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Novel insights into the athlete's heart: is myocardial work the new champion of systolic function?

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Aims We sought to investigate the correlation between speckle-tracking echocardiography (STE)-derived myocardial work (MW) and invasively measured contractility in a rat model of athlete's heart. We also assessed MW in elite athletes and explored its association with cardiopulmonary exercise test (CPET)-derived aerobic capacity.

Methods and results Sixteen rats underwent a 12-week swim training program and were compared to controls ($n = 16$). STE was performed to assess global longitudinal strain (GLS), which was followed by invasive pressure-volume analysis to measure contractility [slope of end-systolic pressure–volume relationship (ESPVR)]. Global MW index (GMWI) was calculated from GLS curves and left ventricular (LV) pressure recordings. In the human investigations, 20 elite swimmers and 20 healthy sedentary controls were enrolled. GMWI was calculated through the simultaneous evaluation of GLS and non-invasively approximated LV pressure curves at rest. All subjects underwent CPET to determine peak oxygen uptake (VO_2/kg). Exercised rats exhibited higher values of GLS, GMWI, and ESPVR than controls (-20.9 ± 1.7 vs. -17.6 ± 1.9%, 2745 ± 280 vs. 2119 ± 272 mmHg·%, 3.72 ± 0.72 vs. 2.61 ± 0.40 mmHg/μL, all $P_{Exercise} < 0.001$). GMWI correlated robustly with ESPVR ($r = 0.764$, $P < 0.001$). In humans, regular exercise training was associated with decreased GLS (-17.6 ± 1.5 vs. -18.8 ± 0.9%, $P_{Exercise} = 0.002$) but increased values of GMWI at rest (1899 ± 136 vs. 1755 ± 234 mmHg·%, $P_{Exercise} = 0.025$). GMWI exhibited a positive correlation with VO_2/kg ($r = 0.527$, $P < 0.001$).

Conclusions GMWI precisely reflected LV contractility in a rat model of exercise-induced LV hypertrophy and captured the supernormal systolic performance in human athletes even at rest. Our findings endorse the utilization of MW analysis in the evaluation of the athlete's heart.

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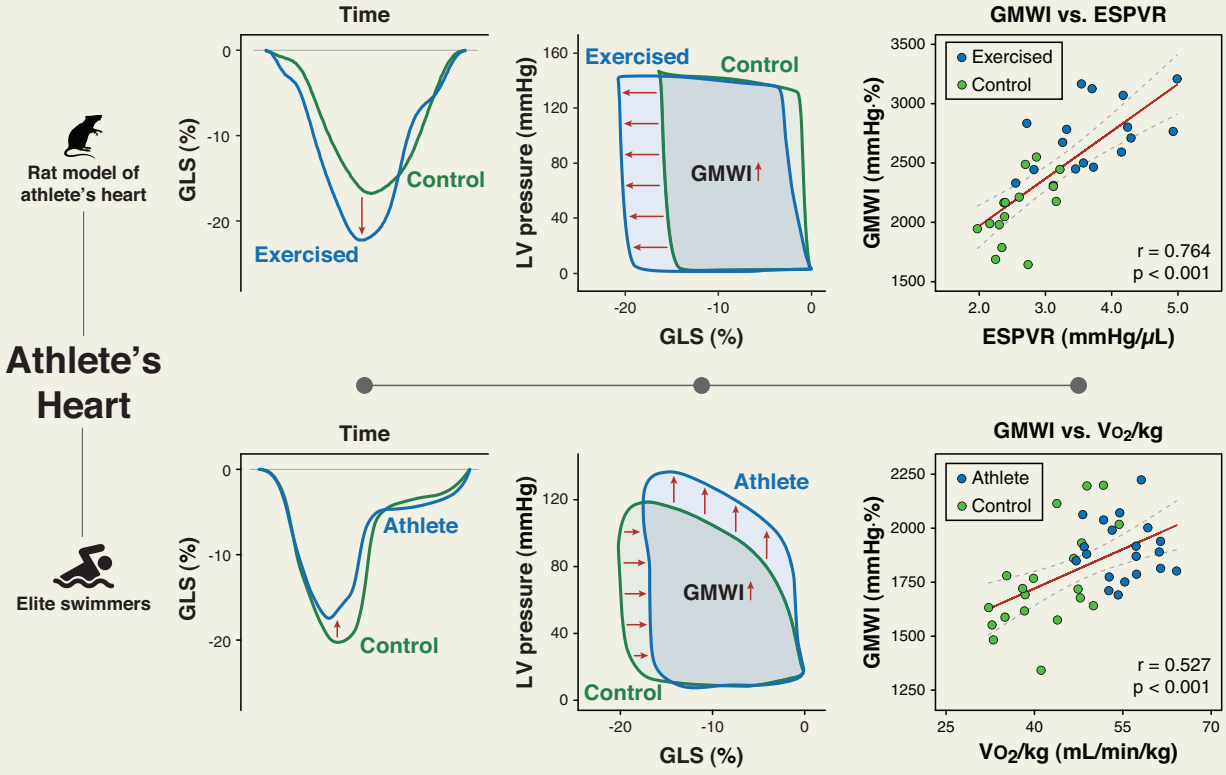
Graphical Abstract



ESPVR, slope of end-systolic pressure–volume relationship (i.e. the slope of the curve connecting the end-systolic points of the pressure–volume loops recorded during the transient occlusion of inferior vena cava); GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular; VO_2/kg, peak oxygen uptake.

Keywords speckle-tracking echocardiography • myocardial work • athlete's heart • contractility

Introduction

Long-term, intense exercise training induces adaptive changes in cardiac structure and function that enable the heart to meet the haemodynamic demands of the increased cardiac output during effort.[1,2] This physiological remodelling leads to enhanced myocardial contractility, which represents the intrinsic ability of the myocardium to shorten independently of loading conditions, and as such, is the target feature of the clinical evaluations of the athlete's heart. Nevertheless, instantaneous cardiac performance is significantly affected by preload, afterload, and heart rate (HR).[3] Consequently, most of the conventional indices of left ventricular (LV) systolic function provide only a rough estimation of contractile function. Athletes often present with parameters of systolic function [e.g. ejection fraction (EF)] in the low-normal range at rest despite the increased contractile reserve.[1,2,4,5] This phenomenon may lead to the ambiguous interpretation of resting echocardiograms and hampers the confident differentiation between physiological LV remodelling and pathological processes.

Global longitudinal strain (GLS) by speckle-tracking echocardiography (STE) has emerged as a sensitive parameter of LV systolic function.[6] Previously, our research group has observed a significant correlation between GLS and contractility parameters assessed by pressure–volume (P–V) analysis in a rat model of exercise-induced LV hypertrophy.[7,8] Nevertheless, GLS is also significantly influenced by multiple factors, such as loading conditions, HR, and LV geometry.[6] To mitigate the load-dependency of GLS, the concept of myocardial work (MW, calculated by adjusting myocardial deformation to the instantaneous LV pressure) has been recently proposed and tested in various clinical scenarios.[9] As MW is less dependent on loading conditions than GLS, we may hypothesize that it reflects cardiac contractility more reliably, and thus, it might be a robust resting marker of the athlete's heart.

Accordingly, we sought to investigate the correlation between MW and the invasively measured myocardial contractility in a rat model of athlete's heart. We also aimed to evaluate the MW of elite athletes compared to sedentary volunteers and explore its association with cardiopulmonary exercise test (CPET)-derived aerobic capacity.

Table 1 Myocardial work in the rat model of athlete's heart

	M_{Co}	M_{Ex}	F_{Co}	F_{Ex}	P_{Sex}	$P_{Exercise}$	P_{Inter}
GLS (%)	-16.3 ± 1.3	-20.3 ± 2.0*	-19.0 ± 1.4	-21.5 ± 1.3**	0.001	<0.001	0.195
GMWI (mmHg·%)	1989 ± 268	2600 ± 163*	2248 ± 220	2890 ± 305**	0.004	<0.001	0.859
CMWI (mmHg·%)	2341 ± 290	2915 ± 211*	2550 ± 261	3214 ± 364**	0.018	<0.001	0.658
WMWI (mmHg·%)	11 ± 8	5 ± 4	10 ± 10	17 ± 9	0.085	0.796	0.029
MWE (%)	98 ± 1	99 ± 1	98 ± 1	98 ± 1	0.275	0.519	0.065

Values are mean ± SD.
*$P < 0.05$ vs. M_{Co},
**$P < 0.05$ vs. F_{Co}.
Statistical test: two-way analysis of variance (ANOVA) with the factors 'Sex' and 'Exercise'. The *P*-value for sex-exercise interaction (P_{Inter}) was also calculated.
CMWI, constructive myocardial work index; F_{Co}, female control group; F_{Ex}, female exercised group; GLS, global longitudinal strain; GMWI, global myocardial work index; M_{Co}, male control group; M_{Ex}, male exercised group; MWE, myocardial work efficiency; WMWI, wasted myocardial work index.

Table 2 Myocardial work in human athletes and controls

	M_{Co}	M_{Ath}	F_{Co}	F_{Ath}	P_{Sex}	$P_{Exercise}$	P_{Inter}
GLS (%)	-18.6 ± 1.1	-17.0 ± 1.6*	-19.0 ± 0.7	-18.2 ± 1.2	0.046	0.002	0.344
GMWI (mmHg·%)	1784 ± 280	1916 ± 127	1726 ± 187	1882 ± 149	0.460	0.025	0.846
CMWI (mmHg·%)	2038 ± 253	2187 ± 164	1954 ± 136	2151 ± 134	0.297	0.004	0.676
WMWI (mmHg·%)	66 ± 30	90 ± 27	62 ± 26	64 ± 47	0.170	0.220	0.312
MWE (%)	97 ± 1	96 ± 1	97 ± 1	97 ± 2	0.240	0.451	0.246

Values are mean ± SD.
*$P < 0.05$ vs. M_{Co},
**$P < 0.05$ vs. F_{Co}.
Statistical test: two-way analysis of variance (ANOVA) with the factors 'Sex' and 'Exercise'. The *P*-value for sex-exercise interaction (P_{Inter}) was also calculated.
CMWI, constructive myocardial work index; F_{Ath}, female athlete group; F_{Co}, female control group; GLS, global longitudinal strain; GMWI, global myocardial work index; M_{Ath}, male athlete group; M_{Co}, male control group; MWE, myocardial work efficiency; WMWI, wasted myocardial work index.

Methods

Experimental investigations

Ethical approval and animals

This study was carried out in accordance with the principles of the Basel Declaration and the recommendations of the Guide for the Care and Use of Laboratory Animals provided by the EU Directive 2010/63/EU and the ARRIVE (Animals in Research: Reporting in Vivo Experiments) guidelines. The study protocol was approved by the Ethical Committee for Animal Experimentation of Semmelweis University (Approval No. PEI/001/2374-4/2015). All animals were kept under standard conditions (22 ± 2°C with 12:12-h light/dark cycles) and had access to standard laboratory rat diet and water *ad libitum* during the entire experimental period.

Experimental groups, the rat model of athlete's heart

Young adult (57–61 days old) male ($n = 16$) and female ($n = 16$) Wistar rats (Charles River Laboratories, Sulzfeld, Germany) were included in the current study. After acclimatization, the rats were divided into four experimental groups: male control (M_{Co}, $n = 8$), male exercised (M_{Ex}, $n = 8$), female control (F_{Co}, $n = 8$), and female exercised groups (F_{Ex}, $n = 8$).

Rats of the exercised male and female groups were exposed to 200 min/day swimming, 5 days/week for 12 weeks to induce physiological hypertrophy, as previously described by our research group.[10] For appropriate adaptation, the duration of the first swimming experience was limited to 15 min and was gradually increased by 15 min every second training session until achieving 200 min/day (*Figure 1A*). Untrained control rats were placed into the water for 5 min each day during the 12-week training program (*Figure 1A*). A more thorough description of the training protocol is provided in the Supplementary data online.

Conventional echocardiography and speckle-tracking analysis

After completing the 12-week training program, echocardiographic parameters of LV morphology and function were assessed using a Vivid i ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a 13 MHz linear transducer (12 L-RS, GE Vingmed Ultrasound, Horten, Norway). Beyond the conventional echocardiographic protocol, 2D loops dedicated to STE were obtained from the parasternal long-axis view. Speckle-tracking analysis was performed in accordance with our internal protocol, as described previously.[7]

Haemodynamic measurements, left ventricular pressure–volume analysis

Following the echocardiographic examination, LV P–V analysis was performed using a 2-Fr pressure-conductance microcatheter (SPR-838, Millar Instruments, Houston, TX, USA) according to our previously described protocol.[11] We assessed the following haemodynamic parameters: mean arterial pressure (MAP), LV end-systolic pressure (LVESP), LV end-diastolic pressure (LVEDP), the maximal slope of LV systolic pressure increment (dP/dt_{max}), and diastolic pressure decrement (dP/dt_{min}). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), stroke volume (SV), EF, cardiac output (CO), and stroke work (SW)

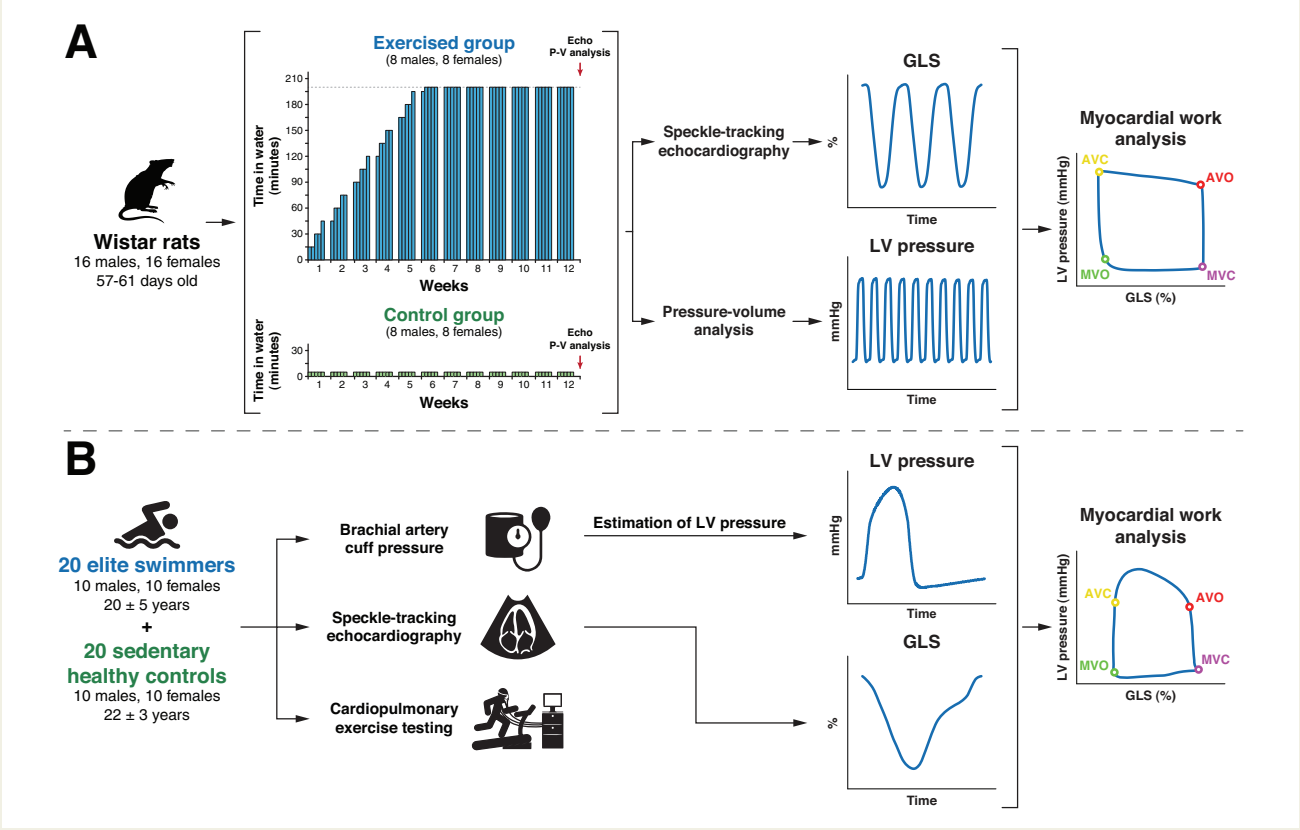


Figure 1 Schematic illustration of the study protocol with main focus on myocardial work analysis. (*A*) the outline of the study protocol in rats. Young adult Wistar rats were included in the current study. Rats of the exercised group were exposed to 200 min/day swimming, 5 days/week for 12 weeks to induce physiological hypertrophy. Untrained control rats were placed into the water for 5 min/day during the 12-week program. Speckle-tracking echocardiography was performed to assess global longitudinal strain, which was followed by invasive P–V analysis to measure contractility. Myocardial work indices were calculated using longitudinal strain curves and LV pressure recordings. (*B*) the steps of human investigations. Twenty elite swimmers and 20 healthy sedentary controls were enrolled. Myocardial work analysis was performed through the simultaneous evaluation of speckle-tracking-derived longitudinal strain and non-invasively approximated LV pressure curves at rest. All subjects underwent cardiopulmonary exercise testing to determine peak oxygen uptake. See further details in text. AVC, closure of the aortic valve; AVO, opening of the aortic valve; GLS, global longitudinal strain; LV, left ventricular; MVC, closure of the mitral valve; MVO, opening of the mitral valve; P–V, pressure–volume.

were calculated and corrected according to in vitro and in vivo volume calibrations. In addition, with the transient occlusion of the inferior vena cava, we obtained the slope of the LV end-systolic P–V relationship (ESPVR, according to the parabolic curvilinear model) that represents a load-independent, gold-standard parameter of contractility. Arterial elastance (E_a) was calculated as LVESP/SV. Ventriculo-arterial coupling (VAC) was described by the ratio of E_a and ESPVR. A more profound description of haemodynamic measurements can be found in the Supplementary data online.

From the haemodynamic and echocardiographic measurements, meridional end-diastolic wall stress (σ_{ED}) was estimated to characterize preload using the following formula: $\sigma_{ED} = 0.334 \times \text{LVEDP} \times [\text{LV end-diastolic diameter}/(1 + \text{posterior wall thickness in diastole/LV end-diastolic diameter})]$.[12]

Assessment of myocardial work

In MW analysis, we followed the principles published previously by Russell *et al.*[9,13] To assess MW in rats, longitudinal strain curves and invasive LV pressure recordings were exported and analysed using our custom-made software (implemented in C#). First, the opening and closure times of the mitral and aortic valves were identified on the analysed echocardiographic loops by visual assessment, whereas the timings of these events were determined automatically on the LV pressure curves during the P–V analysis. Using these temporal reference points, pressure and strain curves were dissected into four sections (i.e. phases of the cardiac cycle), and each section of the given strain curve was matched with the corresponding section of the pressure tracing. Due to the different temporal resolution of the datasets (strain tracing: 218/s, LV pressure: 1000/s), the timestamps of the pressure and strain tracings were normalized in each section, and strain values were interpolated for the timestamps of the LV pressure recording. Then, the four sections of each recording were concatenated, and pressure–strain loops were plotted. The instantaneous power was calculated by multiplying the strain rate (obtained by differentiating the strain curve) and the instantaneous LV pressure. Then, global MW index (GMWI) was computed by integrating the power over time from mitral valve closure until mitral valve opening. Constructive MW index (CMWI) is defined as the work generated by the shortening during systole and lengthening during isovolumetric relaxation, whereas wasted MW index (WMW i.e. the work performed by the LV that does not contribute to LV ejection) quantifies the work

resulting from lengthening during systole and shortening during the isovolumetric relaxation phase. Finally, MW efficiency (MWE) can be calculated as CMWI/(CMWI + WMWI).

Human investigations

Study participants and ethical approval

In our current study, 20 elite swimmer athletes (10 women and 10 men, members of the national team) were selected from the database of our complex sports cardiology screening program (approved by the Medical Research Council; ETT-TUKEB No. 13687-0/2011-EKU). The participants gave written informed consent before entering the program. All examinations were performed during the in-competition phase and ≥24 h following the last training session. After the echocardiographic examination, all athletes underwent CPET to quantify peak oxygen uptake (VO_2 and VO_2/kg, see Supplementary data online for further details). Twenty healthy, age- and sex-matched sedentary healthy volunteers (no previous participation in intensive training, <3 h of exercise/week) were selected from our existing database and served as the control group. The outline of the study protocol is illustrated in *Figure 1B*.

Echocardiography and myocardial work analysis

After a 5-min rest period, brachial artery cuff pressure was measured for each subject while lying in the left lateral decubitus position preceding the echocardiographic examination. Echocardiographic acquisitions were obtained using a Vivid E95 ultrasound system equipped with a 4Vc-D transducer (GE Vingmed Ultrasound, Horten, Norway). A detailed description of the echocardiographic protocol is provided in the Supplementary data online.

MW analysis was performed using the dedicated module of a commercially available software solution (AFI, EchoPAC v203, GE Healthcare, Chicago, IL, USA). Further details of the MW analysis can be found in the Supplementary data online.

Statistics

After verifying the normal distribution of each continuous variable using the Shapiro–Wilk test, two-way analysis of variance (ANOVA) with the factors 'Sex' and 'Exercise' was performed, and the *P*-value for sex and exercise interaction (P_{Inter}) was calculated as well. To determine differences between subgroups (M_{Co} vs. M_{Ex}/M_{Ath} and F_{Co} vs. F_{Ex}/F_{Ath}), pairwise comparisons were performed using Tukey's *post hoc* test. Continuous variables are expressed as mean ± standard deviation. Pearson correlation coefficients were computed to assess the correlation between continuous variables. For multivariable analysis, ordinary least squares (OLS) modelling was used (see Supplementary data online for further details). The importance of each predictor in the OLS models with bootstrapped standard errors was determined with ANOVA using the F statistics and the Akaike information criterion. Intra- and inter-observer variability of the most relevant echocardiographic parameters (in both rats and humans) was assessed using the coefficient of variation and the intra-class correlation coefficient (see detailed description in the Supplementary data online). A two-sided *P*-value <0.05 was considered statistically significant. Statistical analysis was performed in R (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Experimental investigations

Conventional echocardiography-derived parameters

Both the M_{Ex} and F_{Ex} groups showed the characteristic echocardiographic features of exercise-induced myocardial hypertrophy (Supplementary data online, *Table S1*). Exercised animals exhibited increased wall thickness values and higher LV mass compared to controls in both sexes (*Figure 2*). The extent of relative LV hypertrophy was more pronounced in female animals than males (+20 to 25% vs. +10 to 15% increase in calculated LV mass). Significantly increased values of fractional shortening could be observed as the result of regular exercise training in both sexes (Supplementary data online, *Table S1*).

Invasive haemodynamic parameters

Basic haemodynamic parameters (MAP, LVESP, LVEDP, dP/dt_{max}, and dP/dt_{min}) did not differ between the control and exercised groups (Supplementary data online, *Table S2*). Exercise training was associated with lower values of LVESV, which in combination with the unaltered LVEDV, resulted in increased SV in both sexes. Markedly increased values of EF and ESPVR (the load-independent index of contractility) were found in the exercised groups compared to control animals (Supplementary data online, *Table S2*). The presence of these adaptive changes was independent of sex. Long-term swim training was associated with decreased E_a values, which (in combination with the improved contractility) led to a notable decrease in VAC in both male and female exercised animals (Supplementary data online, *Table S2*). σ_{ED} (the indicator of preload) did not differ between the exercised and control groups (Supplementary data online, *Table S2*).

Myocardial work analysis in the rat model of athlete's heart

GLS was significantly increased in the exercised groups compared to controls, with female rats having higher strain values than males (*Figure 2, Table 1*). In addition, GMWI and CMWI showed higher values in exercised animals, with similar sex-related differences as seen in GLS (*Figure 2, Table 1*). WMWI and MWE did not differ between the experimental groups (*Table 1*).

Correlation of contractility with myocardial work indices

GLS showed a strong correlation with ESPVR both in male and female animals (r = -0.766 and r = -0.757, both $P < 0.001$, Supplementary data online, *Table S3*), as well as in the pooled animal cohort (r = -0.716, $P < 0.001$, *Figure 3*). According to our experimental data, MW indices are robustly correlated with LV contractility: both GMWI and CMWI demonstrated strong positive correlation with ESPVR ($r = 0.764$ and $r = 0.729$, both $P < 0.001$, *Figure 3*).

Determinants of global longitudinal strain and myocardial work indices

OLS analysis was performed to determine the relative importance of five predefined factors [(i) preload (defined as σ_{ED}), (ii) afterload (defined as E_a), (iii) LV contractility (defined as ESPVR), (iv) exercise training, and (v) sex] that were assumed to substantially influence the values of GLS, GMWI, and CMWI (separate multivariable models for these three outcome variables, Supplementary data online, *Table S4*). This analysis revealed that GLS was predominantly determined by sex and afterload, whereas the major determinants of GMWI and CMWI were rather contractility and exercise (*Figure 3*,

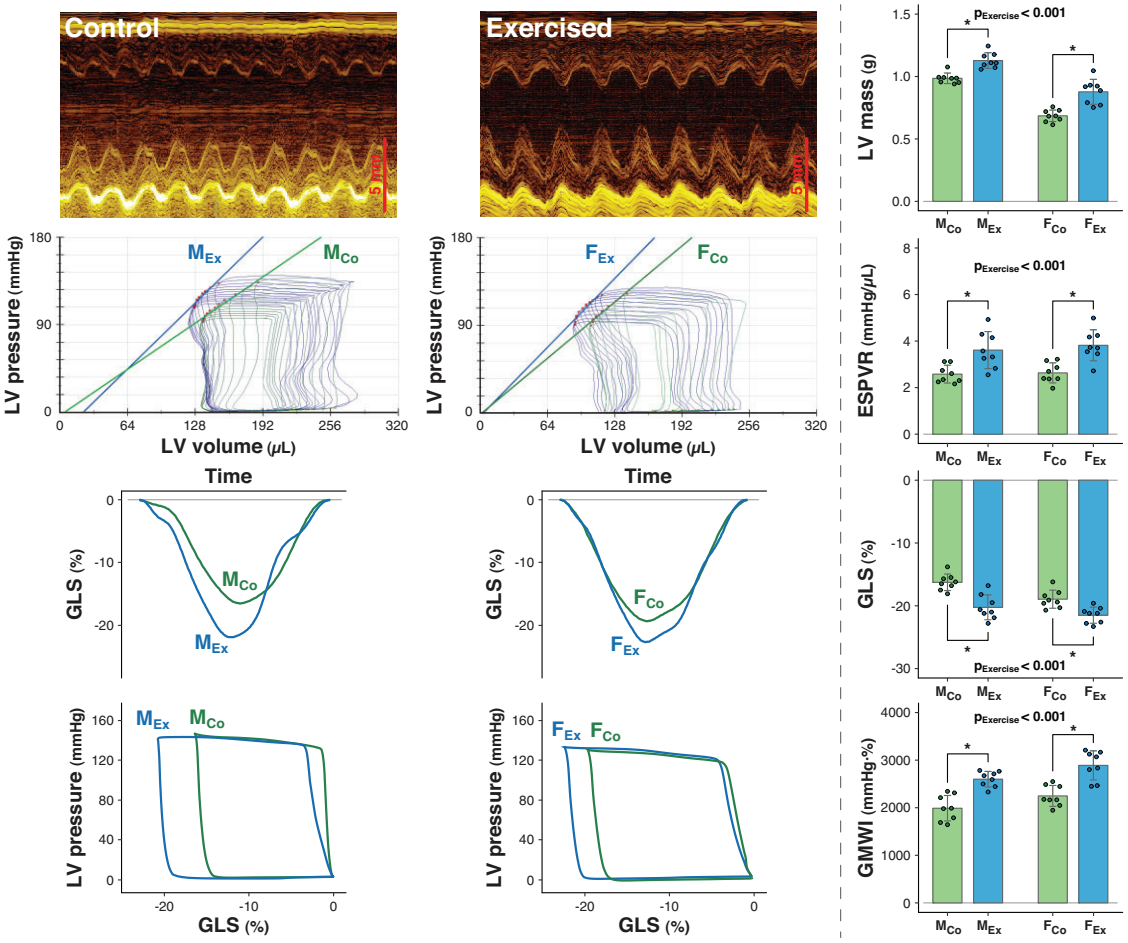


Figure 2 Exercise-induced structural and functional adaption in the rat model of athlete's heart. *Left panel* illustrates M-mode echocardiographic recordings, pressure-volume loops, strain curves, and pressure-strain loops of representative animals. *Right panel* depicts the group comparisons of LV mass, ESPVR, GLS, and GMWI. *$P < 0.05$, Tukey's *post hoc* test (following two-way analysis of variance with the factors 'Sex' and 'Exercise'). ESPVR, slope of end-systolic pressure-volume relationship (i.e., the slope of the curve connecting the end-systolic points of the pressure-volume loops recorded during the transient occlusion of inferior vena cava); F_{Co}, female control group; F_{Ex}, female exercised group; GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular; M_{Co}, male control group; M_{Ex}, male exercised group.

Supplementary data online, *Figures S1–S3*; Supplementary data online, *Tables S5–S7*).

Human investigations

Morphometric and echocardiographic characteristics

The included elite athletes had been competitively participating in swimming for 14 ± 5 years, with a current average training duration of 23 ± 4 h per week. Athletes had significantly higher resting systolic blood pressure and lower resting HR compared to control subjects (Supplementary data online, *Table S8*). As expected, higher values of CPET-derived peak oxygen uptake were measured in athletes than in controls (Supplementary data online, *Table S8*). In athletes, exercise-induced adaptive changes could be observed in the echocardiographic parameters of cardiac structure and function (Supplementary data online, *Table S8*; *Figure 4*).

Myocardial work analysis in elite athletes

Regular exercise training resulted in the reduction of GLS ($P_{Exercise}$ = 0.002), and sex was observed to have a slight impact on GLS (P_{Sex} = 0.046) (*Table 2*, *Figure 4*). In contrast, exercise training was associated with higher values of GMWI ($P_{Exercise}$ = 0.025) and CMWI ($P_{Exercise}$ = 0.004), and sex did not have a significant effect on their values (P_{Sex} = 0.460 and P_{Sex} = 0.297, respectively) (*Table 2*, *Figure 4*). WMWI and MWE did not differ between athletes and controls (*Table 2*).

Correlation of LV functional parameters with peak oxygen uptake

In the pooled study cohort, LVEF and GLS correlated weakly to moderately with VO_2/kg (r = -0.341, P = 0.032 and r = 0.494, P = 0.001, *Figure 5*). Both GMWI and CMWI exhibited moderate positive correlation with CPET-derived VO_2/kg (r = 0.527 and r = 0.584, both $P < 0.001$, *Figure 5*). Correlations of similar strength were observed in

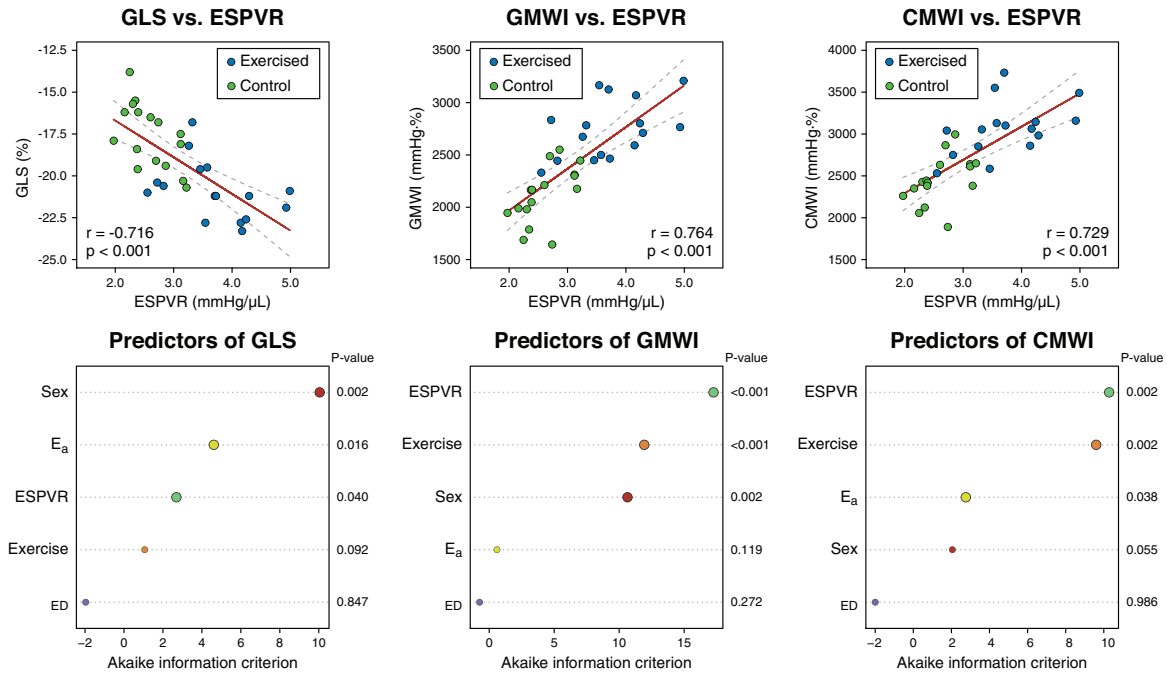


Figure 3 Correlations between LV contractility and LV deformation parameters in rats (upper panel), predictors of LV deformation parameters assessed using multivariable analysis (lower panel). σ_{ED}, meridional end-diastolic wall stress; CMWI, constructive myocardial work index; E_a, arterial elastance; ESPVR, slope of end-systolic pressure–volume relationship (i.e. the slope of the curve connecting the end-systolic points of the pressure–volume loops recorded during the transient occlusion of inferior vena cava); F_{Co}, female control group; F_{Ex}, female exercised group; GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular; M_{Co}, male control group; M_{Ex}, male exercised group.

the subgroups containing males or females exclusively (Supplementary data online, *Table S9*).

Reproducibility

Intra- and inter-observer variability analysis confirmed high reproducibility of the GLS, GMWI, and CMWI measurements in both rats and humans (Supplementary data online, *Tables S10* and *S11*).

Discussion

In our study, we comprehensively investigated the role of STE-derived MW in the functional evaluation of the athlete's heart (*Graphical Abstract*). First, we provided experimental data by performing both non-invasive (STE) and invasive (P–V analysis) measurements in a rodent model of exercise-induced LV hypertrophy. In addition, human data from elite athletes were obtained by advanced echocardiography and functional testing (CPET). We observed that exercised rats had higher values of GLS, GMWI, CMWI, and ESPVR than the control animals. In our cohort of elite swimmer athletes and controls, regular exercise training was associated with decreased GLS but increased GMWI and CMWI. Moreover, MW indices correlated with the invasively measured LV contractility in rats and maximal aerobic capacity in human athletes.

One of the most extensively investigated features of the athlete's heart is the enhancement of its systolic performance. Although the separation of the distinct determinants of systolic function (e.g. inotropy, preload, and afterload) might be attainable by invasive haemodynamic assessment, these procedures cannot be routinely performed in athletes. Despite the unprecedented expansion in the arsenal of cardiovascular imaging technologies over the past decades, still, none of the non-invasively measured parameters can reliably and accurately characterize the exercise-induced enhancement of LV systolic function at rest. Advanced echocardiographic techniques offer several valuable parameters (such as myocardial velocities or strains); however, alterations of the loading conditions have a substantial impact on these metrics.[6,14,15] The recently introduced MW analysis (by adjusting myocardial deformation to instantaneous LV pressure) might produce less load-dependent indicators of LV systolic function than mere strain.[9,16] Thus, it may better reflect intrinsic cardiac contractility in exercise-induced LV hypertrophy as well.

According to our knowledge, this is the first experimental study investigating the correlation between MW indices and load-independent metrics of contractility in the athlete's heart. Animal models enable the profound and standardized investigation of cardiac function and haemodynamics using both invasive and non-invasive techniques. A previously validated and characterized rat model of athlete's heart served as the basis of our current investigation,[10] in which the observed ~10–20% degree of physiological LV hypertrophy is comparable to other relevant animal models.[17] Our preceding works revealed that LV strain parameters could accurately monitor the changes in the systolic function during both the

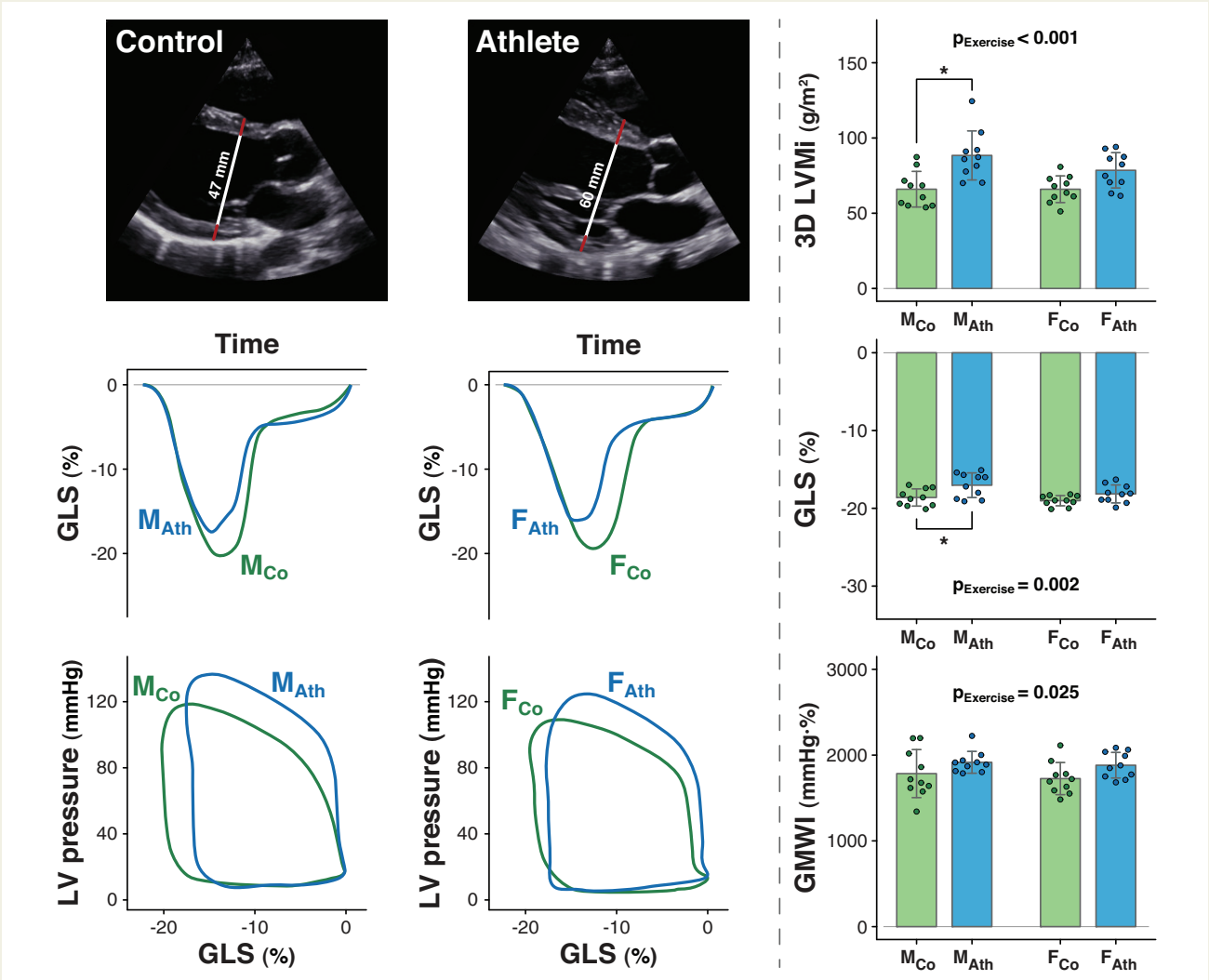


Figure 4 Exercise-induced structural and functional adaptation in human athletes. *Left panel* illustrates 2D echocardiographic images, strain curves, and pressure-strain loops of representative athletes and control subjects. *Right panel* depicts the group comparisons of LVMi, GLS, and GMWI. *p<0.05, Tukey's post hoc test (following two-way analysis of variance with the factors 'Sex' and 'Exercise'). GMWI, global myocardial work index; GLS, global longitudinal strain; F_{Ath}, female athlete group; F_{Co}, female control group; LV, left ventricular; LVMi, left ventricular mass index; M_{Co}, male control group, M_{Ath}, male athlete group.

development and the regression of exercise-induced hypertrophy, and these metrics also exhibited good correlations with load-independent measures of LV contractility.[7,8] Although STE-derived strains were shown to be promising descriptors of the LV inotropic state, there is an immense body of evidence about their load-dependency.[6,14] This represents an obvious issue in athletes as HR and loading conditions vary significantly during the course of the exercise-induced adaptation or even after a single exercise session.[18,19] In our experiments, GLS and MW indices suggested enhanced systolic performance in swim-trained rats that was also confirmed by their robust correlations with the invasively measured contractile function (*Figure 3*). Nevertheless, it is important to emphasize that indicators of preload (σ_{ED}) and afterload (E_a) did not considerably affect GMWI in contrast to GLS (*Figure 3*). From another point of view, ESPVR was found to be the strongest determinant of both GMWI and CMWI, whereas it played a less dominant role in determining GLS (*Figure 3*). These findings imply the superiority of GMWI and CMWI over conventional functional parameters in the characterization of the contractile function of the athlete's heart.

We also aimed to investigate whether the aforementioned favourable features of MW analysis could be translated to clinical sports cardiology. In clinical settings, MW indices are easily obtainable by a commercially available and validated software solution: after assessing GLS, the investigator should add systolic and diastolic pressures measured by a simple brachial cuff, and the software automatically generates the pressure–strain loops and the corresponding metrics. In elite swimmers, we have demonstrated that despite the slightly reduced GLS, both GMWI and CMWI were significantly higher than the control group, implying enhanced systolic performance even during resting conditions. This feature of MW analysis may be a

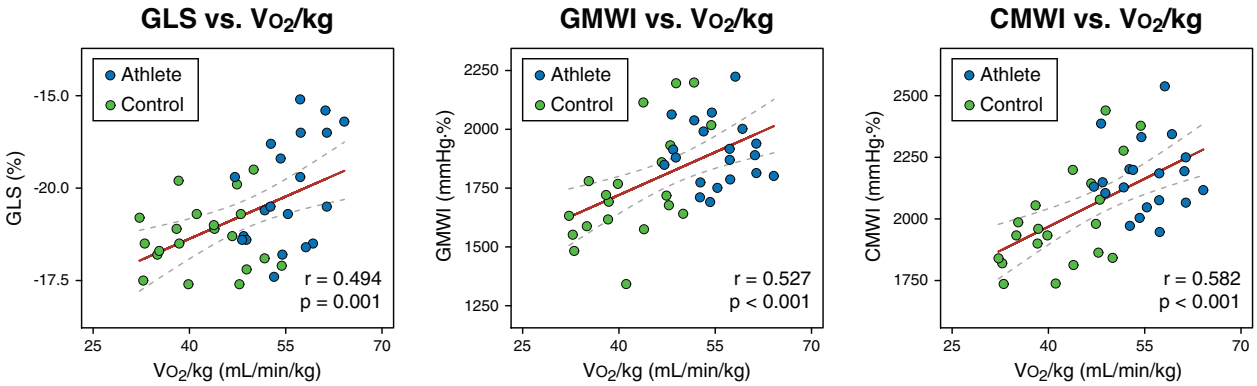


Figure 5 Correlations between peak oxygen uptake and left venitrcular deformation parameters in human athletes. CMWI, constructive myocardial work index; GLS, global longitudinal strain; GMWI, global myocardial work index; VO_2/kg, peak oxygen uptake.

meaningful addition to the everyday clinical practice, as LVEF and GLS can be reduced in athletes prohibiting the confident exclusion of overlapping cardiac disorders with athlete's heart.[1,2,20] Importantly, MW indices correlated moderately with CPET-derived VO_2/kg, justifying that supernormal values of GMWI and CMWI measured during resting conditions indicate better performance during exercise. Of note, a significant correlation between peak oxygen uptake and GMWI was observed previously in pathological conditions as well, such as in heart failure patients[21] or hypertensive patients.[22] Our findings coincide with the results of a recently published study, which reported that GLS was reduced in endurance athletes compared to control subjects, whereas WMWI and MWE were comparable between the two groups.[23] In our study, GMWI and CMWI (the parameters showing strong correlations with LV contractility in the experimental setting) were also evaluated and found to be supernormal in athletes at rest. Thus, our experimental and clinical findings endorse the utilization of MW analysis in the evaluation of the athlete's heart as MW indices reflect LV contractility in a less load-dependent manner and are markers of exercise capacity.

Although MW indices implied supernormal systolic function in exercised rats as well as in human athletes, there are apparent dissimilarities in the underlying factors of this phenomenon between the two settings. In the rat model of athlete's heart, GLS is higher compared to control animals, whereas LV pressures are similar. Therefore, the augmentation of GMWI and CMWI is mainly attributable to the enhancement of myocardial deformation. The relatively less pronounced exercise-induced LV dilation and the anaesthesia (during the echocardiographic examination) generated a physiological set-up that could diminish the differences between the experimental groups in LV geometry, preload, and afterload.[24] Thus, GLS will be supernormal in the exercised rats and will adequately reflect the increased LV contractility.[7,8] On the other hand, the exercise-induced cardiovascular adaptation of human swimmer athletes is different in two pivotal aspects. First, unlike in the rat model, swimming resulted in the marked dilation of the LV. Thus, the reduction in GLS values and the consequent uncoupling between myocardial deformation and contractility are partly attributable to the alterations in the LV geometry, as in the case of LV dilation, less myocardial deformation is sufficient to generate a normal stroke volume.[6] Second, in line with our findings, it has been previously reported that elite swimmer athletes often present with elevated resting systolic blood pressure due to vascular remodelling and altered sympathoadrenergic regulation.[25] Therefore, we can expect to measure preserved or even elevated values of GMWI and CMWI as the increase in LV pressures might countervail the reduction of GLS. Nevertheless, the calculation of MW by interpreting LV deformation in the context of instantaneous LV pressure can overcome these differences between the rat model and human athletes; hence MW indices seem to be universal and reliable markers of the LV systolic function in this scenario.

Limitations

Our study has several limitations that should be acknowledged. First, although both experimental and human data were acquired to explore the potentials of MW analysis in the evaluation of exercise-induced LV hypertrophy, we involved only swim-trained rats and elite swimmer athletes in the current study. Thus, the generalizability of our results to other sport disciplines remains to be clarified in future investigations. Second, the number of subjects in the human study is limited, which could be attributable to our relatively strict inclusion criteria. Third, cardiac contractility was measured directly only in the rat model but not in humans. Fourth, in humans, STE was performed in images acquired from apical views, whereas in the rat model, GLS was assessed from the parasternal long-axis view. Nevertheless, evidence suggests that the insonation angle has only a modest effect on the measurement of GLS.[26] Last, in rats, echocardiography and P–V analysis were performed under anaesthesia, which might influence parameters dependent on the autonomic nervous system, such as HR and pressure values.[24] Nonetheless, P–V analysis might provide parameters that are independent of loading conditions.

Conclusions

MW reflected LV contractility accurately in a rat model of exercise-induced LV hypertrophy and was able to capture the supernormal

LV systolic performance of human athletes even during resting conditions. Our results confirmed that MW is less dependent on loading conditions and sex-related differences, which further endorses the widespread utilization of this novel, non-invasive technique in the evaluation of the athlete's heart.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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