducted a complete echocardiographic examination, the ESV in this study exceeded their normal values while in the article *Recommendations for Cardiac Chamber Quantification* by the European Association of Cardiovascular Imaging and the American Society of Echocardiography [41], the ESV is in their upper normal values. There is, however, no adequate evidence that the result suggests anything in particular, but is probably fully normal or a lesser physiological adaptation in some that may have developed from doing dynamic training for a longer period of time [62]. During exertion, an average increase in EDV is seen while ESV starts to decrease at about 85% of maximum heart rate. Even so, the study material is too small to be able to determine if there is a statistically significant difference in volume in the left ventricle during exertion. From the statistical analysis, just over one-third show an increase, which is not enough to draw an adequate conclusion. Thus, a larger population of athletes is needed who exhibit either a predominant increase or decrease in ventricle volume in order for the change to be considered significant [42].

Furthermore, for the systolic variables, it is seen that EF and GLS are below the reference values for most athletes. Normally, EF is >55% with the Simpsons biplane method [41,60] and GLS is between -15.9% and -22.1% [63]. One possible explanation for these results may be the lack of angular correction. A gap between the transducer and the skin or simply wrongly tilted transducer and the ventricle is either deformed or obscured, which affects the measuring ability with the Simpsons biplane method and even more with GLS which is dependent on good image quality to follow speckles. In turn, this affects the credibility of the statistical analysis, which states that the difference from rest to post-exertion is not significant. However, after two minutes, EF shows a predominant increase among the athletes, which indicates that the variable is improved with exercise. Unfortunately, excessive movement and breathing became too much of an obstruction at higher heart rates. These conditions need to be improved for an adequate evaluation of ejection fraction during exercise.

SV is not routinely used for diagnostics in echocardiography because other more reliable and proven variables such as EF and GLS exist (remark that diagnostic analysis is primarily done at rest). Thus, there are no concrete reference values within echocardiography, but many of the values refer to studies comparing MR and echocardiography [57,64]. SV in these studies is between 80 and 140 ml, which is not seen here. This is partly due to the fact that SV is not calculated according to the same method, and partly to the lack of angular correction in this study, which gave misleading blood flow velocities for proper calculation of SV. This, in turn, affects the statistical analysis as before. MAPSE and TDI are less sensitive to angular errors and poor image quality compared to SV and GLS. This is also seen here where the majority have shown a systematic difference that suggests an improved systolic ability during exertion. Both MAPSE and TDI s' correspond with reference values at rest and which are clearly improved during exertion, without much deviation. After the test, they both regress to baseline [17,26,65,66]. Reference values for CI calculated with echocardiography are limited and the variable is only occasionally used as an alternative to EF in the diagnosis of heart failure [67]. Thus, there is nothing to compare the results with within echocardiography. However, the statistical analysis indicates that CI shows a systematic difference throughout the test. The amount of blood pumped out per square meter increased more than twice as much during the exertion in all athletes and returned almost to baseline afterward.

For the mitral inflow, the E-wave and the A-wave could only be obtained at rest and after the exertion test. During the test, the A-wave fused with the E-wave, which is due to the short amount of time the left atrium and left ventricle have to fill and pump out blood [17]. For diagnostic purposes, the E/A ratio is of interest to assess if there is any restriction that prevents heart filling. But when fusion occurs during exertion, the variable does not provide any new information that can potentially distinguish pathologically changes from physiological adaptations [17]. The values for TDI e´ do not match the reference values and this may depend on both the angle correction and the sample volume which may not always be correctly positioned, which in turn may have recorded a lower velocity [17,26]. In contrast, TDI e´ just like TDI s´ shows a systematic difference in diastolic relaxation, which indicates that the left ventricle relaxes quicker with increasing heart rate. Although the filling pressure is within the limit value (≤8) and with low deviation [68,69], the statistical analysis indicates that there is no systematic difference among the athletes. This may be due, as before, to the low number of participants, which does not make it possible to draw a conclusion about a larger population.

Validity

An important aspect to consider is that the study has in addition to measuring the systolic and diastolic variables for evaluating the left ventricular function, also tested a new product (the attachment device) as well as using an own designed examination protocol. The ultrasound examinations were performed by two licensed biomedical scientists, while data processing was performed by a student in a small study population. There is thus a potential observer variation between the two scientists in how they collected all the variables while potential measurement errors may have occurred by the student. To increase the validity of the method and thus obtain more reliable results, the method needs to be carried out on a larger population of athletes and untrained individuals as a control group. And that several experienced ultrasound technicians conduct the same protocol and process the data to see if a significant variation occurs.

Conclusion

In conclusion, the purpose of this study was to investigate the left ventricular function's systolic and diastolic variables in athletes during exercise and increase the knowledge beyond what we know about the variables at rest and post-exertion. The results of this study have shown that the majority of the variables have a positive increase, which indicates an improved pumping ability and heart filling during exertion. Performing echocardiographic measurements during movement is not a simple feat and do not always provide reliable results. However, cardiac index, MAPSE, and tissue Doppler imaging have shown to be, in this study, fairly robust variables for examining cardiac function during exercise. Nonetheless, this is a pilot experiment and further studies need to be conducted in a larger population of athletes and untrained individuals as well as further developing the current examination protocol.

REFERENCES

1. D'Andrea A, Bossone E, Radmilovic J, Caso P, Calabro R, Russo M G, Galderisi M, (2015) The role of new echocardiographic techniques in athlete's heart. *F1000Research, 4*, 289.

2. D'Andrea A, Gerche A, Golia E, Padalino R, Calabro R, Russo M G, Bossone E, (2015) Physiologic and pathophysiologic changes in the right heart in highly trained athletes. *Herz 40*, 369–378.

3. Dores H, Cardim N, (2017) Echocardiography in non-ischemic cardiomyopathies: differential diagnosis from athlete's heart. *Contin. Cardiol. Educ. 3*, 134–140.

4. La Gerche A, (2013) Can Intense Endurance Exercise Cause Myocardial Damage and Fibrosis? *Curr. Sports Med. Rep. 12*, 63–69.

5. Siscovick D, Weiss N, Fletcher R, Lasky T, (1984) The incidence of primary cardiac arrest during vigorous exercise. *New Engl. J. Med. 14,* 874–877.

6. Dores H, Freitas A, Malhotra A, Mendes M, Sharma S, (2015) The hearts of competitive athletes: An up-to-date overview of exercise-induced cardiac adaptations. *Rev. Port. Cardiol. 34,* 51–64.

7. Atchley A E, Douglas P S, (2007) Left Ventricular Hypertrophy in Athletes Morphologic Features and Clinical Correlates. *Cardiol. Clin. 25,* 371–382.

8. Halabchi F, Seif-Barghi T, Mazaheri R, (2011) Sudden cardiac death in young athletes; a literature review and special considerations in Asia. *Asian J. Sports Med. 2*, 1–15.

9. Morganroth J, (1975) Comparative Left Ventricular Dimensions in Trained Athletes. *Ann. Intern. Med. 82*, 521.

10. Mihl C, Dassen W R M, Kuipers H, (2008) Cardiac remodelling: concentric versus eccentric hypertrophy in strength and endurance athletes. *Neth. Heart J. 16*, 129–33.

11. Palatini P, Mos L, Munari L, Valle F, Del Torre M, Rossi A, Varotto L, Macor F, Martina S, Pessina A C, Dal Palu C, (1989) Blood pressure changes during heavy-resistance exercise. *J. Hypertens. 7*, 72-73.

12. Lentini A C, McKelvie R S, McCartney N, Tomlinson C W, MacDougall J D, (1993) Left ventricular response in healthy young men during heavy-intensity weight-lifting exercise. *J. Appl. Physiol. 75*, 2703–10.

13. Wernstedt P, Sjöstedt C, Ekman I, Du H, Thuomas K A, Areskog N H, Nylander E, (2002) Adaptation of cardiac morphology and function to endurance and strength training. A comparative study using MR imaging and echocardiography in males and females. *Scand. J. Med. Sci. Sport. 12*, 17–25.

14. Berglund E, Jönsson B-A, (2007) *Medicinsk Fysik*. Lund, Studentlitteratur.

15. D'Andrea A, Galderisi M, Sciomer S, Nistri S, Agricola E, Ballo P, Buralli S, D'Errico A, Losi M A, Mele D, Mondillo S, (2009) Echocardiographic evaluation of the athlete's heart: from morphological adaptations to myocardial function. *G. Ital. Cardiol. (Rome). 10,* 533–44.

16. Chengode S, (2016) Left ventricular global systolic function assessment by echocardiography. *Ann. Card. Anaesth. 19,* 26–34.

17. Nagueh S F, Smiseth O A, Appleton C P, Byrd B F, Dokainish H, Edvardsen T, Flachskampf F A, Gillebert T C, Klein A L, Lancellotti P, Marino P, Oh J K, Popescu B A, Waggoner A D, (2016) Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur. Hear. J. Cardiovasc. Imaging 17,* 1321–1360.

18. Wandt B, Bojö L, Tolagen K, Wranne B, (1999) Echocardiographic assessment of ejection fraction in left ventricular hypertrophy. *Heart 82,* 192–198.

19. Jones C J, Raposo L, Gibson D G, (2007) Functional importance of the long axis dynamics of the human left ventricle. *Heart 63,* 215–220.

20. LANG R, Badano L P, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf F A, Lancellotti P, Muraru D, Picard M H, Rietzschel E R, Rudski L, Spencer K T, Tsang W, Voigt J-U, (2006) Recommendations for chamber quantification. *Eur. J. Echocardiogr. 7,* 79–108.

21. Hu K, Hermann S, Liu D, Niemann M, Gaudron P D, Voelker W, Ertl G, Bijnens B, Weidemann F, (2013) Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. *Eur. Hear. J. - Cardiovasc. Imaging 14,* 205–212.

22. Simonson J S, Schiller N B, (1989) Descent of the Base of the Left Ventricle: An Echocardiographic Index of Left Ventricular function. *J. Am. Soc. Echocardiogr. 2,* 25–35.

23. Oh D-J, Hong H-O, Lee B-A, (2016) The effects of strenuous exercises on resting heart rate, blood pressure, and maximal oxygen uptake. *J. Exerc. Rehabil. 12,* 42–6.

24. Evangelista A, Garcia-Dorado D, Del Castillo H G, Gonzalez-Alujas T, Soler-Soler J, (1995) Cardiac index quantification by Doppler ultrasound in patients without left ventricular outflow tract abnormalities. *J. Am. Coll. Cardiol. 25,* 710–716.

25. Smiseth O A, Torp H, Opdahl A, Haugaa K H, Urheim S, (2016) Myocardial strain imaging: how useful is it in clinical decision making? *Eur. Heart J. 37,* 1196–1207.

26. Kadappu K K, Thomas L, (2015) Tissue Doppler imaging in echocardiography: value and limitations. *Heart. Lung Circ. 24,* 224–33.

27. Thomas J D, Popović Z B, (2006) Assessment of Left Ventricular Function by Cardiac Ultrasound. *J. Am. Coll. Cardiol. 48,* 2012–2025.

28. Park J-H, Marwick T H, (2011) Use and Limitations of E/e' to Assess Left Ventricular Filling Pressure by Echocardiography. *J. Cardiovasc. Ultrasound 19,* 169–73.

29. Oikawa M, Kobayashi A, Sato T, Suzuki S, Akiomi Y, Nakazato K, Suzuki H, Saitoh S L, Takeishi Y, (2017) The usefulness of combined assessment of E/E' ratio and transmitral flow pattern to interpret cardiac condition. *Fukushima J. Med. Sci. 63,* 16–21.

30. Klein A L, Tajik A J, (1991) Doppler Assessment of Pulmonary Venous Flow in Healthy Subjects and in Patients with Heart Disease. *J. Am. Soc. Echocardiogr. 4*, 379–392.

31. Tabata T, Thomas J D, Klein A L, (2003) Pulmonary venous flow by doppler echocardiography: revisited 12 years later. *J. Am. Coll. Cardiol. 41,* 1243–1250.

32. Douglas P S, O'Toole M L, Hiller W D, Reichek N, (1986) Left ventricular structure and function by echocardiography in ultraendurance athletes. *Am. J. Cardiol.* 58, 805–809.

33. D'Elia E, Ferrero P, Vittori C, Calabrese A, Duino V, Perlini S, Senni M, (2017) Global Longitudinal Strain in master athletes and in hypertensive patients with the same degree of septal thickness. *Scand. J. Med. Sci. Sports 27,* 1411–1416.

34. Rawlins J, Bhan A, Sharma S, (2009) Left ventricular hypertrophy in athletes. *Eur. J. Echocardiogr. 10,* 350–356.

35. Grazioli G, Merino B, Montserrat S, Vidal B, Azqueta M, Pare C, Brugada-Sarquella G, Yanguas X, Pi R, Escoda J, Brugada J, Sitges M, (2014) Usefulness of Echocardiography in Preparticipation Screening of Competitive Athletes. *Rev. Española Cardiol. (English Ed.) 67,* 701–705.

36. Neilan T G, Jassal D, Popovic Z B, Douglas P S, Halpern E F, Ton-Nu T, (2006) Myocardial Adaptation to Short-term High-intensity Exercise in Highly Trained Athletes. *J. Am. Soc. Echocardiogr. 19,* 1280–1285.

37. Caso P, D'Andrea A, Galderisi M, Liccardo B, Severino S, Simone L D, Izzo A, D'Andrea L, Mininni N, (2000) Pulsed Doppler tissue imaging in endurance athletes: relation between left ventricular preload and myocardial regional diastolic function. *Am. J. Cardiol. 85,* 1131–1136.

38. Eun L Y, Chae H W, (2016) Assessment of myocardial function in elite athlete's heart at rest - 2D speckle tracking echocardiography in Korean

elite soccer players. *Sci. Rep. 6,* 39772.

39. Alsafi Z, Malmgren A, Gudmundsson P, Stagmo M, Dencker M, (2017) Myocardial performance index in female athletes. *Cardiovasc. Ultrasound* 15, 20.

40. Mitchell C, Rahko P S, Blauwert L A, Canaday B, Finstuen J A, Foster M C, Horton K, Ogunyankin K O, Palma R A, Velazquez E J, (2019) Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *J. Am. Soc. Echocardiogr. 32,* 1–64.

41. Lang R M, Badano L P, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf F A, Foster E, Goldstein S A, Kuznetsova T, Lancellotti P, Muraru D, Picard M H, Rietzschel E R, Rudski L, Spencer K T, Tsang W, Voigt J-U, (2015) Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr. 28,* 1–39.

42. Björk J, (2011) *Praktisk statistik för medicin och hälsa*. Stockholm, Liber.

43. Whitley E, Ball J, (2002) Statistics review 6: Nonparametric methods. *Crit. Care 6,* 509–13.

44. Wahlgren L, (2013) *SPSS steg för steg*. Lund, Studentlitteratur.

45. Bring J, Taube A, Wikman P, (2015) *Introduktion till medicinsk statistik*. Lund, Studentlitteratur.

46. Fleck S, (1994) Detraining: Its Effects on Endurance and Strength. *Strength. Cond. J. 16,* 22–28.

47. Neufer P D, (1989) The Effect of Detraining and Reduced Training on the Physiological Adaptations to Aerobic Exercise Training. *Sport. Med. 8,* 302–321.

48. Evans C, White R D, (2008) *Exercise Testing for Primary Care and Sports Medicine Physicians*. Springer International Publishing.

49. Fletcher G F, Ades P A, Kligfield P, Arena R, Balady G J, Bittner V A, Coke L A, Fleg J L, Forman D E, Gerber T C, Gulati M, Madan K, Rhodes J, Thompson P D, Williams M A, (2013) Exercise Standards for Testing and Training. *Circulation 128,* 873–934.

50. Löllgen H, Leyk D, (2018) Exercise Testing in Sports Medicine. *Dtsch. Arztebl. Int. 115,* 409–416.

51. Miller A E, MacDougall J D, Tarnopolsky M A, Sale D G, (1993) Gender differences in strength and muscle fiber characteristics. *Eur. J. Appl. Physiol. Occup. Physiol. 66,* 254–62.

52. Brauer K, Jorfeldt L, Pahlm O, (2003) *Det kliniska arbetsprovet*. Lund, Studentlitteratur.

53. Baum B S, Li L, (2003) Lower extremity muscle activities during cycling are influenced by load and frequency. *J. Electromyogr. Kinesiol. 13*, 181–190.

54. Bieuzen F, Lepers R, Vercruyssen F, Hausswirth C, Brisswalter J, (2007) Muscle activation during cycling at different cadences: Effect of maximal strength capacity. *J. Electromyogr. Kinesiol. 17*, 731–738.

55. Skulstad H, Aakhus S, (2012) Stressekkokardiografi med liggesykkel. *Tidsskr. Den Nor. legeforening 132*, 2175–2178.

56. Ciliberti P, McLeod L, Cairello F, Kaski J P, Fenton M, Giardini A, Marek J, (2015) Semi-supine exercise stress echocardiography in children and adolescents: feasibility and safety. *Pediatr. Cardiol. 36*, 633–639.

57. Wernstedt P, Sjöstedt C, Ekman I, Du H, Thuomas K A, Areskog N H, Nylander E, (2002) Adaptation of cardiac morphology and function to endurance and strength training. A comparative study using MR imaging and echocardiography in males and females. *Scand. J. Med. Sci. Sport. 12*, 17–25.

58. Luijkx T, Cramer M J, Prakken N H, Buckens C F, Mosterd A, Rienks R, Backx F J, Mali W P, Velthuis B K, (2012) Sport category is an important determinant of cardiac adaptation: an MRI study. *Br. J. Sports Med. 46*, 1119–1124.

59. Le V-V, Mitiku T, Sungar G, Myers J, Froelicher V, (2008) The Blood Pressure Response to Dynamic Exercise Testing: A Systematic Review. *Prog. Cardiovasc. Dis. 51*, 135–160.

60. Kou S, Caballero L, Dulgheru R, Voilliot D, De Sousa C, Kacharava G, Athanassopoulos G D, Barone D, Baroni M, Cardim N, (2014) Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. *Eur. Hear. J. - Cardiovasc. Imaging 15*, 680–690.

61. Crawford M H, Petru M A, Rabinowitz C, (1985) Effect of isotonic exercise training on left ventricular volume during upright exercise. *Circulation, 72*, 1237-1243.

62. Ginzton L E, Conant R, Brizendine M, Laks M M, (1989) Effect of long-term high intensity aerobic training on left ventricular volume during maximal upright exercise. *J. Am. Coll. Cardiol. 14*, 364–71.

63. Yingchoncharoen T, Agarwal S, Popović Z B, Marwick T H, (2013) Normal Ranges of Left Ventricular Strain: A Meta-Analysis. *J. Am. Soc. Echocardiogr. 26*, 185–191.

64. Maceira A, Prasad S, Khan M, Pennell D, (2006) Normalized Left Ventricular Systolic and Diastolic Function by Steady State Free Precession Cardiovascular Magnetic Resonance. *J. Cardiovasc. Magn. Reson. 8,* 417–426.

65. Chahal N S, Lim T K, Chambers J C, Kooner J S, Senior R, (2010) Normative reference values for the tissue Doppler imaging parameters of left ventricular function: a population-based study. *Eur. J. Echocardiogr. 11*, 51–56.

66. Matos J, Kronzon I, Panagopoulos G, Perk G, (2012) Mitral annular plane systolic excursion as a surrogate for left ventricular ejection fraction. *J. Am. Soc. Echocardiogr. 25,* 969–974.

67. Szabó B, Marosi E K, Vargová K, Nyolczas N, (2018) Cardiac Index by Transthoracic Echocardiography (CITE) study. *PLoS One 13,* e0207269.

68. Sharp A S P, Tapp R J, Thom S A, Francis D P, Hughes A D, Stanton A V, Zambanini A, O'Brien E, Chaturvedi N, Lyons S, (2010) Tissue Doppler E/E’ ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy. *Eur. Heart J. 31,* 747–752.

69. D’Andrea A, Vriz O, Golino P, (2018) Reference Ranges and Physiologic Variations of Left E/e’ Ratio in Healthy Adults: Clinical and Echocardiographic Correlates. *J. Cardiovasc. Echogr. 28,* 101–108.

APPENDIX 1

Appendix 1. Information letter used during the recruitment process.

Projektets titel: Utvärdering av den systoliska och diastoliska vänsterkammarfunktionen under fysisk ansträngning hos idrottande individer.	**Datum:** Januari 2019 – Mars 2019
Studieansvarig: Dejan Bilal **E-post** **Handledare:** Andreas Malmgren, Doktorand Lunds Universitet	**Studerar vid Malmö universitet, Fakulteten för Hälsa och Samhälle, 205 06 Malmö, Tfn 040–6657000** **Utbildning:** Biomedicinska analytikerprogrammet **Nivå:** Kandidat

Till friska idrottande individer!

Mitt namn är Dejan Bilal och jag är en biomedicinsk analytikerstudent som för närvarande läser mitt sista år vid Malmö Universitet. Inom de kommande veckorna ska jag påbörja mitt examensarbete inom ultraljud av hjärtat, en undersökning där hjärtats funktion granskas.

Ändamålet med studien är att undersöka hjärtfyllnaden och pumpförmågan under fysisk ansträngning hos idrottande individer för att bättre försöka förstå hjärtats fysiologiska respons vid maximal träning.

Som deltagare kommer du att genomgå en ultraljudsundersökning av hjärtat i vila. Därefter utförs ett ansträngningsprov på en ergometercykel i syfte att belasta hjärtat. Under denna tid samlas ultraljudsbilder in vilka sedan kommer att granskas och utvärderas i syfte att studera hur fysiologin förändras under fysisk ansträngning. Hela undersökningen beräknas ta cirka en timme och genomförs på Skånes Universitetssjukhus i Malmö på avdelningen för Klinisk fysiologi och Nuklearmedicin.

All insamling av ultraljudsbilder och databearbetning lagras i en intern databas på sjukhuset. Vid sammanställning av informationen kommer dina uppgifter att avidentifieras och ersättas med en unik kod för att enskilda individer inte ska kunna urskiljas. Dessutom omfattas allt material, från personuppgifter till undersökningsresultat, av sekretess och tystnadsplikt och är endast behörigt av de som är involverade i projektet, det vill säga studentansvarig, handledare och medicinskt ansvarig läkare. I händelse av att en avvikelse eller sjukdom identifieras kommer du att meddelas på plats och data sparas i din patientjournal. All annan data förstörs när projektet har bedömts som godkänt.

Resultaten publiceras i samband med presentation av examensarbetet på Malmö Universitet och kommer därefter att finnas tillgängligt på universitetets databas Malmö University Electronic Publishing (MUEP).

Ditt deltagande i studien är helt frivilligt och du har rätt till att när som helst avbryta eller avstå från undersökningen utan att behöva uppge någon anledning. Detta kommer inte påverka din rätt till framtida sjukvård hos oss. Ingen ersättning för deltagande ges.

Har du några funderingar eller frågor kan du kontakta mig via ovanstående mailaddress.

Härmed tillfrågas **Du** om deltagande i studien.

APPENDIX 2

Appendix 2. Letter of consent for each participant.

Samtycke från deltagare i projektet

Projektets titel: Utvärdering av den systoliska och diastoliska vänsterkammarfunktionen under fysisk ansträngning hos idrottande individer.	**Datum:** Januari 2019 – Mars 2019
Studieansvarig: Dejan Bilal **E-post:**	**Studerar vid Malmö universitet, Fakulteten för Hälsa och samhälle, 205 06 Malmö, Tfn 040-6657000** **Utbildning:** Biomedicinska analytikerprogrammet

Härmed tillfrågas **Du** om deltagande i en forskningsstudie vars ändamål är att undersöka hjärtats fysiologiska respons under fysisk ansträngning.

Dina personuppgifter och undersökningsresultat omfattas av sekretess och tystnadsplikt och är endast behörigt för projektansvariga. Deltagandet i undersökningen är frivilligt och kan när som helst utan närmare förklaring avbrytas genom att säga till studentansvarig eller handledare. Fullständig eller avbruten medverkan kommer inte påverka din rätt till framtida sjukvård. Enligt dataskyddsförordningen har du rätt till att få dina lagrade personuppgifter inom projektet raderade och om så önskas, kontakta studentansvarig. I händelse av att en avvikelse eller sjukdom identifieras kommer du att meddelas på plats och data sparas i din patientjournal för framtida medicinskbehandling eller eventuell vidare åtgärd.

Jag har muntligen informerats om studien och tagit del av bifogad skriftlig information samt är medveten om att mitt deltagande är helt frivilligt.

Jag lämnar härmed mitt samtycke till att delta i ovanstående studie:

Datum: ______________ **E-post:** _________________________

Deltagarens underskrift: ______________________________________