Stimulus-specific functional remodeling of the left ventricle in endurance and resistance-trained men

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ABTRACT

Left ventricular (LV) structural remodeling following athletic training has been evidenced through training-specific changes in wall thickness and geometry. Whether the LV response to changes in hemodynamic load also adapts in a training-specific manner is unknown. Using echocardiography, we examined LV responses of endurance-trained (*n*=15), resistance-trained (*n*=14), and non-athletic males (*n*=13) to (i) 20%, 40%, and 60% one-repetition-maximum (1RM) leg-press exercise, and (ii) intravascular Gelofusine infusion (7ml·kg^{-1}) with passive leg-raise. While resting heart rate was lower in endurance-trained vs. controls (*P*=0.001), blood pressure was similar between groups. Endurance-trained individuals had lower wall thickness, but greater LV mass relative to body surface area vs. controls, with no difference between resistance-trained and controls. Leg-press evoked a similar increase in blood pressure; however, resistance-trained preserved stroke volume (SV; -3±8%) vs. controls at 60% 1RM (-15±7%, *P*=0.001). While the maintenance of SV was related to the change in longitudinal strain across all groups (R=0.537; *P*=0.007), time-to-peak strain was maintained in resistance-trained but delayed in endurance-trained individuals (1% vs. 12% delay; *P*=0.021). Volume infusion caused a similar increase in end-diastolic volume (EDV) and SV across groups, but leg-raise further increased EDV only in endurance-trained individuals (5±5% to 8±5%; *P*=0.018). Correlation analysis revealed a relationship between SV and longitudinal strain following infusion and leg-raise (R=0.334, *P*=0.054), however, we observed no between-group differences in longitudinal myocardial mechanics. In conclusion, resistance-trained individuals better maintained SV during pressure loading, whereas endurance-trained individuals demonstrated greater EDV reserve during volume loading. These data provide novel evidence of training-specific LV functional remodeling.

New and Noteworthy

Training-specific *functional* remodeling of the LV in response to different loading conditions has recently been suggested, but not experimentally tested in the same group of individuals. Our data provide novel evidence of a dichotomous, training-specific left ventricular adaptive response to hemodynamic pressure or volume loading.

INTRODUCTION

The theoretical framework for dichotomous structural remodeling of the left ventricle (LV) in response to repetitive hemodynamic pressure or volume overload caused by resistance or endurance based athletic-training was first suggested by Morganroth et al. (36). Despite this hypothesis being proposed over 45 years ago, our understanding of the athlete's heart has been based largely upon the resting assessment of LV structure in highly trained athletes. However, there is growing acceptance that most sport disciplines likely convey a mixed hemodynamic stimulus involving an acute increase in both pressure and volume loading (23, 54). Even so, athletes who demonstrate marked structural adaptations (e.g. increased LV wall thickness, cavity size and relative wall thickness) (41, 42) may also exhibit divergent changes in resting LV function. Several reports indicate that endurance training results in enhanced LV diastolic function (4, 31), possibly due to alterations in blood volume (8), chamber compliance (30), pericardial remodeling (18, 26) and/or underlying cellular adaptation (16, 33). Conversely, strength training has been shown to reduce diastolic function at rest, perhaps due to a reduction in LV compliance resulting from concentric hypertrophy (4, 34). However, greater wall thicknesses in highly trained resistance athletes, and or those with underlying hypertension, may enhance the heart's ability to maintain stroke volume (SV) when arterial pressure is elevated (46).

Analogous to skeletal muscle (55), even in the absence of structural remodeling, it is possible that chronic exercise training may result in training-specific adaptations in the LV functional response to changes in hemodynamic load. Evaluation of LV longitudinal strain (i.e. myocardial deformation) characteristics alongside conventional volumetric measurements provides the opportunity to simultaneously examine functional LV remodeling and the mechanisms that may explain potential training-specific adaptations. In highly trained, but non-elite, endurance and resistance-trained males and non-athletic controls, we sought to compare the LV response to (i) isometric leg-press exercise (i.e. pressure load) and (ii) an intravenous Gelofusine volume infusion with and without passive leg-raise (i.e. progressive volume load). We hypothesized that athletic training would be associated with training-specific adaptation in the LV functional response to a change in load. This would be characterized by a maintenance of stroke volume (SV) in resistance-trained individuals in response to isometric exercise, and an augmented SV in endurance-trained individuals when challenged with an increased circulating volume. To investigate the mechanisms responsible

for potential training-specific functional remodeling, we conducted a secondary exploratory analysis of changes in LV longitudinal myocardial deformation characteristics in the three groups.

METHODS

Study participants

Non-elite endurance-trained (n = 15; runners, cyclists and triathletes), resistance-trained (n = 14; weightlifters and bodybuilders) and non-athletic males (n = 13) were recruited to participate in this study. Average weekly training distance was 44 km for runners, 198 km for cyclists and 158 km for triathletes. All resistance trained men exclusively performed moderate to high-intensity full-body resistance training programs and did not engage in any aerobic exercise. Exclusion criteria included: the use of cardioactive drugs and prescribed medications, the reported use of performance enhancing drugs, history of cardiovascular, musculoskeletal or metabolic disease, or any contra-indications to exercise, asthma, smoking and competitive performers subject to doping control. All procedures conformed to the ethical guidelines of the 1975 Declaration of Helsinki, with the exception of being registered as a trial. Written, informed consent was obtained from all participants following a detailed explanation of experimental procedures, as approved by the Cardiff School of Sport and Health Sciences Research Ethics Committee.

Study design

Participants were assessed on three separate visits, having refrained from caffeine, alcohol and vigorous exercise in the preceding 24 hours. The first testing session involved the completion of a health and training questionnaire, anthropometric measurements, resting blood pressure measurement, and the assessment of a seated leg-press one-repetition maximum (1RM). After a minimum of 30-minutes recovery, to assess cardiorespiratory fitness ($\dot{V}O_{2\ peak}$; peak volume of oxygen consumption), an incremental cycling test was completed. The subsequent experimental visit involved either a pressure load or a volume load, with the final visit involving the second experimental condition. During the pressure loading visit, transthoracic echocardiographic measurements were obtained at rest and during isometric leg-press exercise at 20%, 40% and 60% 1RM, respectively. The volume loading condition involved a resting echocardiogram before and after an intravenous Gelofusine infusion (7 $ml \cdot kg^{-1}$) and again following passive leg elevation to 45° (Figure 1).

Exercise testing

Resistance exercise was performed on a commercially available leg-press machine (Linear Leg Press, Life Fitness Ltd, Queen Adelaide, UK). The 1RM protocol for the 45° inclined double leg-press was determined according to the National Strength and Conditioning Association guidelines (3). Participants initially completed a 5 to 10 repetition warm-up against light resistance. After a 2-minute rest period, the first attempt was performed using a load that was ~50% of the participants' weight-predicted 1RM. Following a 3-5-minute rest, participants repeated the exercise with an increased load. This process was repeated until participants could only perform a single repetition and required between 3 and 5 attempts to achieve the correct load. $\dot{V}O_{2\ peak}$ was determined using an upright incremental test on an electronically braked cycle ergometer (Lode Corival, Groningen). Exercise was started at 50 watts for both the resistance-trained and the controls, and at 120 watts for endurance-trained individuals, and was subsequently increased by 20 watts every minute until volitional exhaustion. Measurements of ventilatory gas exchange were obtained using a mask-based breath-by-breath gas analysis system (Jaeger, Oxycon Pro, Warwickshire, UK). Peak oxygen uptake was defined as the highest $\dot{V}O_2$ over a 30-second consecutive period.

Experimental pressure load

Isometric leg-press exercise was used to elicit progressive increases in systemic blood pressure, as has been shown previously (22, 52). Baseline echocardiographic measurements were obtained with the participant seated on the leg-press machine with legs elevated, and feet positioned on the weight-bearing platform. Blood pressure was acquired continuously using finger plethysmography (Finometer PRO; Finapres Medical Systems FMS, Arnhem, The Netherlands) and was calibrated to manual blood pressure obtained at baseline. Individuals were then instructed to push against the weight-bearing platform, maintaining a knee joint angle of 120° for two-minutes. Transthoracic echocardiography was performed between the first and second minute of isometric exercise; individuals were instructed to refrain from performing a Valsalva maneuver throughout each repetition. This protocol was repeated for progressive loads corresponding to 20%, 40% and 60% of 1RM, with a two-minute recovery between each effort.

Experimental volume load

Baseline echocardiography was completed with participants in the left lateral decubitus position. Thereafter, an intravenous cannula was inserted and 7 $ml \cdot kg^{-1}$ Gelofusine

(succinylated gelatin 4%) was infused over a 30-minute period under the supervision of a clinician. Gelofusine was specifically chosen as the infusion substance, instead of saline, as it is maintained in the intravascular space for longer, therefore causing a larger and more consistent volume challenge (32). Heart rate and blood pressure were monitored continuously and changes in blood volume were calculated according to Dill and Costill (15), utilizing hemoglobin concentration and assuming blood volume pre-infusion was 100%. Venous blood was sampled before, mid-way and post-infusion and analyzed for sodium (assessment termination criteria: < 133 $mmol \cdot l^{-1}$), potassium (assessment termination criteria: < 3.5 $mmol \cdot l^{-1}$), hemoglobin concentration, and hematocrit (assessment termination criteria: < 40%) using a handheld point of care device (i-STAT1, i-STAT System, Abbott Point of Care, Princeton, New Jersey). Immediately after the completion of the Gelofusine infusion and subsequent echocardiographic assessment, both legs were passively raised to an angle of 45° for two-minutes prior to further image acquisition to further increase central blood volume.

Transthoracic cardiac ultrasound imaging: resting measures

All transthoracic echocardiography examinations were performed using a commercially available ultrasound machine (Vivid E9, GE Healthcare, Chalfont St Giles, Bucks, UK) with a 1.5 to 4.6-MHz-phased array transducer (M5S-D, GE Healthcare, Chalfont St Giles, Bucks, UK). Images were obtained at end-expiration following a minimum of 10-minutes of rest and the average of three consecutive cardiac cycles were then analyzed offline using commercially available software (EchoPac version 202, GE, Norway). LV posterior wall thickness (PWT) and internal diameter ($LVID_d$) were measured from the 2D parasternal long-axis view at end diastole. Relative wall thickness (RWT) was calculated as 2 x $PWT/LVID_d$. LV mass was calculated according to the cube formula using 2D imaging (28) and scaled ratiometrically with body surface area (BSA), calculated using the Du Bois and Du Bois (17) formula. LV length at end-diastole ($LV\ length_d$) was determined as the length from the mitral valve annulus to the apical subendocardium from the four-chamber view. LV sphericity index was calculated as $LV\ length_d/diameter_d$ from the apical 4 chamber view (14). LV volumes were analyzed using Simpson's biplane approach from the apical four chamber and two-chamber view by tracing the endocardial border at end-diastole and end-systole for end-diastolic volume (EDV) and end-systolic volume (ESV), respectively. SV was calculated by subtracting ESV from EDV and cardiac output was calculated as the product of heart rate and SV. Pulsed-wave Doppler recordings were obtained from an apical four-chamber view to

assess trans-mitral early (E) and late (A) diastolic filling velocities, with the sample volume placed between the tips of the open valve.

Transthoracic cardiac ultrasound imaging: Experimental measures

LV SV was calculated using Simpson's biplane approach before and after Gelofusine infusion and during the passive leg-raise. Due to body position and nature of the strenuous activity during leg-press exercise, we were not able to collect apical two chamber images in most participants during the experimental pressure loading condition. Therefore, LV volumes were calculated using Simpson's monoplane approach from the apical four-chamber view throughout the leg-press intervention. Trans-mitral diastolic filling velocities were obtained as described above for each stage of the experimental design.

Global LV longitudinal deformation characteristics, as assessed via strain and strain rate, were acquired from an apical four-chamber view at a frame-rate of 60 - 90 frames per second. All images were analyzed offline using 2D speckle-tracking analysis (EchoPac, V202, GE Healthcare). To time-align and adjust for inter- and intra-individual variability of heart rate and frame rate, post-processing was completed as described previously (51). Intra-observer coefficient of variation for myocardial deformation within our group has previously been reported to be between 8 and 11% (49). Frame by-frame data were exported to bespoke software (2D Strain Analysis Tool; Stuttgart, Germany), and cubic spline interpolation was applied. The time it took to achieve peak strain and strain rate from the onset of systole were expressed as a percentage of the cardiac cycle, in accordance with previous work (39, 48, 50).

Statistical analysis

All data were first assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots. One-way analysis of variance (ANOVA) was used to compare baseline measures between groups. The changes in hemodynamic and LV deformation measurements that occurred during either the pressure or volume loading conditions were expressed as percentage change of the mean values at baseline. Differences in the response between groups were compared using a two-factor repeated measures ANOVA (time*training status) with Sidak post-hoc analyses. Correlational analyses were used to explore potential relationships between the change in stroke volume and global longitudinal strain characteristics from baseline to the final stage of each condition. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (SPSS Inc.,

Illinois, United States of America). Alpha was set at $P < 0.05$ and data were expressed as mean ± standard deviation (SD).

RESULTS

Study participants

Baseline characteristics of the study population are shown in Table 1. Lifetime training years and training frequency were not different between the athletic groups. By design, $\dot{V}O_{2\ peak}$ was higher in those who were endurance-trained in comparison to non-athletic ($P < 0.001$) and resistance-trained males ($P < 0.001$). Additionally, 1RM was significantly greater in the resistance-trained group, compared to both endurance-trained ($P < 0.001$) and non-trained controls ($P < 0.001$). Resting heart rate was significantly lower in endurance-trained compared with controls ($P = 0.001$), however no significant differences were observed in resting systolic ($P = 0.791$) or diastolic blood pressures between groups ($P = 0.978$).

Left ventricular structure and function at rest

LV PWT ($P = 0.186$) and sphericity index ($P = 0.514$) were similar between groups. In the endurance-trained group, LV mass/BSA was greater and RWT was significantly lower, in comparison to controls ($P = 0.017$ and $P = 0.024$, respectively), with no difference observed between resistance-trained and controls (LVmass/BSA, $P = 0.239$ and RWT, $P = 0.912$, respectively). SV and SV/BSA were significantly greater in endurance-trained individuals compared to controls ($P = 0.007$ and $P = 0.009$, respectively). EDV was significantly greater in both endurance ($P < 0.001$) and resistance-trained ($P = 0.011$), in comparison to controls. However, when scaled to BSA, only endurance-trained had a greater EDV/BSA in comparison to controls ($P = 0.001$). Similarly, ESV was significantly greater in both endurance ($P < 0.001$) and resistance-trained ($P = 0.011$), compared to controls. When scaled to BSA, ESV was only greater in endurance-trained in comparison to controls ($P = 0.001$). LV longitudinal strain ($P = 0.716$), time-to-peak strain ($P = 0.582$), and time-to-peak strain rate ($P = 0.911$) were similar between groups at baseline. However, strain rate was significantly greater in controls in comparison to endurance-trained individuals at rest ($P = 0.048$).

Left ventricular response to incremental pressure load

Heart rate and blood pressure increased to a similar extent during leg-press exercise across all three groups (Table 2). At lower intensities, no differences in SV were observed between groups (20% 1RM; $P = 0.445$ and 40% 1RM; $P = 0.190$). In contrast, the increase in cardiac output at 60% 1RM was significantly greater among resistance-trained individuals in comparison to controls (92 ± 15% vs. 58 ± 16%, $P < 0.001$). Furthermore, in line with our hypothesis, when challenged with leg-press exercise at 60% 1RM, the resistance-trained group maintained SV closer to baseline values in comparison to the reduction in SV in controls (Figure 2A; resistance-trained vs. controls, $P = 0.004$). EDV was not different to baseline values and remained similar between groups at 20% 1RM; however, at both 40% and 60%, the reduction in EDV was markedly greater in controls in comparison to both athletic cohorts (Figure 2B). In contrast, ESV appeared to increase in endurance-trained individuals while remaining relatively constant or decreasing minimally in resistance-trained and non-trained individuals (time*training status, $P = 0.086$; supplementary Figure 1, DOI: https://doi.org/10.6084/m9.figshare.12763598). As a result, ESV was different between endurance-trained and controls at 40% 1RM ($P = 0.038$) and 60% 1RM, though not meeting statistical convention for significance at the higher intensity ($P = 0.088$; Figure 2C). The pattern of change in trans-mitral Doppler measures E, A, and E/A across each stage was similar between groups (Table 2).

Secondary correlational analysis of longitudinal deformation characteristics during leg-press at 60% 1RM revealed a significant relationship between the change in SV and strain across all individuals (R = 0.537, $P = 0.007$; Figure 3). Subsequent between group analysis identified a significant delay in the time-to-peak strain in endurance-trained individuals in comparison to resistance-trained individuals (12 ± 14% vs. 1 ± 6%, respectively; $P = 0.021$). As such, peak longitudinal strain was delayed until after the systolic period in endurance-trained individuals and occurred after 10% of the diastolic period had been completed (i.e. "*post-systolic shortening*", Figure 4). However, in non-athletic controls the 8 ± 8% increase in time-to-peak strain was not significantly different to either the endurance-trained ($P = 0.522$) or resistance trained individuals ($P = 0.364$).

Left ventricular response to volume loading

Gelofusine infusion (7 $ml \cdot kg^{-1}$) was successfully completed in 13 endurance-trained (absolute infusion volume; 531 ± 47 ml), 13 resistance-trained (607 ± 51 ml) and 11 control participants (533 ± 58 ml). Participant noncompliance was due to needle phobia ($n = 1$,

277 resistance-trained) and participant attrition (n = 2, control and n = 2, endurance-trained).
278 Blood volume increased by a similar extent amongst all groups from pre- to post-infusion (12
279 ± 3%, 12 ± 4% and 13 ± 4%; endurance, resistance and control, respectively; P = 0.867) and
280 blood pressure remained similar between groups throughout the experimental stages (Table
281 3). Differences in the heart rate response to volume expansion were noted between groups: no
282 change was observed in endurance and resistance-trained individuals, whereas non-athletic
283 controls experienced an increase of five beats per minute (Figure 5), though failing to reach
284 conventional statistical significance (P = 0.061).

285 Contrary to our initial hypothesis, the mean increases in SV following plasma volume
286 expansion were statistically similar between groups and remained comparable following the
287 45° passive leg-raise (P = 0.350). However, unlike the resistance-trained and controls,
288 endurance-trained individuals showed an additional increase in EDV following passive leg
289 elevation after volume expansion (5 ± 5% to 8 ± 5%, P = 0.018; Figure 2B and
290 supplementary Figure 2, DOI: https://doi.org/10.6084/m9.figshare.12763598). ESV remained
291 similar between groups following infusion and passive leg-raise (P = 0.618). Despite
292 differences in the heart rate response between groups, no significant differences in cardiac
293 output, E, A or E/A were found between groups (Table 3). Though we found a positive
294 relationship between the change in SV and longitudinal strain across all individuals (R =
295 0.334, P = 0.054; Figure 4), subsequent analysis of longitudinal strain characteristics revealed
296 no between group differences.

297 **DISCUSSION**

298 The primary findings of this study are that: i) during high-intensity isometric leg-press
299 exercise, SV is well maintained in resistance-trained males only (Figure 2A), which may be a
300 consequence of preserved timing of peak LV longitudinal myocardial deformation (Figure 4);
301 ii) following an acute plasma volume expansion, the increase in EDV and SV are similar
302 between endurance-trained, resistance-trained and controls, however, iii) further
303 augmentation of EDV via passive leg-raise was only observed in the endurance-trained group
304 (Figure 2B). To our knowledge, this is the first study to examine the LV functional response
305 to both isometric resistance exercise and increasing circulating blood volume in the same
306 group of individuals. Together, these data support the potential of training-specific functional
307 remodeling of the LV to different stimuli, even in the absence of marked structural
308 adaptations. Furthermore, our data highlight the potential physiological trade-off that may

accompany training-specific LV adaptation, whereby the ability to functionally respond to either a volume or pressure load may be at the detriment of managing the alternate stimulus.

Adaptation in the left ventricular functional response to isometric leg-press exercise

In the present study, as has been shown previously (23, 40, 47, 53), well-trained but non-elite resistance-trained individuals did not possess the concentric LV remodeling pattern previously suggested (4, 9, 34, 36, 43). Despite this, the resistance-trained group were better able to maintain SV at near baseline values across each incremental stage of isometric exercise, even with similar increases in blood pressure across all groups. In contrast, at 60% 1RM the endurance-trained group and non-athletic controls experienced a decrement in SV of ~11% and ~15% respectively.

The mechanisms underlying the divergent LV volumetric response to resistance exercise remain speculative, but may involve changes in specific cellular and molecular adaptation of the myocardium and extracellular matrix (16, 33). Cardiomyocyte contractility may increase following resistance training via myosin ATPase activity and enhanced Ca^{2+} influx, as has been shown in rodent studies (12, 19). In turn, these adaptations would increase the force of contraction, thereby improving the myocardial capacity to maintain efficient ejection in the face of an increased afterload. Our secondary analysis of LV longitudinal deformation supports this argument, with our data showing that those with the greatest increase in myocardial deformation during heavy resistance exercise were better able to maintain stroke volume (Figure 5A). In contrast, cardiac adaptation with endurance-training may have had a detrimental influence on the LV response to isometric exercise. The increase in time-to-peak strain in the endurance cohort is suggestive of a compromised systolic functional response, with a substantial portion of shortening occurring after aortic valve closure, which therefore does not contribute to the ejection of blood and impedes early diastolic relaxation. This pattern of post-systolic shortening of the LV is similar to that previously observed in systemic hypertension (38) and in the RV of healthy populations during an acute increase in pulmonary artery pressure (13, 37, 48). Additionally, whilst the more compliant chamber of an endurance athlete is beneficial when venous return increases (30), greater chamber compliance may cause a disproportionately larger decrease in SV when venous return is reduced, for example during some forms of isometric exercise (1). The heterogeneous EDV response and relative maintenance of SV in resistance-trained individuals may also be related to differential cardiopulmonary interactions between the

groups. Abdominal pressure, intrathoracic pressure, right atrial pressure, and lung volumes are likely to have increased during leg-press exercise, thereby reducing venous return (1, 7). Indeed, the decrease in SV in controls was accompanied by a reduction in EDV, suggestive of an underfilling of the LV, which differs mechanistically to endurance athletes, in whom a decrease in SV appears to be driven by an increase in ESV. This elevation in ESV may reflect a compromised ability to maintain systolic performance during an acute afterload challenge, reflected by a significant increase in post-systolic shortening. The additional residual volume in the ventricle after ejection, combined with venous return, likely moderates the reduction in EDV in the endurance-trained group, in comparison to controls. As recently proposed by Shave et al. (46), it is possible that the divergent hemodynamic stimuli brought about by chronic endurance and resistance training leads to differential cardiac adaptations, which compromise the heart's ability to accommodate the alternate volume or pressure challenge. Our data further support this contention, highlighting a potential physiological trade-off in the endurance athlete's capacity to cope with increasing systolic pressure. Other multimodality, mechanistic investigation in rat hearts, has shown that while resting LV functional measures are relatively unchanged by intense lifetime exercise, due to the disproportionate increase in RV wall stress during intense exercise (27) the right ventricle (RV) may be more susceptible to detrimental remodeling at the extremes of exercise load (45). Further research is warranted to examine both the mechanisms responsible for our divergent results and also functional RV remodeling in response to hemodynamic perturbation.

Adaptation in the left ventricular functional response to an increased circulating blood volume

Previous studies using lower body negative pressure and saline infusion to manipulate cardiac preload have shown that for any given LV filling pressure, endurance athletes have a greater EDV (30). The findings from this seminal study indicates that endurance athletes have greater LV chamber compliance in comparison to sedentary controls. Consistent with these findings, we also found that endurance-trained individuals, unlike resistance-trained individuals and healthy controls, were capable of further EDV augmentation (through passive leg elevation) even when already volume-expanded. Within the methodological confines of the present study, it is difficult to ascertain the acute limitation to ventricular filling between groups, though it likely reflects a dependency upon both the compliance characteristics of the myocardium and pericardial constraint (26). It is possible that the "tightness" of the pericardium ultimately limits ventricular filling and that pericardial remodeling (18),

subsequent to the repetitive increases in circulating blood volume associated with prolonged-training, may explain the ability for endurance-trained individuals to "accept" a greater EDV.

Interestingly, whilst cardiac output increased across all groups following volume loading, this was achieved via increased SV in athletic populations compared to an augmentation of heart rate with preserved SV in controls (Figure 5). Following 30 $ml \cdot kg^{-1}$ saline infusion, Levine, Lane, Buckey, Friedman and Blomqvist (30) also observed a significant elevation in heart rate in non-athletes, by 12 bpm ($P < 0.01$), but not in endurance athletes (7 bpm, $P > 0.05$). This chronotropic sensitivity in untrained individuals may be due to mechanical factors, such as reduced cardiac chamber compliance (6, 30) and peripheral vascular distensibility (2, 44), or perhaps due to intrinsic pressure receptor reflexes (5, 35). It is unlikely, however, that this is a response of a single autonomic reflex, but rather a reflection of the complex relationship between baseline autonomic tone (11), sinoatrial remodeling (10), pressure receptor reflexes (21) and/or altered stretch receptor sensitivity (20).

Study limitations

There are several limitations that must be acknowledged. First, we recognize that the small sample size is a significant limitation; however, this is the first study to compare the LV response to incremental pressure and volume perturbations in the same group of differentially trained individuals. Further investigation of sport-specific functional LV remodeling is warranted in a larger cohort, and should also consider responses in individuals with substantial cardiac remodeling. We did not capture a detailed history of training intensity and therefore cannot discern the influence of overall training load. Additionally, we acknowledge that the endurance-trained cohort was older than those resistance-trained, however controlling for age as a covariate did not alter the findings of this study. We used isometric exercise performed without a Valsalva maneuver to facilitate data collection, however this exercise is unlikely to perfectly reflect the typical training conditions of resistance athletes. Furthermore, from our data and others (1, 22, 29), it is evident that certain forms of resistance exercise, including heavy leg-press, can cause LV underfilling. As such, different forms of resistance exercise may influence preload as well as afterload, which may be relevant for physiologic adaptation. In the present study, it is difficult to ascertain the mechanisms which underpin the preserved LV filling in resistance-trained individuals, and whether this is due to a difference in cardiopulmonary interaction and subsequent modulation of LV filling, or enhanced LV

406 deformation. Additionally, data reported are only relevant for young healthy men. Specific
407 studies to examine the female athlete's heart which are adequately powered to explore sex
408 differences are warranted and are currently being undertaken by our group (56) and others
409 (24, 25).

410

411

412 **CONCLUSION**

413 This study provides novel data that supports the potential of stimulus-specific functional
414 remodeling of the LV, even in the absence of marked structural adaptations. In response to a
415 marked hemodynamic pressure load, resistance-trained individuals better maintained SV,
416 which was coupled with preserved longitudinal deformation characteristics. Conversely, in a
417 volume-loaded state, only endurance athletes were capable of further increasing EDV.
418 Further research is warranted to examine the mechanisms which underpin these training-
419 specific differential responses.

420 **Author Contributions**

421 This study was performed at Cardiff Metropolitan University in Cardiff, United Kingdom.
422 TGD, RES, MS, conceived and designed the research. TGD, BAC, ALD, RNL, CR, MB, FL,
423 ZY and MS acquired the data. TGD and BAC analyzed the data. TGD, MS and RES
424 interpreted the data. All authors revised the manuscript and provided intellectual feedback
425 and agree to be accountable for all aspects of the work.

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432 **Disclosures**

433 None

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Figures

Figure 1. Schematic of the experimental protocol. Non-athletic controls, endurance-trained men and resistance-trained men performed isometric leg-press exercise at 20%, 40% and 60% of one repetition maximum (1RM). Transthoracic echocardiography (indicated by ultrasound probe) was undergone at rest and during 1-2 minutes of exercise at each load. On a separate visit, cardiac preload was increased via 7 $ml \cdot kg^{-1}$ intravenous Gelofusine infusion, and further augmented by a 45° passive leg-raise. Echocardiography was performed at rest, post-infusion and during the passive leg-raise. Brachial blood pressure was measured continuously via finger plethysmography, which was calibrated to manual blood pressure obtained at rest.

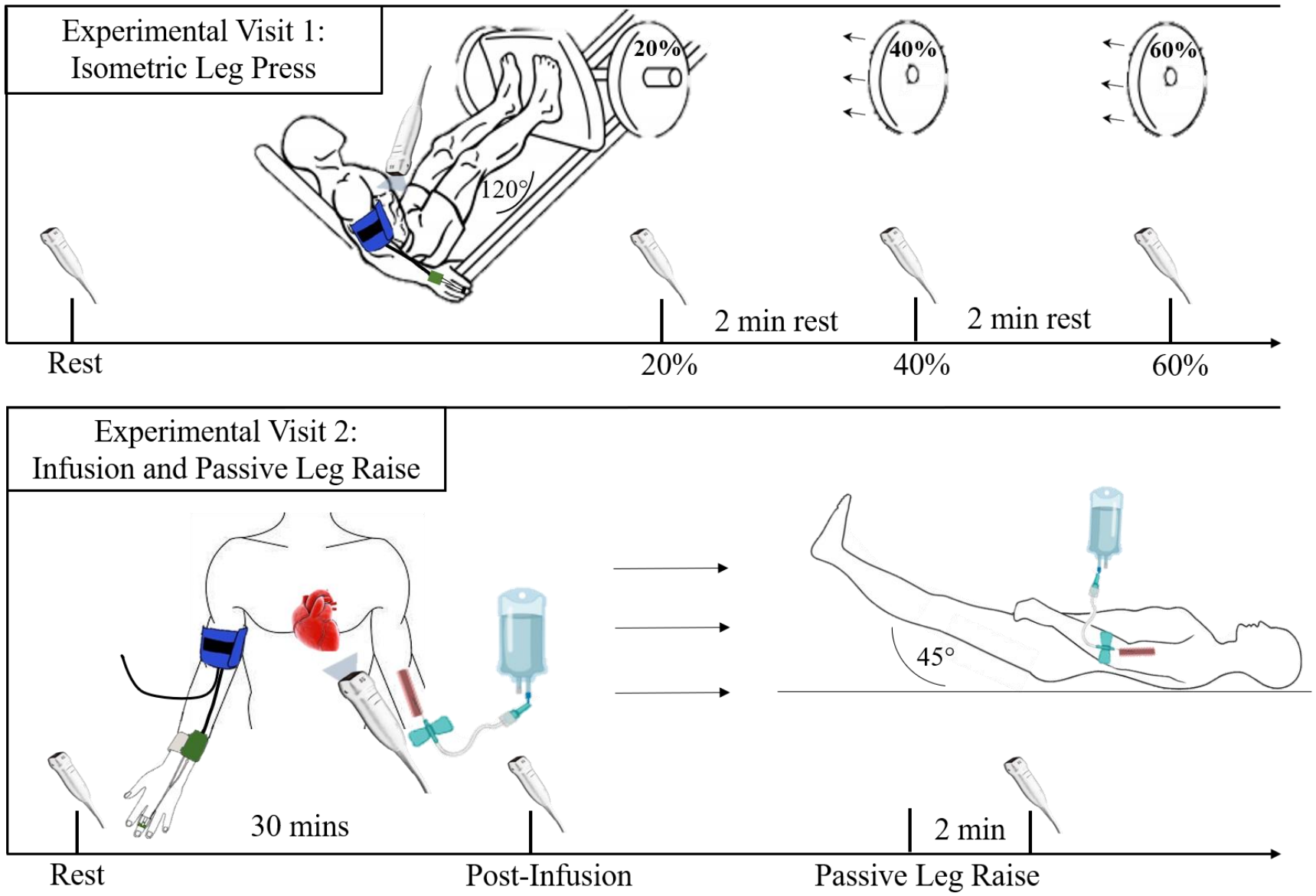
Figure 2. Hemodynamic left ventricular response following static double leg-press exercise at 20%, 40% and 60% of 1RM (left panels) and following 7 $ml \cdot kg^{-1}$ intravenous Gelofusine infusion and combined 45° passive leg-raise (PLR; right panels) in endurance athletes (blue; $n = 15$ and $n = 13$ for leg-press and infusion condition, respectively), resistance athletes (red; $n = 14$ and $n = 13$, respectively) and non-athletic controls (green; $n = 13$ and $n = 11$, respectively). Data are displayed as percentage change from baseline. Panel *A* shows the change in stroke volume (SV), panel *B* shows end-diastolic volume (EDV) and panel *C* shows end-systolic volume (ESV) following both interventions.
* significant difference vs. non-athletic controls at the same time-point ($P < 0.05$). ‡ significant difference within group between time-points ($P < 0.05$).

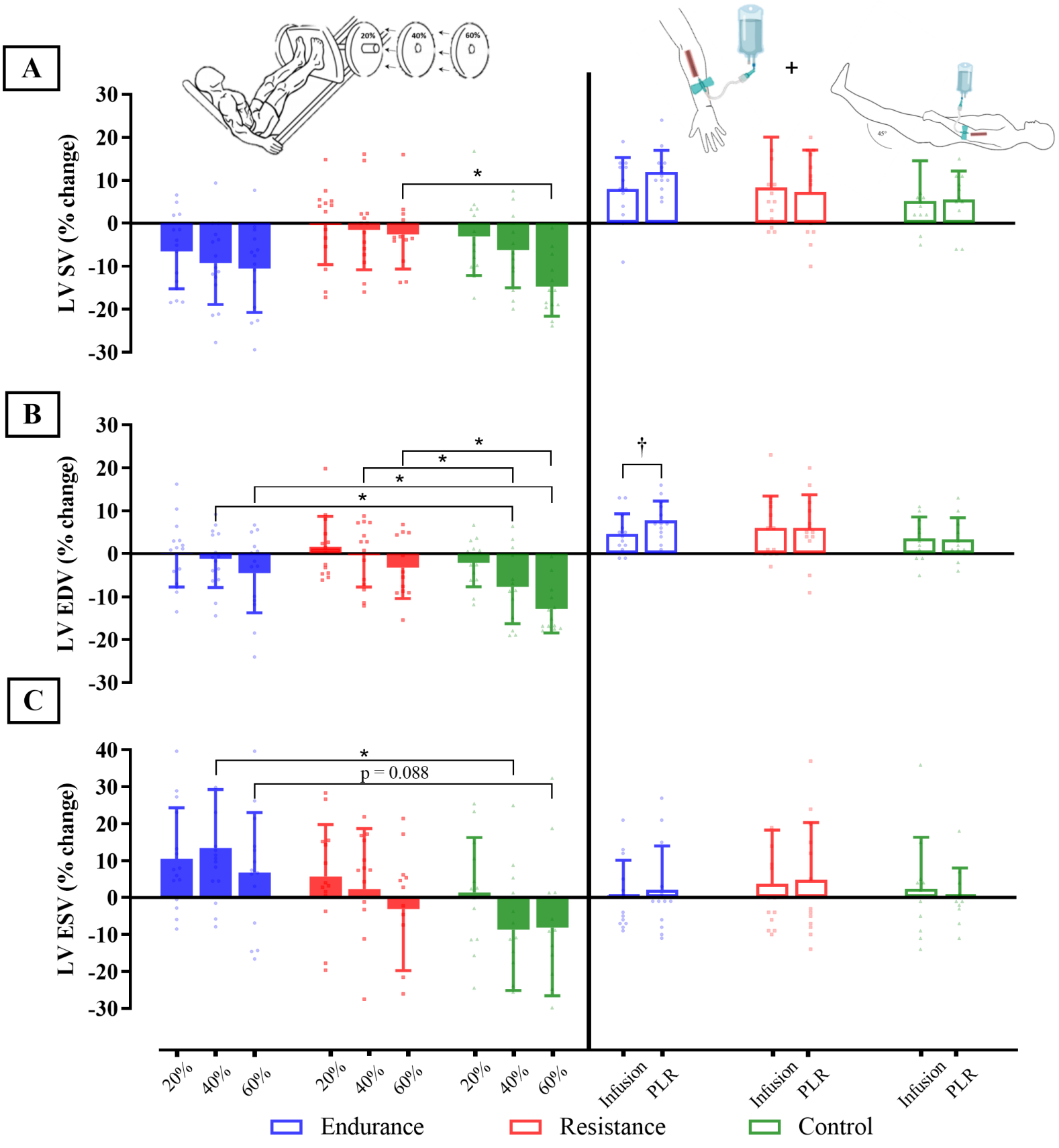
Figure 3. *A*. Grouped correlation analysis between the change in left ventricular (LV) stroke volume (%) and the change in LV longitudinal strain (%) during 60% 1RM leg-press exercise across all individuals (black line). Individual data points represent endurance-trained individuals (blue circles; $n = 15$), resistance-trained individuals (red squares; $n = 14$) and non-athletic controls (green triangles; $n = 13$). *B*. Grouped correlation analysis between the change in LV stroke volume (%) and the change in LV longitudinal strain (%) following combined 7 $ml \cdot kg^{-1}$ Gelofusine infusion and passive leg-raise

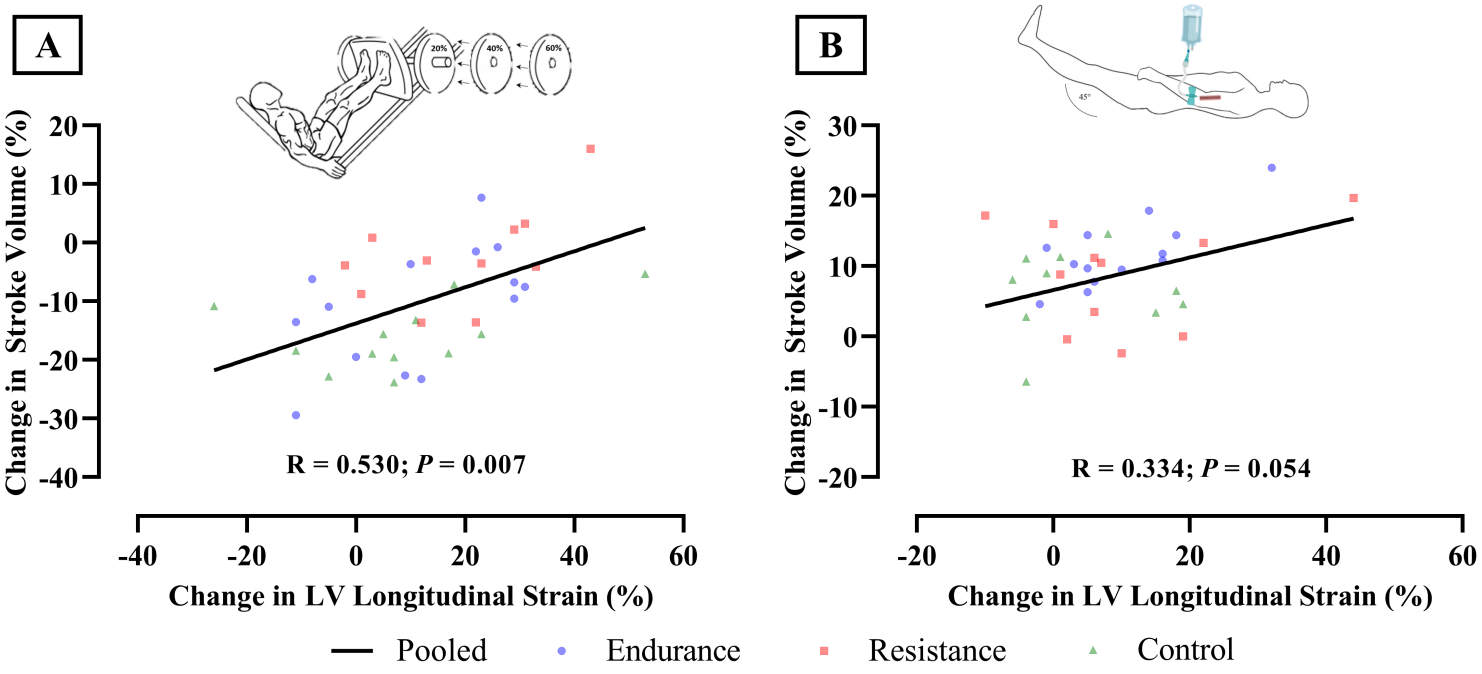
across all individuals. Individual data represent endurance-trained individuals (n = 13), resistance-trained individuals (n = 13) and non-athletic controls (n = 11).

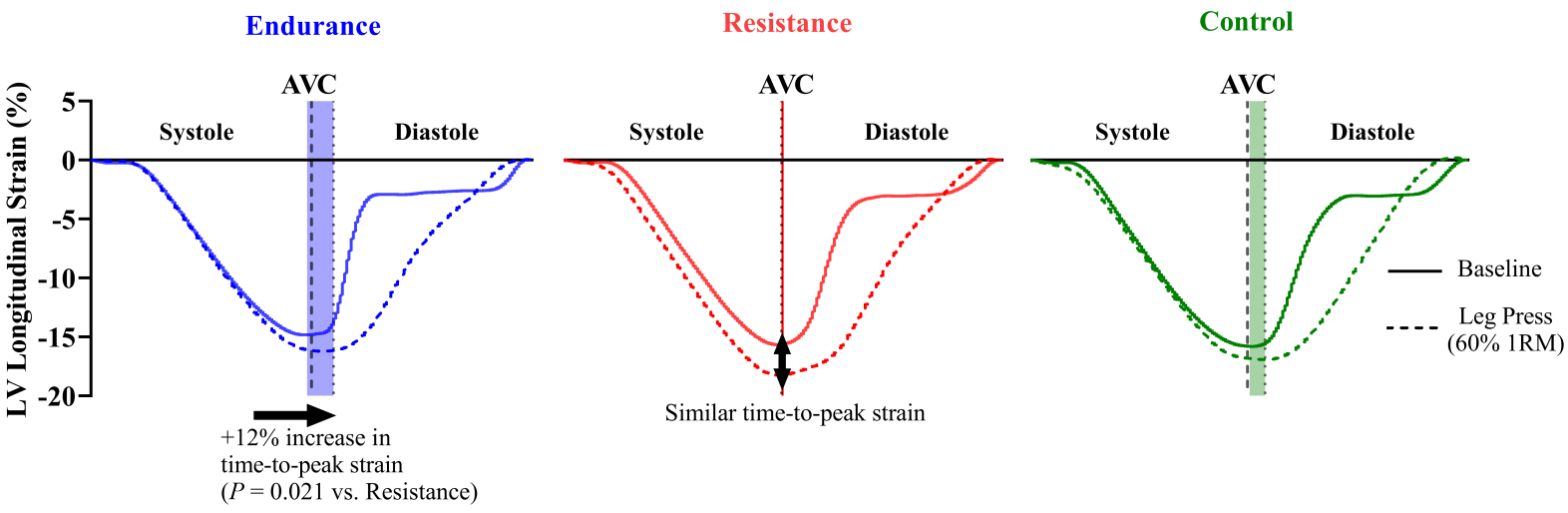
Figure 4. Temporal representation of left ventricular (LV) strain between groups at baseline (solid line) and during 60% 1RM leg-press exercise (corresponding dashed line) in endurance-trained individuals (blue, n = 15), resistance-trained individuals (red, n = 14) and non-athletic controls (green, n = 13) and pooled data (black). Shaded area after aortic valve closure (AVC) represents post-systolic shortening following leg-press exercise as a % of the cardiac cycle.

Figure 5. Heart rate response (% change) following 7 $ml \cdot kg^{-1}$ Gelofusine infusion and subsequent passive leg-raise in endurance-trained individuals (blue circles; n = 13), resistance-trained individuals (red squares; n = 13) and healthy controls (green triangles; n = 11). Data are displayed as percentage change from baseline.


Experimental Visit 1:
Isometric Leg Press
20%
40%
60%
120°
2 min rest
2 min rest
Rest
20%
40%
60%
Experimental Visit 2:
Infusion and Passive Leg Raise
45°
30 mins
2 min
Rest
Post-Infusion
Passive Leg Raise


A
B
C
LV SV (% change)
LV EDV (% change)
LV ESV (% change)
30
20
10
0
-10
-20
-30
40
20%
40%
60%
*
†
p = 0.088
+
45°
Infusion
PLR
Endurance
Resistance
Control


A
20%
40%
60%
Change in Stroke Volume (%)
20
10
0
-10
-20
-30
-40
R = 0.530; P = 0.007
-40
-20
0
20
40
60
Change in LV Longitudinal Strain (%)
B
45°
Change in Stroke Volume (%)
30
20
10
0
-10
-20
R = 0.334; P = 0.054
-20
0
20
40
60
Change in LV Longitudinal Strain (%)
Pooled
Endurance
Resistance
Control


Endurance
Resistance
Control
AVC
AVC
AVC
Systole
Diastole
Systole
Diastole
Systole
Diastole
LV Longitudinal Strain (%)
5
0
-5
-10
-15
-20
Baseline
Leg Press
(60% 1RM)
+12% increase in
time-to-peak strain
(P = 0.021 vs. Resistance)
Similar time-to-peak strain

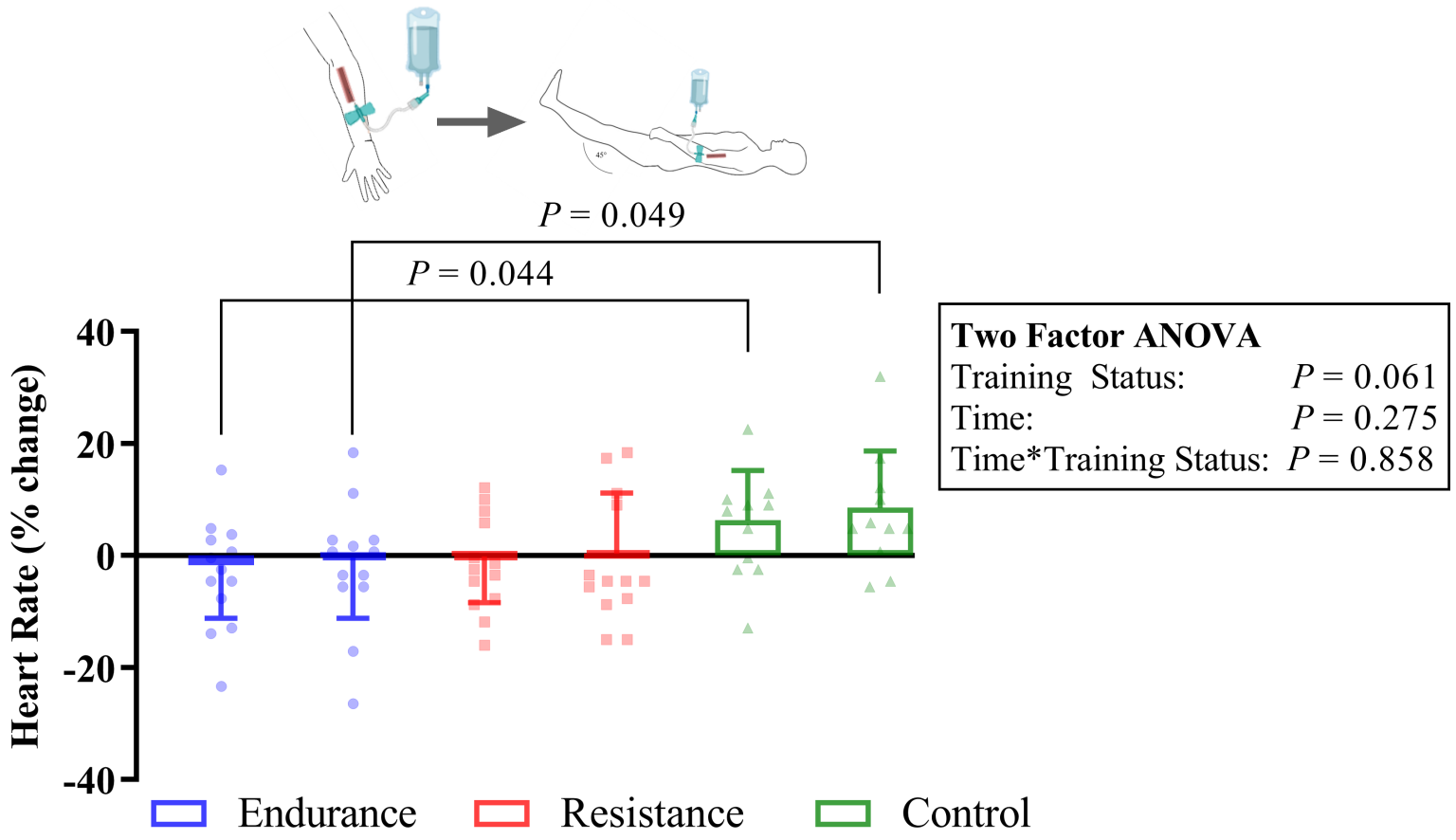

P = 0.049
P = 0.044
40
20
0
-20
-40
Heart Rate (% change)
Endurance
Resistance
Control
Two Factor ANOVA
Training Status: P = 0.061
Time: P = 0.275
Time*Training Status: P = 0.858

Table 1. Baseline participant characteristics.

	Control (n = 13)	Endurance (n = 15)	Resistance (n = 14)	One-way ANOVA P value
Demographics				
Age (years)	23 ± 3	29 ± 5*	24 ± 3†	**0.002**
Height (cm)	180 ± 9	180 ± 6	181 ± 6	0.870
Body Mass (kg)	75 ± 7	75 ± 6	87 ± 7*†	**< 0.001**
BMI (m^2)	23.8 ± 4	23.2 ± 1.7	26.8 ± 1.6*†	**< 0.001**
BSA (m^2)	1.94 ± 0.11	1.95 ± 0.11	2.08 ± 0.11*†	**0.004**
Body Fat %	15.5 ± 6.3	12.4 ± 4.8	12.5 ± 3.6	0.279
$\dot{V}O_{2\ peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	40 ± 5	55 ± 9*	40 ± 4†	**< 0.001**
$\dot{V}O_{2\ peak}$ ($ml \cdot min^{-1}$)	2995 ± 244	4156 ± 498*	3467 ± 348*†	**< 0.001**
Leg-press 1RM (kg)	245 ± 62	275 ± 59	458 ± 38*†	**< 0.001**
Training History (years)		5 ± 2	6 ± 3	**0.543**
Training Freq. (session·wk)	1 ± 1	7 ± 2*	5 ± 1*	**< 0.001**
Hemodynamic				
SBP (mmHg)	124 ± 6	122 ± 8	123 ± 8	0.791
DBP (mmHg)	76 ± 7	75 ± 7	76 ± 7	0.978
Heart Rate (bpm)	58 ± 6	50 ± 6*	56 ± 8	**0.017**
LV Geometry				
LV end-diastolic length (cm)	9.2 ± 0.6	9.4 ± 0.6	9.6 ± 0.9	0.476
LV mass (g)	136 ± 17	156 ± 16*	158 ± 24*	**0.008**
LV mass/BSA (g/m^2)	70 ± 8	80 ± 8*	76 ± 11	**0.021**
LV PWT (cm)	0.81 ± 0.05	0.80 ± 0.05	0.83 ± 0.05	0.186
LV RWT	0.33 ± 0.03	0.30 ± 0.02*	0.32 ± 0.03	**0.019**
Sphericity Index	1.77 ± 0.16	1.79 ± 0.10	1.74 ± 0.16	0.514
LV Function				
LV EDV (ml)	124 ± 12	155 ± 23*	146 ± 20*	**< 0.001**
LV ESV (ml)	48 ± 6	62 ± 11*	58 ± 9*	**< 0.001**
LV SV (ml)	76 ± 9	92 ±15*	88 ± 14	**0.007**
LV EDV/BSA (ml/m^2)	64 ± 7	79 ± 11*	71 ± 10	**0.001**
LV ESV/BSA (ml/m^2)	25 ± 4	32 ± 5*	28 ± 5	**0.001**

LV SV/BSA (ml/m^2)	39 ± 5	47 ± 8*	42 ± 7	**0.009**
EF (%)	61 ± 4	60 ± 4	60 ± 4	0.651
E (cm·s^{-1})	0.90 ± 0.19	0.90 ± 0.15	0.80 ± 0.15	0.319
A (cm·s^{-1})	0.41 ± 0.08	0.38 ± 0.06	0.38 ± 0.08	0.803
E/A	2.28 ± 0.47	2.45 ± 0.48	2.12 ± 0.38	0.507
LV Longitudinal Strain Characteristics				
Strain (%)	-17.8 ± 2.4	-17.2 ± 1.0	-17.4 ± 2.3	0.716
Strain Rate (%·s^{-1})	-0.95 ± 0.16	-0.84 ± 0.07*	-0.86 ± 0.08	**0.048**
TTP Strain (%)	100 ± 5	100 ± 5	98 ± 4	0.582
TTP Strain Rate (%·s^{-1})	44 ± 11	47 ± 10	53 ± 10	0.911
Diastolic Strain (%)	1.61 ± 0.22	1.56 ± 0.21	1.43 ± 0.18	0.802
Diastolic Strain Rate (%·s^{-1})	119 ± 3	116 ± 2	119 ± 2	0.197

Hemodynamic and LV geometry measurements were obtained with the participant rested in the left lateral decubitus position. BMI, body mass index; BSA, body surface area; 1RM, one-repetition maximum; SBP, systolic blood pressure; DBP diastolic blood pressure; LV, left ventricle; PWT, posterior wall thickness; RWT, relative wall thickness; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; TTP, time-to-peak.

*significant difference vs. control ($P < 0.05$), † significant difference vs. endurance ($P < 0.05$).

Table 2. Percentage change in hemodynamic variables from baseline in response to isometric leg-press exercise.

	20% 1RM			40% 1RM			60% 1RM		
	Control	Endurance	Resistance	Control	Endurance	Resistance	Control	Endurance	Resistance
SBP (%)	17 ± 7	18 ± 7	17 ± 7	22 ± 8	24 ± 9	22 ± 7	22 ± 8	24 ± 10	26 ± 7
DBP (%)	16 ± 6	18 ± 9	20 ± 8	23 ± 6	26 ± 10	27 ± 9	25 ± 9	27 ± 12	31 ± 7
Heart Rate (%)	52 ± 17	69 ± 35	43 ± 19	77 ± 19	94 ± 39	70 ± 25	86 ± 19	107 ± 52	99 ± 23
Q (%)	47 ±19	57 ± 31	42 ± 24	67 ± 25	77 ± 42	67 ± 27	58 ± 16	86 ± 51	92 ± 15*
LV EDV (%)	-2 ± 6	0 ± 8	2 ± 7	-8 ± 9	-1 ± 7*	-0 ± 7*	-13 ± 6	-5 ± 9*	-3 ± 7*
LV ESV (%)	1 ± 15	11 ± 14	6 ± 14	-9 ± 17	13 ± 16*	2 ± 16	-8 ± 18	7 ± 16	-3 ± 17
LV SV (%)	-3 ± 9	-7 ± 9	0 ± 9	-6 ± 9	-9 ± 10	-2 ± 9	-15 ± 7	-11 ± 10	-3 ± 8*
E (%)	15 ± 13	10 ±16	9 ± 15	30 ± 23	18 ± 16	13 ± 16	39 ± 23	28 ± 22	22 ± 22
A (%)	85 ± 53	97 ± 63	81 ± 35	128 ± 65	140 ± 74	139 ± 83	179 ± 55	167 ± 86	194 ± 92
E/A (%)	-31 ± 17	-40 ± 19	-37 ± 14	-41 ± 21	-49 ± 15	-49 ± 12	-51 ± 7	-47 ± 18	-54 ± 11

1RM, one-repetition maximum; SBP, systolic blood pressure; DBP diastolic blood pressure; Q, cardiac output; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; E, peak early diastolic left ventricular filling velocity; A, peak late diastolic left ventricular filling velocity.

* significant difference vs. non-athletic controls at the same time-point ($P < 0.05$).

Table 3. Percentage change in primary variables from baseline in response to 7 ml·kg^{-1} intravenous Gelofusine infusion and subsequent passive leg-raise.

	Infusion			Passive Leg-Raise		
	Control	Endurance	Resistance	Control	Endurance	Resistance
SBP (%)	0 ± 6	-1 ± 4	-2 ± 5	-4 ± 12	3 ± 10	0 ± 7
DBP (%)	-3 ± 10	3 ± 8	-1 ± 9	1 ± 9	3 ± 5	2 ± 10
Heart rate (%)	6 ± 9	-2 ± 9	0 ± 8	9 ± 10	0 ± 11	0 ± 11
Q (%)	12 ± 15	7 ± 13	8 ± 14	15 ± 12	12 ± 14	8 ± 16
LV EDV (%)	4 ± 5	5 ± 5	6 ± 7	3 ± 5	8 ± 5‡	6 ± 8
LV ESV (%)	2 ± 14	0 ± 10	4 ± 14	0 ± 8	2 ± 12	5 ± 16
LV SV (%)	5 ± 9	8 ± 7	8 ± 12	5 ± 7	12 ± 5	7 ± 10
E (%)	12 ± 12	10 ± 26	15 ± 16	11 ± 11	18 ± 22	18 ± 23
A (%)	12 ± 12	7 ± 23	18 ± 34	15 ± 24	11 ± 21	18 ± 33
E/A (%)	4 ± 19	10 ± 32	1 ± 15	-2 ± 15	11 ± 21	-1 ± 20

SBP, systolic blood pressure; DBP diastolic blood pressure; Q, cardiac output; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; E, peak early diastolic left ventricular filling velocity; A, peak late diastolic left ventricular filling velocity.

‡ significant difference within group between time-points ($P < 0.05$).