

Strain and strain rate by speckle-tracking echocardiography correlate with pressure-volume loop-derived contractility indices in a rat model of athlete's heart

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Kovács A, Oláh A, Lux Á, Mátyás C, Németh BT, Kellermayer D, Ruppert M, Török M, Szabó L, Meltzer A, Assabiny A, Birtalan E, Merkely B, Radovits T. Strain and strain rate by speckle-tracking echocardiography correlate with pressure-volume loop-derived contractility indices in a rat model of athlete's heart. *Am J Physiol Heart Circ Physiol* 308: H743–H748, 2015. First published January 23, 2015; doi:10.1152/ajpheart.00828.2014.—Contractile function is considered to be precisely measurable only by invasive hemodynamics. We aimed to correlate strain values measured by speckle-tracking echocardiography (STE) with sensitive contractility parameters of pressure-volume (P-V) analysis in a rat model of exercise-induced left ventricular (LV) hypertrophy. LV hypertrophy was induced in rats by swim training and was compared with untrained controls. Echocardiography was performed using a 13-MHz linear transducer to obtain LV long- and short-axis recordings for STE analysis (GE EchoPAC). Global longitudinal (GLS) and circumferential strain (GCS) and longitudinal (LSr) and circumferential systolic strain rate (CSr) were measured. LV P-V analysis was performed using a pressure-conductance microcatheter, and load-independent contractility indices [slope of the end-systolic P-V relationship (ESPVR), preload recruitable stroke work (PRSW), and maximal dP/dt -end-diastolic volume relationship ($dP/dt_{\max}$ -EDV)] were calculated. Trained rats had increased LV mass index (trained vs. control; 2.76 ± 0.07 vs. 2.14 ± 0.05 g/kg, $P < 0.001$). P-V loop-derived contractility parameters were significantly improved in the trained group (ESPVR: 3.58 ± 0.22 vs. 2.51 ± 0.11 mmHg/ μ l; PRSW: 131 ± 4 vs. 104 ± 2 mmHg, $P < 0.01$). Strain and strain rate parameters were also supernormal in trained rats (GLS: -18.8 ± 0.3 vs. $-15.8 \pm 0.4\%$; LSr: -5.0 ± 0.2 vs. -4.1 ± 0.1 Hz; GCS: -18.9 ± 0.8 vs. $-14.9 \pm 0.6\%$; CSr: -4.9 ± 0.2 vs. -3.8 ± 0.2 Hz, $P < 0.01$). ESPVR correlated with GLS ($r = -0.71$) and LSr ($r = -0.53$) and robustly with GCS ($r = -0.83$) and CSr ($r = -0.75$, all $P < 0.05$). PRSW was strongly related to GLS ($r = -0.64$) and LSr ($r = -0.71$, both $P < 0.01$). STE can be a feasible and useful method for animal experiments. In our rat model, strain and strain rate parameters closely reflected the improvement in intrinsic contractile function induced by exercise training.

speckle-tracking echocardiography; pressure-volume analysis; athlete's heart; contractility; strain

LONG-TERM EXERCISE TRAINING induces physiological left ventricular (LV) hypertrophy, a molecular and cellular growth process of the heart in response to altered loading conditions (6). In

contrast to pathological hypertrophy, this adaptation leads to maintained or even enhanced cardiac function (2, 14). Hemodynamic changes of exercise-induced hypertrophy were characterized by our research group in a rat model, focusing also on the improved LV inotropic state (23). Contractility is the intrinsic ability of the myocardium to generate force and to shorten independently of changes in preload or afterload with fixed heart rates. In the past few decades, efforts have been made to transfer the physiological concept of contractility to the intact beating heart (4).

Pressure-volume (P-V) analysis recently became the gold standard to investigate in vivo hemodynamics in animal models. During preload reduction maneuvers such as gradual occlusion of vena cava inferior, load-independent indices of myocardial contractility could be obtained (20). The slope of the LV end-systolic P-V relationship (ESPVR), preload recruitable stroke work (PRSW), and the slope of the maximal dP/dt -end-diastolic volume relationship ($dP/dt_{\max}$ -EDV) reliably reflect the intrinsic inotropic state of the LV (9, 11, 18). However, the invasive nature of this precise method demands the subsequent euthanization of the animal, thus prohibiting consecutive data collection. Serial assessment of myocardial contractility could be an important issue in describing the inotropic state during or following a training program in small animal models of athlete's heart.

Transthoracic echocardiography could be a feasible alternative; however, diagnostic arsenal regarding systolic parameters is scant, especially when supernormal function has to be evaluated. Furthermore, conventional indices of LV systolic function (such as ejection fraction or fractional shortening) are highly dependent on loading conditions and provide only rough estimation of contractile function (17). Therefore, identifying such noninvasive parameters that closely reflect contractility (ideally during resting conditions) is of high importance not just for animal experiments but for human investigations as well.

In the present study, we aimed at correlating strain values measured by speckle-tracking echocardiography (STE) with sensitive contractility parameters of P-V analysis in a rat model of exercise-induced LV hypertrophy.

METHODS

Ethical approval and experimental groups. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and published by the

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Table 1. Endurance exercise training-induced LV morphological changes and echocardiography data

	Control (n = 12)	Exercised (n = 10)	P Value
Heart weight, g	1.34 ± 0.03	1.48 ± 0.03	0.007
Heart weight/body weight, g/kg	2.89 ± 0.07	3.66 ± 0.11	<0.001
Anterior wall diastole, mm	2.15 ± 0.02	2.36 ± 0.03	<0.001
Anterior wall systole, mm	3.12 ± 0.07	3.48 ± 0.07	0.001
Posterior wall diastole, mm	1.96 ± 0.03	2.08 ± 0.02	0.002
Posterior wall systole, mm	2.97 ± 0.05	3.16 ± 0.06	0.028
End-diastolic diameter, mm	6.69 ± 0.09	6.61 ± 0.07	0.496
End-systolic diameter, mm	3.96 ± 0.10	3.40 ± 0.06	<0.001
Fractional shortening, %	40.9 ± 1.1	48.6 ± 0.6	<0.001
LV mass, g	1.00 ± 0.01	1.10 ± 0.02	<0.001
LV mass index, g/kg	2.14 ± 0.05	2.76 ± 0.07	<0.001

Values are means ± SE. LV, left ventricular.

National Institutes of Health (NIH Publication No. 86-23, revised 1996). Procedures and handling of the animals during the study were reviewed and approved by the Ethical Committee of Hungary for Animal Experimentation (permission no. 22.1/1162/3/2010).

Young adult (12-wk-old, $m = 275$ – 300 g) male Wistar rats ($n = 22$) (Charles River Laboratories, Sulzfeld, Germany) were housed in a room with a constant temperature of $22 \pm 2^\circ\text{C}$ and a 12:12-h light-dark cycle, fed a standard laboratory rat diet ad libitum, and given free access to water.

After acclimation, rats from the exercise group ($n = 10$) underwent a 12-wk-long swim training program; untrained animals served as controls (control group: $n = 12$). Echocardiographic measurements and invasive hemodynamic assessments were performed after completion of the training program. Hearts were removed, and heart weight was measured immediately after euthanization.

Swim training protocol: rat model of exercise-induced cardiac hypertrophy. Exercise training was performed in a water tank divided into six lanes filled with tap water warmed to ~ 30 – 32°C at the same time of day in all training sessions, as described previously (23). Exercised rats swam for a total period of 12 wk, 200-min long sessions/day and 5 days/wk. For adequate adaptation, the duration of first swimming experience was limited to 15 min and increased by 15 min every second training session until 200 min was reached. Control rats were placed into the water for 5 min each day during the 12-wk training program.

Echocardiography. Rats were anesthetized with pentobarbital sodium (60 mg/kg ip). Animals were placed on controlled heating pads, and the core temperature was maintained at 37°C . After the anterior chest was shaved, transthoracic echocardiography was performed in the supine position by one investigator blinded to the experimental groups. Standard two-dimensional and M-mode long- and short-axis (at the midpapillary level) images were acquired using a 13-MHz linear transducer (12L-RS; GE Healthcare, Horten, Norway) connected to a commercially available system (Vivid i; GE Healthcare). Archived recordings were analyzed by a blinded investigator using dedicated software (EchoPac v113; GE Healthcare). On two-dimensional recordings of the short-axis at the midpapillary level, LV anterior (AWT) and posterior (PWT) wall thickness in diastole (index: d) and systole (index: s) as well as LV end-diastolic (LVEDD) and end-systolic diameter (LVESD) were measured. End systole was defined as the time point of minimal LV dimensions, whereas end diastole was defined as the time point of maximal dimensions. All values were averaged over three consecutive cycles.

Fractional shortening (FS) was determined from the measurements of LV chamber diameters: $\text{FS} = [(\text{LVEDD} - \text{LVESD})/\text{LVEDD}] \times 100$. LV mass was calculated according to the following formula: $\text{LV mass} = [(\text{LVEDD} + \text{AWTd} + \text{PWTd})^3 - \text{LVEDD}^3] \times 1.04 \times 0.8 + 0.14$ (24). To calculate LV mass index, we normalized the LV mass values to the body weight of the animal.

Speckle-tracking echocardiography. Strain is a dimensionless measure of relative deformation that enables us to characterize different directions of myocardial function on both global and regional levels. The novel method of STE allows us to quantify strain and its temporal derivative strain rate, resulting in promising new parameters of systolic and diastolic function (3). Loops of long- and short-axis views of the LV dedicated for speckle tracking were acquired at least three times, with each axis using a constant frame rate of 218 Hz. Speckle-tracking analysis was done by a blinded operator with remarkable expertise on the software environment (EchoPAC v113). To calculate global longitudinal strain (GLS) and longitudinal systolic strain rate (LSr) indices, three different long-axis loops from each animal and three cardiac cycles from each loop were analyzed. To calculate global circumferential strain (GCS) and circumferential systolic strain rate (CSr), the same repetition of measurements was performed using the short-axis recordings. After manual delineation of the endocardial border on the end-diastolic frame, the software automatically divided the region of interest to six segments and tracked them throughout the cardiac cycles. In case of low tracking quality, the tracing was corrected manually and analyzed again by the software. Acceptance or rejection of a certain segment to be included in statistical analysis was guided by the software's recommendation. Ideally, for each parameter ($3 \times 3 \times 6$) 54 segmental values were averaged. Animals with <36 segmental values (due to technically suboptimal tracking quality despite the aforementioned efforts) were excluded from the study. Based on these criteria, eight trained and 12 control rats were eligible to be included in the statistical analysis.

Hemodynamic measurements of contractility indices. After anesthetizing using intraperitoneal pentobarbital sodium (60 mg/kg), rats were tracheotomized and intubated to facilitate breathing. Animals were placed on controlled heating pads, and the core temperature was maintained at 37°C . A polyethylene catheter was inserted into the left external jugular vein for fluid administration. P-V analysis was performed as described previously (22). A 2-Fr pressure-conductance catheter (SPR-838; Millar Instruments, Houston, TX) was introduced into the right carotid artery and advanced into the LV. After stabilization, signals were recorded continuously using a P-V conductance system (MPVS-Ultra; Millar Instruments) connected to a PowerLab 16/30 data acquisition system (AD Instruments, Colorado Springs, CO), stored, and displayed by the LabChart 5 Software System (AD Instruments). LV P-V relations were also registered during transient compression of the inferior vena cava (reducing preload) under the diaphragm with a cotton-tipped

Table 2. Baseline hemodynamic data of pressure-volume analysis

	Control (n = 12)	Exercised (n = 10)	P Value
Mean arterial pressure, mmHg	144.4 ± 2.7	141.9 ± 5.8	0.517
Heart rate, 1/min	410 ± 8	402 ± 8	0.491
LV end-systolic pressure, mmHg	160.1 ± 3.3	158.3 ± 9.2	0.848
LV end-diastolic pressure, mmHg	3.2 ± 0.2	3.8 ± 0.6	0.226
Maximal dP/dt, mmHg/s	9,228 ± 360	9,720 ± 723	0.527
Minimal dP/dt, mmHg/s	−12,156 ± 402	−12,056 ± 728	0.901
LV end-diastolic volume, μl	229.9 ± 2.9	234.9 ± 4.9	0.367
LV end-systolic volume, μl	111.3 ± 1.8	100.1 ± 1.9	<0.001
Stroke volume, μl	118.7 ± 3.5	135.6 ± 4.3	0.007
Ejection fraction, %	52.3 ± 1.2	58.1 ± 0.9	0.002
Cardiac output, ml/min	49.0 ± 1.3	55.9 ± 1.6	0.003
Total peripheral resistance, mmHg/(ml/min)	2.94 ± 0.09	2.56 ± 0.13	0.024
Stroke work, mmHg·ml	14.1 ± 0.6	17.8 ± 0.9	0.003

Values are means ± SE.

applicator. With the use of a special P-V analysis program (PVAN; Millar Instruments), we calculated basic hemodynamic parameters: heart rate (HR), mean arterial pressure (MAP), LV end-systolic pressure (LVESP), LV end-diastolic pressure (LVEDP), the maximal slope of LV systolic pressure increment ($dP/dt_{\max}$), diastolic pressure decrement ($dP/dt_{\min}$), LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), stroke volume (SV), ejection fraction (EF), cardiac output (CO), and stroke work (SW). Total peripheral resistance (TPR) was calculated as the ratio of MAP and CO. We also determined sensitive indices of LV contractility, which are less influenced by loading conditions: ESPVR (according to the parabolic curvilinear model), PRSW, and $dP/dt_{\max}$ -EDV. Conductance signal was converted to absolute volume by conductance calibration, as described previously (20).

Statistics. For statistical analysis, we used Statistica 8.0 software (StatSoft, Tulsa, OK). Normal distribution of variables was assessed by Shapiro-Wilk test. To compare variables, Student's *t*-test was used. Relationships were calculated with Pearson correlation test. Data are presented as means $\pm$ SE. *P* values <0.05 were considered statistically significant.

RESULTS

Morphological markers of LV hypertrophy. Echocardiographic morphological data showed increased wall thickness

values both in the anterior and posterior regions in exercised animals compared with controls (Table 1). The calculated LV mass and LV mass index values indicated LV hypertrophy after the completion of the exercise training protocol. Echocardiographic data were underpinned by postmortem measured heart weight data, which showed increased heart weight values. The difference was even more pronounced when heart weight/body weight ratio was calculated (Table 1).

Basic hemodynamics. There was no difference between the groups regarding pressure values (MAP, LVESP, LVEDP, $dP/dt_{\max}$, and $dP/dt_{\min}$) and HR (Table 2). LVESV was decreased in trained rats compared with control ones, along with unaltered LVEDV. Consequently, our data of systolic parameters revealed an increase in SV, EF, CO, and SW, whereas TPR was shown to be decreased in exercised animals (Table 2).

LV contractility indices derived from P-V analysis at different preloads. Figure 1 shows representative original P-V loops recorded during reducing preload (transient occlusion of the inferior vena cava) in exercised and control animals. ESPVR, PRSW, and $dP/dt_{\max}$ -EDV were shown to be steeper in exercised animals compared with controls. The slope values of

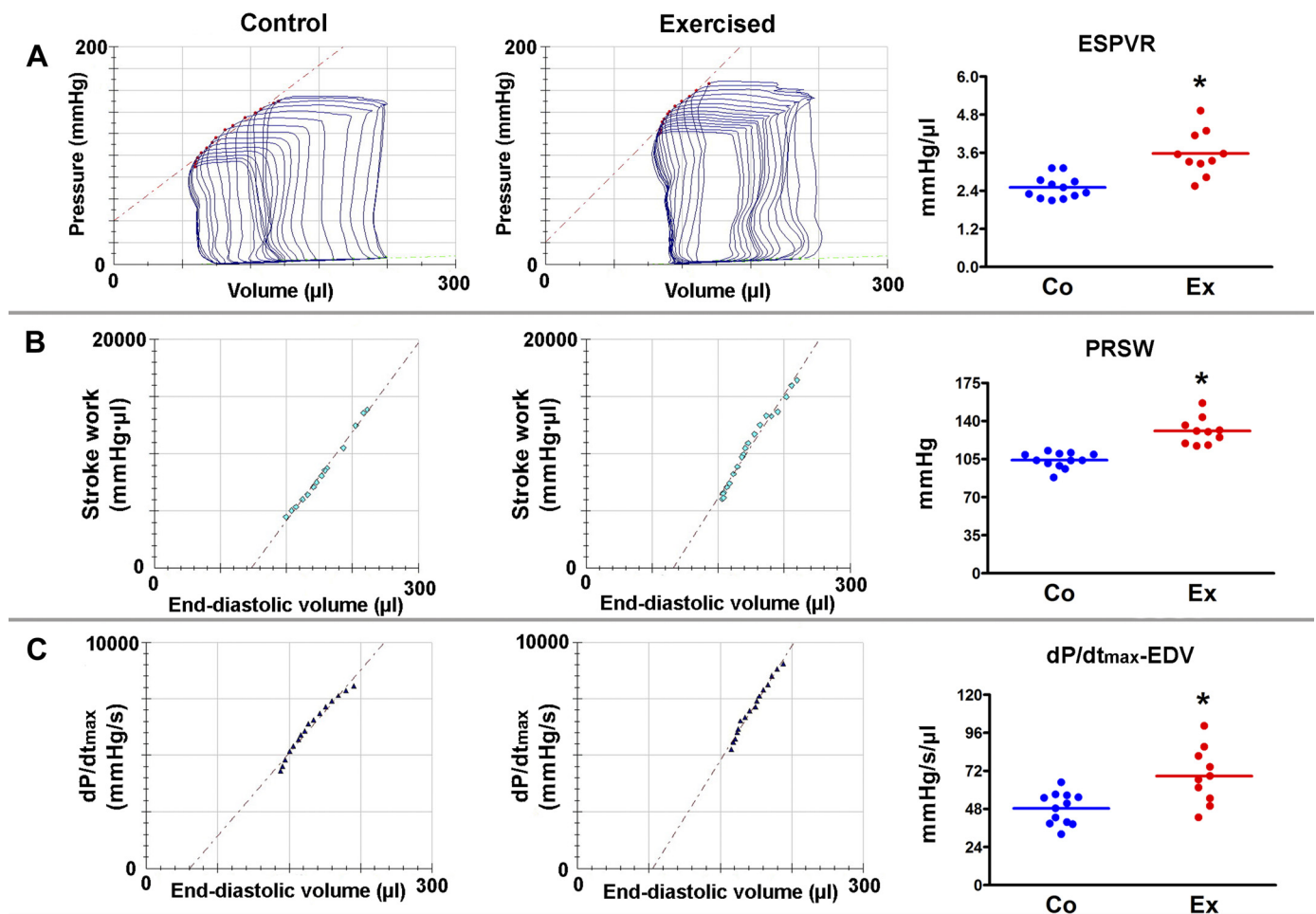


Fig. 1. Contractility parameters measured by left ventricular pressure-volume analysis. The slope of end-systolic pressure-volume relationship (ESPVR; A); preload recruitable stroke work (PRSW), the slope of the relationship between stroke work and end-diastolic volume (B); and maximal slope of the systolic pressure increment-end-diastolic volume relationship ($dP/dt_{\max}$ -EDV; C) in representative rats from control (Co) and exercised (Ex) groups. As seen on the dot plots, all of these contractility parameters are markedly increased in the Ex group, suggesting improved inotropic state in exercise-induced cardiac hypertrophy. Horizontal lines represent mean values. * $P < 0.05$ vs. Co.

these relationships were significantly higher after endurance exercise training, indicating a markedly increased LV contractility (Fig. 1).

Indices derived from speckle-tracking analysis. In line with contractility indices, exercised rats showed marked superiority over controls regarding myocardial mechanics. Both longitudinal and circumferential strain and systolic strain rate were increased significantly compared with the untrained rats (Fig. 2).

Correlations between P-V measurements and STE parameters. ESPVR correlated with GLS ($r = -0.71$, $P < 0.001$) and LSr ($r = -0.53$, $P = 0.016$) and robustly with GCS ($r = -0.83$, $P < 0.001$) and CSr ($r = -0.75$, $P < 0.001$) (Fig. 3). PRSW was strongly related to GLS ($r = -0.64$, $P = 0.002$) and LSr ($r = -0.71$, $P = 0.001$), but less so to CSr ($r = -0.51$, $P = 0.023$), whereas it tended to be correlated with GCS ($r = -0.34$, $P = 0.082$). We also found moderate correlations between $dP/dt_{\max}$ -EDV and strain parameters (GLS: $r = -0.59$, $P = 0.005$; LSr: $r = -0.57$, $P = 0.009$; GCS: $r = -0.46$, $P = 0.042$; CSr: $r = -0.51$, $P = 0.021$).

DISCUSSION

The main findings of our rodent experimental study are that both pressure-volume analysis and speckle-tracking echocardiography demonstrate increased systolic function of the trained heart and that invasive, load-independent contractility indices are closely reflected by strain and strain rate parameters, allowing us to estimate cardiac contractility noninvasively in a consecutive manner and even during resting conditions.

In agreement with previous results of the rat model of exercise-induced cardiac hypertrophy, an increase in postmortem-assessed cardiac mass was observed after swimming training protocol (23). The observed increase in cardiac mass was underpinned by increased wall thickness values and calculated LV mass data using echocardiography (Table 1). The degree of cardiac hypertrophy was comparable with other small animal models of exercise-induced cardiac hypertrophy (25).

Regular exercise training-induced physiological hypertrophy is associated with normal or enhanced function of the heart (19). Echocardiographic data indicated an increased fractional shortening in trained animals that was a consequence of decreased end-systolic dimensions along with unchanged end-diastolic dimensions. Accordingly, our baseline hemodynamic data obtained with the pressure-volume system showed an increase in systolic parameters (SV, EF, CO, and SW) in trained animals along with unaltered pressure values and heart rate as well as with decreased TPR (Table 2). These results are in good agreement with our previous hemodynamic data of exercise-induced hypertrophy using another anesthesia protocol (ketamine-xylazine) (23).

Contractility is the capacity of the myocardium to contract independently of alterations in preload or afterload. The slope of the ESPVR is the most commonly used and perhaps the most reliable index of LV contractility in the intact circulation and is almost insensitive to alterations in preload or afterload (5). As shown in Fig. 1, ESPVR was steeper in trained rats, indicating an improved inotropic state of the LV myocardium. During the transient occlusion of vena cava inferior, two

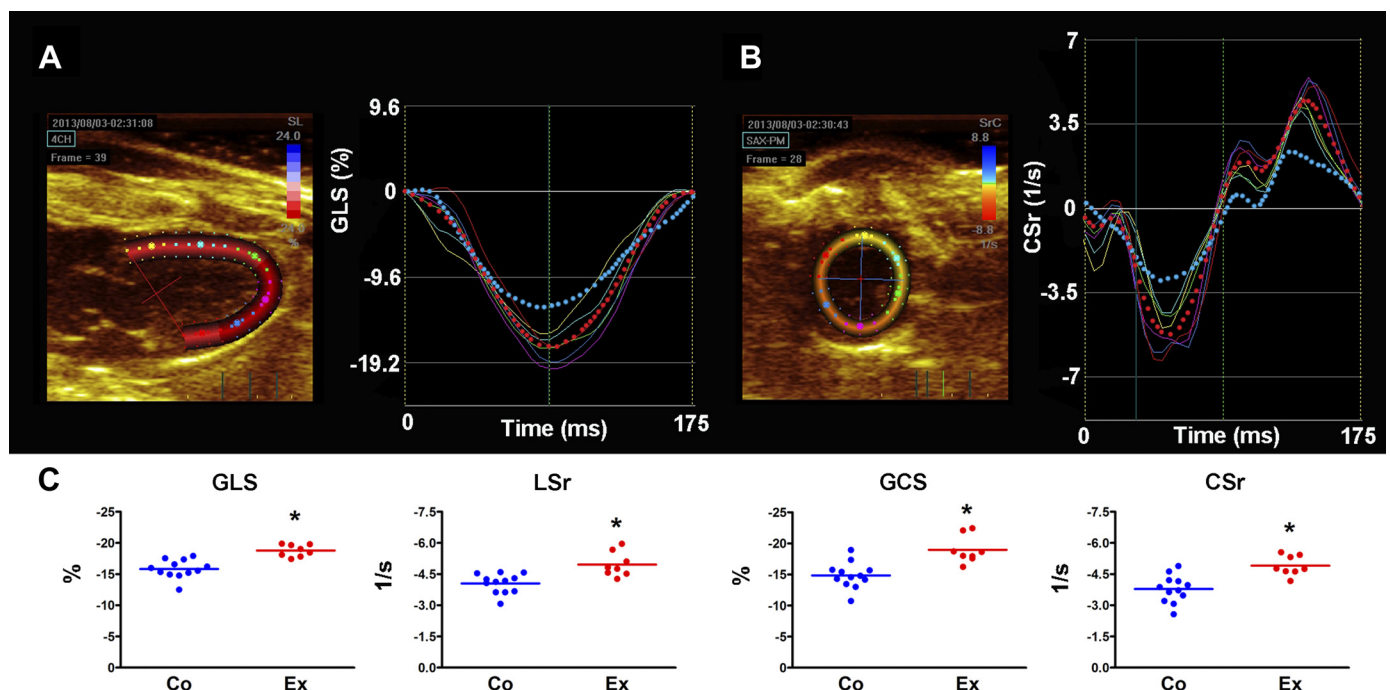


Fig. 2. Layout and results of the speckle-tracking analysis. Representative original recordings of an exercised rat. Each continuous curve represents a given segment with the same color on the echocardiographic image. Average value of the 6 segments is delineated with a red dotted line and compared with an original recording from a control rat (blue dotted line). A: determination of longitudinal strain on a long-axis image. The negative peak of the averaged curve represents the global longitudinal strain (GLS). B: determination of circumferential strain rate (CSr) on a midpapillary short-axis view. The peak negative value of the averaged curve is the systolic strain rate. C: as depicted by the dot plots, all measured strain and strain rate indices [GLS, longitudinal systolic strain rate (LSr), global circumferential strain (GCS), and CSr] were improved in Ex compared with Co, in line with the invasive contractility parameters. Horizontal lines represent mean values. * $P < 0.05$ vs. Co.

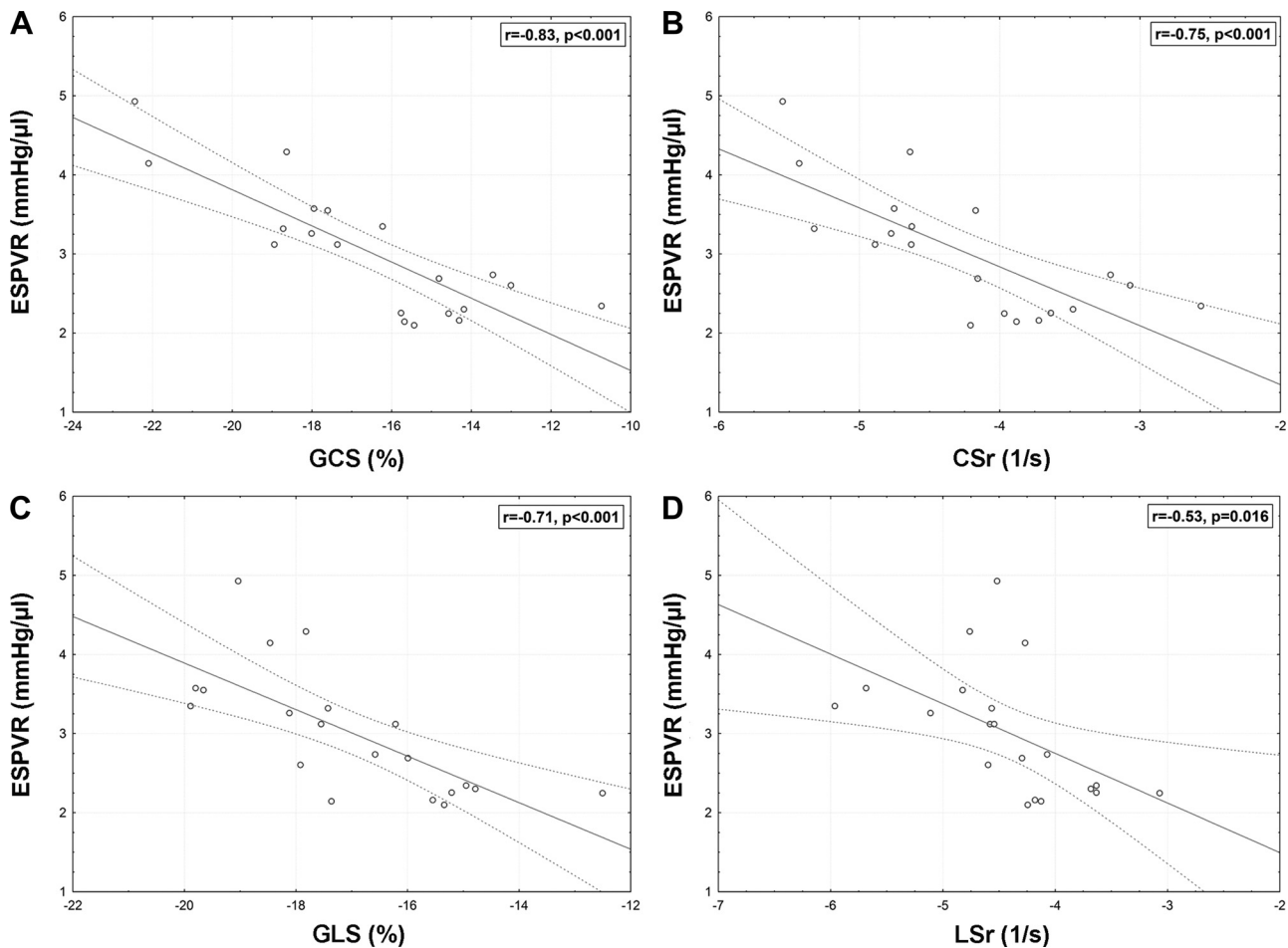


Fig. 3. Correlations between the slope of left ventricular ESPVR and GCS (A), CSr (B), GLS (C), and LSr (D) in trained and control rats ($n = 20$).

additional sensitive contractility indices could be acquired: the slope of the linear relation between SW and EDV (the so-called PRSW) and the slope of the linear relation between $dp/dt_{\max}$ and EDV ($dp/dt_{\max}$ -EDV) (20). Both of these indices were increased in trained hearts compared with control ones, confirming the improved contractile state in exercise-induced cardiac hypertrophy (Fig. 1).

The search for powerful systolic parameters is an ongoing quest for echocardiographic research, but even precise evaluation of supernormal function is a major issue. Speckle-tracking echocardiography gained particular interest, as it allows quantitative evaluation of myocardial motion at both global and regional levels (21).

Superiority of speckle tracking-derived parameters in detecting subtle myocardial injury was suggested by numerous works not just in humans but also in animal models (12, 15, 16). Strain indices were shown to be able to sensitively and continually reflect the progression of heart failure as well (13).

Nevertheless, available data encompasses the value of strain indices in reduced myocardial function exclusively, but less is known about its added value in supernormal states, especially in the trained heart. In our experiments, both longitudinal and circumferential strain and strain rate successfully reflected increased contractile function. We also found robust correlations between invasive contractility indices and longitudinal or circumferential strain and strain rate as well.

In a recent publication, Ferferieva et al. (7) demonstrated similar results regarding circumferential strain and PRSW. Nevertheless, their experiments were conducted in mice models of transaortic constriction and myocardial infarction, whereas our correlations originated from an athlete's heart model of supernormal contractility, a scenario where conventional echocardiography usually lacks the power to measure myocardial function precisely. They also compared tissue Doppler imaging and speckle-tracking measurements of strain parameters and demonstrated the superiority of tissue Doppler imaging in the case of higher heart rates. Temporal resolution is an obvious advantage of the Doppler technique; however, its angle dependency is certainly an issue in terms of reproducibility (8). Because of that reason and also the possibility of measuring longitudinal strain and strain rate, we propose speckle-tracking echocardiography as the method of choice during resting conditions. Longitudinal strain gained huge value in human echocardiographic examinations, and despite its unusual application on long-axis images (in contrast to apical views in humans), longitudinal strain and strain rate were also found to be robust parameters in our experiments. Longitudinal and circumferential deformation can represent the function of different layers of myofiber architecture, and therefore, valuable regional alterations (i.e., subendocardial ischemia) could be assessed as well (1, 10). However, limitations of the speckle-tracking technique known from human investigations may also apply;

acquisition of proper images with optimal spatial and temporal resolution is of high importance (3). Out-of-plane speckle motion to reduce tracking quality is implied in the two-dimensional approach.

CONCLUSIONS

In a rat model of athlete's heart, speckle tracking-derived indices were in close relationship with invasive load-independent measurements of cardiac contractility.

Correlations between P-V analysis and strain parameters are promising in terms of widespread use of speckle-tracking echocardiography during consecutive evaluation of physiological myocardial hypertrophy in small-animal models.

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DISCLOSURES

All authors declare no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

A.K., A.O., B.M., and T.R. conception and design of research; A.K., A.O., Á.L., C.M., B.T.N., D.K., M.R., M.T., L.S., A.M., A.A., E.B., and T.R. performed experiments; A.K., A.O., Á.L., C.M., B.T.N., A.A., B.M., and T.R. analyzed data; A.K., A.O. and T.R. interpreted results of experiments; A.K. and A.O. drafted manuscript; A.K., A.O., Á.L., C.M., B.T.N., D.K., M.R., M.T., L.S., A.M., A.A., E.B., B.M., and T.R. approved final version of manuscript; A.O. prepared figures; B.M. and T.R. edited and revised manuscript.

REFERENCES

- Bachner-Hinzenon N, Ertracht O, Malka A, Leitman M, Vered Z, Binah O, Adam D. Layer-specific strain analysis: investigation of regional deformations in a rat model of acute versus chronic myocardial infarction. *Am J Physiol Heart Circ Physiol* 303: H549–H558, 2012.
- Bernardo BC, Weeks KL, Pretorius L, McMullen JR. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol Ther* 128: 191–227, 2010.
- Blessberger H, Binder T. NON-invasive imaging: Two dimensional speckle tracking echocardiography: basic principles. *Heart* 96: 716–722, 2010.
- Bombardini T. Myocardial contractility in the echo lab: molecular, cellular and pathophysiological basis. *Cardiovasc Ultrasound* 3: 27, 2005.
- Cingolani OH, Kass DA. Pressure-volume relation analysis of mouse ventricular function. *Am J Physiol Heart Circ Physiol* 301: H2198–H2206, 2011.
- Fagard R. Athlete's heart. *Heart* 89: 1455–1461, 2003.
- Ferferieva V, Van den Bergh A, Claus P, Jasaityte R, La Gerche A, Rademakers F, Herijgers P, D'Hooge J. Assessment of strain and strain rate by two-dimensional speckle tracking in mice: comparison with tissue Doppler echocardiography and conductance catheter measurements. *Eur Heart J Cardiovasc Imaging* 14: 765–773, 2013.
- Fontana A, Zambon A, Cesana F, Giannattasio C, Trocino G. Tissue Doppler, triplane echocardiography, and speckle tracking echocardiography: different ways of measuring longitudinal myocardial velocity and deformation parameters. A comparative clinical study. *Echocardiography* 29: 428–437, 2012.
- Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation* 71: 994–1009, 1985.
- Ishizu T, Seo Y, Kameda Y, Kawamura R, Kimura T, Shimojo N, Xu D, Murakoshi N, Aonuma K. Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease. *Hypertension* 63: 500–506, 2014.
- Kass DA, Yamazaki T, Burkhoff D, Maughan WL, Sagawa K. Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique. *Circulation* 73: 586–595, 1986.
- Kim YH, Kim M, Park SM, Kim SH, Lim SY, Ahn JC, Song WH, Shim WJ. Discordant impairment of multidirectional myocardial deformation in rats with Doxorubicin induced cardiomyopathy. *Echocardiography* 29: 720–728, 2012.
- Koshizuka R, Ishizu T, Kameda Y, Kawamura R, Seo Y, Aonuma K. Longitudinal strain impairment as a marker of the progression of heart failure with preserved ejection fraction in a rat model. *J Am Soc Echocardiogr* 26: 316–323, 2013.
- Kovacs A, Apor A, Nagy A, Vago H, Toth A, Nagy AI, Kovacs T, Sax B, Szeplaki G, Becker D, Merkely B. Left ventricular untwisting in athlete's heart: key role in early diastolic filling? *Int J Sports Med* 35: 259–264, 2014.
- Kovacs A, Tapolyai M, Celeng C, Gara E, Faludi M, Berta K, Apor A, Nagy A, Tisler A, Merkely B. Impact of hemodialysis, left ventricular mass and FGF-23 on myocardial mechanics in end-stage renal disease: a three-dimensional speckle tracking study. *Int J Cardiovasc Imaging* 30: 1331–1337, 2014.
- Kramann R, Erpenbeck J, Schneider RK, Rohl AB, Hein M, Brandenburg VM, van Diepen M, Dekker F, Marx N, Floege J, Becker M, Schlieper G. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. *J Am Soc Nephrol* 25: 2351–2365, 2014.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 7: 79–108, 2006.
- Little WC. The left ventricular dp/dtmax-end-diastolic volume relation in closed-chest dogs. *Circ Res* 56: 808–815, 1985.
- McMullen JR, Jennings GL. Differences between pathological and physiological cardiac hypertrophy: novel therapeutic strategies to treat heart failure. *Clin Exp Pharmacol Physiol* 34: 255–262, 2007.
- Pacher P, Nagayama T, Mukhopadhyay P, Batkai S, Kass DA. Measurement of cardiac function using pressure-volume conductance catheter technique in mice and rats. *Nat Protoc* 3: 1422–1434, 2008.
- Popovic ZB, Benjam C, Bian J, Mal N, Drinko J, Lee K, Forudi F, Reeg R, Greenberg NL, Thomas JD, Penn MS. Speckle-tracking echocardiography correctly identifies segmental left ventricular dysfunction induced by scarring in a rat model of myocardial infarction. *Am J Physiol Heart Circ Physiol* 292: H2809–H2816, 2007.
- Radovits T, Korkmaz S, Loganathan S, Barnucz E, Bomicke T, Arif R, Karck M, Szabo G. Comparative investigation of the left ventricular pressure-volume relationship in rat models of type 1 and type 2 diabetes mellitus. *Am J Physiol Heart Circ Physiol* 297: H125–H133, 2009.
- Radovits T, Olah A, Lux A, Nemeth BT, Hidi L, Birtalan E, Keller-mayer D, Matyas C, Szabo G, Merkely B. Rat model of exercise-induced cardiac hypertrophy: hemodynamic characterization using left ventricular pressure-volume analysis. *Am J Physiol Heart Circ Physiol* 305: H124–H134, 2013.
- Reffellmann T, Kloner RA. Transthoracic echocardiography in rats. Evaluation of commonly used indices of left ventricular dimensions, contractile performance, and hypertrophy in a genetic model of hypertrophic heart failure (SHHF-Mcc-facp-Rats) in comparison with Wistar rats during aging. *Basic Res Cardiol* 98: 275–284, 2003.
- Wang Y, Wisloff U, Kemi OJ. Animal models in the study of exercise-induced cardiac hypertrophy. *Physiol Res* 59: 633–644, 2010.