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Evidence of region-specific right ventricular functional adaptation in endurance-trained men in response to an acute volume infusion

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NEW FINDINGS

What is the central question of this study?

Endurance athletes demonstrate altered regional right ventricular (RV) wall mechanics in comparison to non-athletic controls at rest, characterised by lower basal deformation. We tested the hypothesis that regional adaptations at the RV base reflects an enhanced functional reserve capacity in response to haemodynamic volume loading.

What is the main finding and its importance?

Free wall RV longitudinal strain is elevated in response to acute volume loading in both endurance athletes and controls. However, the RV basal segment, longitudinal strain response to acute volume infusion is greater in endurance athletes. Our findings suggest that training-induced cardiac remodelling may involve region-specific adaptation in the RV functional response to volume manipulation.

ABSTRACT

Eccentric remodelling of the right ventricle (RV) in response to increased blood volume and repetitive haemodynamic load during endurance exercise is well established. Structural remodelling is accompanied by decreased deformation at the base of the RV free wall, that may reflect an enhanced functional reserve capacity in response to haemodynamic perturbation. Therefore, this study examined the impact of acute blood volume expansion on RV wall mechanics in 16 young endurance-trained males (aged 24±3 years) and 13 non-athletic male controls (aged 27±5 years). Conventional echocardiographic parameters, as well as longitudinal strain and strain rate were quantified at the basal and apical level of the RV free wall. Measurements were obtained at rest and following 7ml·kg^{-1} intravenous Gelofusine infusion with and without a passive leg raise. Following infusion, blood volume increased by 12±4% and 14±5% in endurance-trained individuals vs. controls, respectively (P=0.264). Both endurance-trained individuals (8±10%) and controls (7±9%) experienced an increase in free wall strain from baseline, which was also similar following leg raise (7±10% and 6±10%, respectively; P=0.464). However, infusion evoked a greater increase in basal longitudinal strain in endurance-trained vs. controls (16±14% vs. 6±11%; P=0.048), which persisted following leg raise (16±18% vs. 3±11%; P=0.032). Apical longitudinal strain and RV free wall strain rates were not different between groups and remained unchanged following infusion across all segments. Endurance training results in a greater contribution of longitudinal myocardial deformation at the base of the RV in response to a haemodynamic volume challenge, which may reflect a greater region-specific functional reserve capacity.

INTRODUCTION

During dynamic exercise, the healthy RV demonstrates a substantial reserve to maintain ventricular function, despite the elevation in heart rate and RV wall stress (La Gerche *et al.*, 2011; Cornwell *et al.*, 2020). Systolic pulmonary artery pressure increases with exercise due to a rise in downstream left atrial pressure, and because of the limited capacity for the pulmonary vasculature to reduce resistance as stroke volume (SV) and cardiac output are increased (La Gerche *et al.*, 2010; Kovacs *et al.*, 2012). Pressure generation within the RV (RVSP) is also elevated to drive RV ejection. Recently**,** it was confirmed that RVSP was greater in endurance-athletes than in non-athletes, both at rest and during intense exercise, likely as a result of the higher cardiac output achieved at peak exercise (Dawkins *et al.*, 2021). This acute increase in RV load with exercise, coupled with the chronic ~10% blood volume expansion with exercise training, provide a potent stimulus for RV remodelling (Convertino, 1991; Sawka *et al.*, 2000), as consistently demonstrated by structural enlargement in endurance athletes (Teske *et al.*, 2009; La Gerche *et al.*, 2012*a*; Oxborough *et al.*, 2012; Arbab-Zadeh *et al.*, 2014).

Owing to the anatomical complexity within the RV, adaptation to haemodynamic loading with exercise training may be greater at the basal segment. Specifically, exercise-induced changes in wall stress may be disproportionately greater at the base of the RV, according to the law of Laplace, due to a larger cavity dimension which becomes narrower and more trabeculated at the apex (Haddad *et al.*, 2008; Jurcut *et al.*, 2010). Furthermore, as the basal section contributes most to overall RV volume (Kong *et al.*, 2012), less deformation of this segment is required to generate the same SV as that achieved with greater deformation at the apex. This may be particularly true for endurance athletes, in whom RV basal dilatation is common (Teske *et al.*, 2009; Oxborough *et al.*, 2011, 2012). A recent meta-analysis has confirmed such region-specific adaptations, highlighting a lower myocardial deformation at the RV base, and greater deformation at the apex in endurance athletes in comparison to non-athletes (Dawkins *et al.*, 2021). However, resting data likely do not reflect the full extent of cardiac remodelling; it is possible that regional RV function, and its response to the repetitive volume load caused by endurance exercise, may also remodel, as previously reported in the left ventricle (Dawkins *et al.*, 2020). Moreover, the lower longitudinal deformation at the base of the endurance athlete's RV may reflect an enhanced reserve capacity to be utilised during exercise, as has been previously shown in the left ventricle (LV) of endurance athletes (Nottin *et al.*, 2008). Given these structural and regional functional adaptations seen at rest,

the purpose of this study was to examine the RV free wall response to acute plasma volume expansion and subsequent passive leg raise in endurance-trained and non-trained individuals. It was hypothesised that RV basal deformation would increase to a greater extent in endurance-trained individuals following an increase in circulating volume, in comparison to non-athletic controls.

METHODS

Study design

Participants for this study included well-trained but non-elite endurance-trained (n = 16; runners, cyclists, and triathletes) and non-athletic males (n = 13). Weekly training distance averaged 46 ± 28 km for runners, 201 ± 68 km for cyclists and 148 ± 94 km for triathletes. Non-athletic controls were performing no more than two forms of brief moderate physical activity per week and not meeting the UK and world health organisation physical activity guidelines (Bull *et al.*, 2020) . Participants were excluded for the use of cardioactive drugs and prescribed medications, history of cardiovascular, musculoskeletal or metabolic disease, or any contra-indications to exercise. Asthmatics and smokers were also excluded, as were any competitive athletes whom were subject to doping controls, since intravenous Gelofusine infusion is considered a prohibited substance by the World Anti-Doping Agency. 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, which was approved by the Cardiff School of Sport and Health Sciences Research Ethics Committee (17/3/01S).

Participants were asked to avoid consumption of caffeine or alcohol and to avoid vigorous exercise in the 24 hours preceding experimental visits. Participants were assessed on two visits. The first visit included anthropometric measurements, resting blood pressure assessment and an incremental cycling test to assess cardiorespiratory fitness ($\dot{V}O_{2\,peak}$; peak volume of oxygen consumption). During the second visit, echocardiography (two-dimensional, M-Mode, Doppler and speckle-tracking) data was collected before and after an intravenous Gelofusine infusion (7 ml·kg^{-1}) and again following subsequent passive leg raise to a 45° degree knee-to-hip angle.

Maximal exercise testing

$\dot{V}O_{2\ peak}$ was determined using an upright incremental cycling test on an electronically braked cycle ergometer (Lode Corival, Groningen, the Netherlands). Exercise was initiated at 50 watts or 120 watts for control and endurance groups, respectively, and 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 (Jaegar, Oxycon Pro, Warwickshire, UK). Peak oxygen uptake was defined as the highest $\dot{V}O_2$ over a 30-second consecutive period.

Gelofusine infusion protocol

Baseline echocardiography was completed with participants in the left lateral decubitus position during end-expiration. Subsequently, an intravenous cannula was inserted into the median cubital vein and 7 $ml \cdot kg^{-1}$ Gelofusine (succinylated gelatin 4%) was infused over a 30-minute period with the supervision of a clinician. Heart rate and blood pressure (FinometerPro, FMS, Groningen Netherlands) were monitored continuously and changes in blood volume were calculated according to Dill and Costill (1974). Echocardiographic assessment was repeated immediately after the completion of the Gelofusine infusion. Both legs were then raised to an angle of 45° for 2 min to further increase central blood volume, after which image acquisition was repeated.

Transthoracic cardiac ultrasound imaging

Transthoracic echocardiography and Doppler examinations were performed using a commercially available ultrasound machine with a 1.5 to 4.6-MHz-phased array transducer (Vivid E9, GE Healthcare, Chalfont St Giles, Bucks, UK). RV end-diastolic area (EDA) and end-systolic area (ESA) were obtained by tracing the endocardial border from 2D images acquired from a RV focused four-chamber apical view. Fractional area change was calculated as the percentage change in RV area from end-diastole to end-systole. From the RV focused four chamber view, linear dimensions were measured at the level of the tricuspid valve (RV basal diameter), half-way between basal diameter and the apex (RV mid-cavity diameter), and RV longitudinal diameter from the apex to the basal diameter. TAPSE was obtained by M-mode, placing the cursor over the RV annulus in the direction of longitudinal excursion in the RV focused view.

RVSP was calculated from the tricuspid regurgitant jet using continuous wave Doppler echocardiography. The greatest value obtained from either the RV-focused apical four chamber or parasternal RV inflow view was utilised. For consistency, subsequent measurements were taken from the same imaging window within each participant. The pressure gradient between the right atrium (RA) and RV quantified using the simplified Bernoulli equation ($4V^2$). RVSP was determined by combining the RV-RA pressure difference, with RA pressure estimated as 3 mmHg for all participants due to the absence of right atrial dilation (RVSP = $4V^2$ + RA pressure) (Rudski *et al.*, 2010).

Two-dimensional speckle tracking was performed on the RV focused four-chamber images at a frame rate of 60 to 90 frames per second, in a accordance with previous investigation (La Gerche, Burns, D'Hooge, et al., 2012; Muraru et al., 2016). Care was taken to optimise the RV free wall throughout systole and diastole. The four-chamber algorithm was selected from the EchoPac software (Version 203) and a region of interest (ROI) was manually traced along the endocardial border at the end of systole. The ROI width was set to match wall thickness across the RV free wall and interventricular septum, resulting in a 6-segment model. The ROI was visually checked and manually adjusted if necessary. RV free wall strain parameters were taken as the arithmetic mean of the base, mid-wall, and apical segment.

Statistical analysis

In line with previous recommendations (Oxborough *et al.*, 2012), RV areas and dimensions were scaled allometrically to body surface area. Scaling exponents for each measure were derived from the slope of the linear log-log plot of body surface area. Baseline participant characteristics were analysed using an independent samples t-test. The changes in haemodynamic and RV structural and functional measurements that followed infusion and passive leg-raise were expressed as percent change of the mean values at baseline. A two-way mixed measures analysis of variance was conducted between group (endurance-trained vs. controls) and loading condition (post-infusion and passive leg-raise). Where a significant main effect was observed, data were analysed for simple main effects using Sidak's adjustment for multiple comparisons. To determine whether meaningful differences were present, effect sizes (Cohen's *d*) were calculated. Bivariate Pearson correlations were used post-hoc to explore the relationship between regional strain and RV end-diastolic area and

peak oxygen uptake. Data were expressed as mean ± standard deviation (SD) and a P value < 0.05 was considered significant.

RESULTS

Participant characteristics and resting right ventricular structure and function

Cardiorespiratory fitness ($\dot{V}O_{2peak}$) was higher in those who were endurance-trained, compared with controls ($P < 0.001$). As shown in **Table 1**, resting heart rate was significantly lower in endurance-trained participants compared with controls ($P = 0.001$); however, no differences were observed in resting systolic ($P = 0.257$) or diastolic blood pressure ($P = 0.968$).

Table 1. Baseline participant characteristics including training-status, and measures of haemodynamic and right ventricular structure and function.

	Controls (***n*** **= 13)**	**Endurance-trained** (***n*** **= 16)**	**t-test** (***P*** **value)**
Demographics			
Age (years)	24 ± 3 (22 – 26)	27 ± 5 (25 – 30)	0.052
Height (cm)	180 ± 8 (176 – 185)	181 ± 6 (178 – 184)	0.840
Body mass (kg)	75 ± 8 (71 – 80)	74 ± 6 (71 – 77)	0.674
Body surface area (m^2)	1.95 ± 0.11 (1.89 – 2.01)	1.94 ± 0.10 (1.89 – 1.99)	0.847
$\dot{V}O_{2\ peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	41 ± 5 (39 – 44)	57 ± 11 (51 – 62)	**< 0.0001**
$\dot{V}O_{2\ peak}$ ($ml \cdot min^{-1}$)	3083 ± 272 (2935 – 3231)	4172 ± 630 (3864 – 4481)	**< 0.0001**
Training (Years)		5 ± 2	
Training Frequency (sessions/wk)	1 ± 1	6 ± 2	**< 0.0001**
Haemodynamic			
Heart Rate ($beats \cdot min^{-1}$)	58 ± 7 (55 – 62)	51 ± 6 (49 – 54)	**0.003**

Systolic BP (mmHg)	118 ± 6 (115 – 122)	122 ± 8 (118 – 125)	0.257
Diastolic BP (mmHg)	72 ± 7 (68 – 76)	72 ± 6 (69 – 75)	0.968

Data presented as mean ± SD (95% confidence intervals). $\dot{V}O_{2\ peak}$, peak volume of oxygen consumption per minute. BP, blood pressure.

S caled and absolute RV areas were significantly greater in the endurance-trained individuals compared with controls, but RV fractional area change was not significantly different (**Table 2**). Absolute and scaled RV basal diameter and RV longitudinal diameter were greater in the endurance-trained group ($P < 0.05$). RVSP was similar between groups ($P = 0.612$) and all other measures of RV function were not significantly different between endurance-trained participants and non-athletic controls at rest (**Table 2)**. Baseline base-to-apex strain gradient was correlated with RV end-diastolic area (R = 0.456, P = 0.015) but was not correlated with peak oxygen uptake (R = 0.319, P = 0.098).

Blood volume and haemodynamic effect of volume loading

There were no statistically significant differences in the total infusion volume (525 ± 43 ml vs. 531 ± 54 ml, endurance vs. control respectively, $P = 0.720$; $d = 0.13$) or the estimated percentage change in blood volume pre-post infusion between the groups (12 ± 4% vs. 14 ± 5%, endurance-trained vs. control respectively; $P = 0.264$; $d = 0.42$). Brachial blood pressure remained similar between groups pre-post infusion.

Effect of plasma volume expansion on right ventricular function in the trained and untrained heart

RV areas and structural dimensions increased to a similar extent in endurance-trained individuals and controls post-infusion and passive leg raise (**Table 2**). The relative increase in global functional measures including TAPSE and RV free wall longitudinal strain were also similar between groups at both time-points (**Table 2**). However, as shown in **Figure 1**, the endurance-trained group displayed a significant increase in RV basal longitudinal strain which was greater than that of controls (ANOVA $P = 0.018$) in response to Gelofusine infusion ($P = 0.048$; $d = 0.79$) and passive leg raise ($P = 0.032$; $d = 0.87$). Peak oxygen uptake was correlated with the change in RV basal strain but was not correlated with mid-wall or apical strain (**Figure 2**). The change in RV end-diastolic area was correlated with the

change RV apical longitudinal strain but not mid-wall or basal strain. Free wall, basal, and apical SR remained similar between groups following both infusion and passive leg-raise.

Table 2. Baseline right ventricular structure and function in controls and endurance-trained individuals and the percent change (Delta %) in RV variables from baseline in response to 7 ml·kg^{-1} intravenous Gelofusine infusion and subsequent passive leg raise.

	Baseline (Absolute)			**Infusion (Delta %)**		**Passive Leg Raise (Delta %)**		**ANOVA (*P* value)**		
Variable, %	**Controls (*n* = 13)**	**Endurance-trained (*n* = 16)**	**T test *P* value**	**Controls**	**Endurance-trained**	**Controls**	**Endurance-trained**	**Between effect**	**Within effect**	**Interaction**
RV Structure										
RV basal diameter (mm)	38 ± 3 (37 – 40)	42 ± 4 (40 – 44)	**0.017**	5 ± 6 (1 – 8)	1 ± 8 (-3 – 5)	5 ± 8 (-2 – 9)	3 ± 7 (0 – 7)	0.332	0.267	0.493
RV mid-cavity diameter (mm)	26 ± 2 (24 – 27)	27 ± 4 (25 – 29)	0.314	3 ± 10 (-2 – 9)	5 ± 13 (-2 – 11)	2 ± 7 (-2 – 6)	4 ± 12 (-2 – 10)	0.599	0.627	0.887
RV longitudinal diameter (mm)	82 ± 4 (80 –	88 ± 8 (84 –	**0.014**	2 ± 5 (0 – 5)	3 ± 4 (1 – 5)	3 ± 4 (1 –	4 ± 3 (2 – 6)	0.467	0.296	0.591

	84)	92)				5)				
RV area diastole (cm^2)	22.4 ± 2.4 (21.1 – 23.7)	25.6 ± 4.4 (23.5 – 27.8)	**0.034**	8 ± 17 (-1 – 17)	7 ± 13 (1 – 13)	6 ± 12 (-1 – 12)	8 ± 11 (2 – 13)	0.937	0.642	0.469
RV area systole (cm^2)	11.2 ± 2.0 (10.1 – 12.4)	12.7 ± 2.5 (11.4 – 14.1)	0.088	9 ± 25 (-4 – 23)	7 ± 14 (0 – 14)	7 ± 12 (0 – 13)	5 ± 15 (-2 – 12)	0.721	0.388	0.98
RV Function										
RVSP (mm Hg)	19 ± 4 (17 – 22)	20 ± 4 (18 – 22)	0.612	21 ± 24 (8 – 34)	16 ± 14 (9 – 23)	25 ± 27 (11 – 39)	22 ± 18 (14 – 31)	0.623	0.011	0.539
RV FAC (%)	51 ± 6 (47 – 54)	50 ± 6 (47 – 53)	0.390	1 ± 8 (-3 – 6)	1 ± 12 (-5 – 7)	0 ± 8 (-5 – 4)	4 ± 14 (-3 – 11)	0.748	0.645	0.177
TAPSE (mm)	23.1 ± 2.3 (21.9 – 24.4)	24.9 ± 4.2 (22.8 – 26.9)	0.200	8 ± 7 (4 – 12)	6 ± 7 (2 – 9)	8 ± 6 (4 – 11)	7 ± 9 (3 – 12)	0.622	0.654	0.438
Total RV free wall strain (%)	25.4 ± 2.6 (24.0 – 26.9)	25.9 ± 2.2 (24.8 – 26.0)	0.202	7 ± 9 (3 – 12)	7 ± 9 (3 – 12)	6 ± 10 (0 – 11)	6 ± 10 (2 – 12)	0.464	0.583	0.405
Basal RV strain (%)	22.4 ± 3.5 (20.5 – 24.4)	21.3 ± 3.1 (19.8 – 22.8)	0.297	6 ± 11 (0 – 12)	16 ± 14* (9 – 22)	3 ± 11 (-3 – 9)	16 ± 18* (7 – 24)	**0.018**	0.576	0.508
Mid RV strain (%)	28.6 ± 2.9 (27.0 –	29.5 ± 5.1 (27.0 –	0.565	7 ± 14 (-1 –	3 ± 10 (-2 – 8)	6 ± 14 (-2 –	2 ± 11 (-3 – 8)	0.450	0.340	0.100

	30.2)	32.0)		14)		13)				
Apical RV strain (%)	25.3 ± 4.3 (22.9 – 27.6)	26.5 ± 3.4 (24.8 ± 28.1)	0.419	10 ± 12 (3 – 17)	7 ± 16 (0 – 15)	9 ± 14 (2 – 17)	7 ± 15 (-1 – 14)	0.572	0.798	0.919
Total RV free wall strain rate (%/s)	1.45 ± 0.31 (1.27 – 1.64)	1.42 ± 0.09 (1.37 – 1.47)	0.720	7 ± 9 (3 – 12)	7 ± 9 (3 – 12)	6 ± 10 (0 - 11)	7 ± 10 (2 – 11)	0.885	0.304	0.726
Basal RV strain rate (%/s)	1.38 ± 0.30 (1.21 – 1.54)	1.25 ± 0.23 (1.14 – 1.36)	0.202	2 ± 25 (-12 – 16)	9 ± 25 (-3 – 22)	-2 ± 13 (-10 – 5)	14 ± 26 (1 – 26)	0.147	0.968	0.286
Mid RV strain rate (%/s)	1.49 ± 0.26 (1.35 – 1.63)	1.52 ± 0.30 (1.37 ± 1.66)	0.794	5 ± 14 (-2 – 13)	0 ± 17 (-9 – 8)	4 ± 17 (-5 – 13)	0 ± 19 (-9 – 10)	0.433	0.975	0.596
Apical RV strain rate (%/s)	1.42 ± 0.38 (1.21 – 1.63)	1.52 ± 0.30 (1.37 – 1.66)	0.459	4 ± 22 (-8 – 16)	15 ± 33 (-2 – 31)	2 ± 28 (-13 – 17)	3 ± 22 (-8 – 14)	0.483	0.236	0.427

Data presented as mean ± SD (95% confidence intervals) in 13 controls and 16 endurance-trained individuals (image clarity for basal RV strain was not sufficient in one endurance-trained participant, therefore n = 15 for this parameter). * $P < 0.05$ significant difference between groups. RV, right ventricle; RVSP, right ventricular systolic pressure; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion.

DISCUSSION

In line with our hypothesis and despite comparable RV free wall longitudinal strain at rest, the primary finding of this study is that regional longitudinal deformation at the base of the RV was augmented in the endurance-trained group when challenged with an acute volume infusion, compared with non-athletic controls. This finding suggests that the RV phenotype associated with endurance training is not simply characterised by differences in resting

structure and function, but also by differences in regional functional responses to haemodynamic perturbation.

Assessment of the right ventricle and pulmonary circulation at rest and in response to increased circulating volume

In the present study, consistent with the athlete's heart phenotype (Oxborough *et al.*, 2012; La Gerche *et al.*, 2012*b*), endurance-trained individuals had larger RV areas, basal diameters, as well as lower resting heart rates. Consistent with prior research (Dawkins *et al.*, 2021), despite mild RV enlargement, no differences in total free wall longitudinal deformation were found between endurance-trained individuals and controls at rest. Furthermore, as has been previously observed in response to exercise (La Gerche *et al.*, 2012*a*, 2015; Claeys *et al.*, 2020), free wall longitudinal deformation and displacement increased in both endurance-trained and control groups by a similar extent in response to acute plasma volume expansion and subsequent passive leg raise, which likely reflects a similar increase in preload status between groups and load dependence of these measures of systolic function. That there was no additive effect of passive leg raise on global and regional measures of RV structure is contrary to what we predicted. Nevertheless, we have reported the experiment as designed.

RVSP was not different between endurance-trained and non-athletic controls at rest, and the increase in RVSP in response to plasma volume expansion and passive leg raise was similar between groups. This finding contradicts prior research which has observed a greater RVSP in athletes that is associated with larger stroke volumes (D'Andrea *et al.*, 2011; Dawkins *et al.*, 2021). Variability in RVSP may be due to a smaller magnitude of difference in stroke volume, and therefore pulsatile blood flow, between endurance and control groups (Dawkins *et al.*, 2020) as compared with others (D'Andrea *et al.*, 2011). Pulmonary artery pressure, and therefore right ventricular systolic load, may also be elevated by increases in downstream left atrial pressure (Tedford *et al.*, 2012; Kovacs *et al.*, 2012; Wright *et al.*, 2021), although there is no evidence to suggest left atrial pressures are abnormal in healthy, young endurance athletes (Levine *et al.*, 1991; Stickland *et al.*, 2006). It has also been suggested that long-term exercise training may elicit a training effect on pulmonary blood volume or pulmonary vascular distensibility (Lalande *et al.*, 2012; Tedjasaputra *et al.*, 2016) permitting an increase in vessel size to accommodate blood flow, thereby mitigating a rise in pressure, although these speculations require further mechanistic investigation.

Regional right ventricular myocardial function in the endurance-trained heart at rest

In contrast to prior investigations (Teske *et al.*, 2009; La Gerche *et al.*, 2012*a*), and despite mild RV basal dilatation among endurance-trained individuals in the present study, no difference was observed in apical or basal RV deformation at rest in comparison with non-athletes. This finding also conflicts with recent meta-analysis, which demonstrated region-specific differences in RV function, characterised by a lower basal RV strain and greater apical RV strain, at rest (Dawkins *et al.*, 2021). Observed regional adaptations in the athlete's RV have been speculated to be a consequence of the morphological differences between the base and the trabeculated apex, such as myofiber alignment, local radii of curvature, and relative dimensions, which may promote a basal portion of the RV that is exposed to greater increases in wall stress during exercise (Teske *et al.*, 2009). Differences between our study and others may reflect differences in athletic status, for example, Teske et al. (2009) demonstrated a significantly lower speckle tracking derived RV basal strain in a large cohort (n = 63) of elite athletes training 24.2 h/week in comparison to non-athletes (n = 61); however, this distinction was not found in our sub-elite athletes training 12.5 h/week.

Regional right ventricular myocardial response to plasma volume expansion in the endurance-trained heart

In accordance with our hypothesis, RV basal strain was augmented beyond that of non-athletic controls following acute artificial plasma volume expansion and confirmed during subsequent passive leg raise, while the magnitude of increase in apical strain was similar between groups. Consistent with the suggested mechanisms that underpin LV remodelling (Weiner *et al.*, 2015), structural and functional RV adaptations associated with long-term training are likely to reflect cellular remodelling (i.e. myocardial hypertrophy and intracellular calcium handling) (Kemi & Wisløff, 2010; Ellison *et al.*, 2012), composition of the extracellular matrix (Xu *et al.*, 2008), autonomic innervation (Manzi *et al.*, 2009) and/or receptor density or sensitivity (Mizuno *et al.*, 2005). Alternatively, it is possible that regional contributions to function following haemodynamic perturbation simply reflect differences or changes in structure. In agreement with Stewart et al. (2020), baseline base-to-apex strain gradient was associated with RV end-diastolic area. However, the change in basal strain during plasma volume expansion and subsequent passive leg raise was not associated with the change in RV end-diastolic area, indicating that the greater increase in basal strain in the athletes is not secondary to a greater ventricular filling. The change in RV basal strain was, nonetheless, correlated with peak oxygen uptake, suggesting that those who are fittest show the greatest change in RV basal strain upon haemodynamic perturbation, perhaps reflecting a

functional remodelling to support increased exercise capacity. However, correlation does not imply causation and so further study is required to interrogate these relationships and underlying mechanisms.

Since the smooth inlet at the RV base and trabecular portions at the RV apex have a different muscular arrangement (Jurcut *et al.*, 2010), the adaptation to haemodynamic stress associated with exercise may also differ regionally. In support of this, it is recognised that endurance training can result in hypertrabeculation of the apex and dilatation of the base (D'Ascenzi *et al.*, 2017). The observed preferential deformation at the base of the RV in response to acute plasma volume expansion may therefore arise as an epiphenomenon associated with exercise-induced structural adaptations, perhaps reflecting a pressure generating reserve capacity that may be engaged during exercise. In contrast to the basal region, apical contribution to RV systolic function may be less associated with pressure generation and more important for creating an efficient and smooth direction of blood flow towards the outflow tract (Calcutteea *et al.*, 2011; Sanz *et al.*, 2019). Given such regional contributions to RV function, it is perhaps unsurprising that endurance training elicits region-specific RV adaptation in response to acute hypervolemia..

Applied perspective

Further assessment of the functional RV response is crucial to improving our understanding of exercise-induced RV remodelling. This study demonstrates that the increase in myocardial deformation at the base of the RV is greater in endurance-trained individuals, in response to an increase in circulating volume, similar to that which follows exercise. As such, the athletic heart phenotype may be extended to incorporate a region-specific *functional* response to a haemodynamic stimulus, which may reflect an enhanced functional reserve capacity.

Study limitations

This study is limited by the exclusion of competitive athletes, since intravenous Gelofusine infusion is considered a prohibited substance by the World Anti-Doping Agency. Those performing the greatest training load may have the most pronounced remodelling and greatest change in resting strain and strain rate in comparison to controls and non-elite athletes (Teske *et al.*, 2009). Whilst elite athletes were not included, trained individuals were performing a substantial volume of training, and had a cardiorespiratory fitness similar to other studies investigating RV myocardial mechanics in athletes (La Gerche *et al.*, 2015). Additionally,

although not statistically significant, endurance athletes were slightly older than controls by approximately 3 years, however controlling for age as a covariate did not alter the findings of this study. In accordance with recent task force consensus (Badano *et al.*, 2018), longitudinal strain of the RV free wall is reported. However, it is recognised that regional shortening of the septum contributes to the ejection phase of the RV (Buckberg & Hoffman, 2014). Nonetheless, the same findings were observed for global RV strain (6-segment strain including free wall and septum). It is appreciated by the authors that a more comprehensive assessment of the functional capacity all four chambers of the athlete's heart is required, although some of this of work is ongoing (Dawkins *et al.*, 2020). Finally, specific studies to examine the female athlete's heart are warranted; separate sex differences studies are currently being undertaken and have previously been investigated by our group (Williams *et al.*, 2018) and others (Sanz-de la Garza *et al.*, 2017; Lakatos *et al.*, 2018).

CONCLUSION

The RV phenotype associated with endurance training is not simply characterised by differences in resting structure and function, but also by a region-specific *functional response* to changes in circulating volume, which is most prominent at the base of the RV. Understanding of these normal regional differences in RV deformation in athletes, both at rest and when challenged, may help to discriminate exercise-induced physiological remodelling from that of pathology, which remains an extremely important consideration for sports cardiologists.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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AUTHOR CONTRIBUTIONS

T.G.D., B.A.C., M.S., and R.E.S conceived and designed the research; T.G.D., B.A.C., A.D., R.N.L, C.R., F.M.L., Z.Y., and M.S. performed experiments; T.G.D. analysed data; T.G.D., M.S., and R.E.S. interpreted results of experiments; T.G.D. prepared figures; T.G.D. drafted manuscript; T.G.D., B.A.C., A.D., R.N.L., C.R., C.J.P., F.M.L., Z.Y., M.S., and R.E.S. edited and revised manuscript; All authors approved the final version of manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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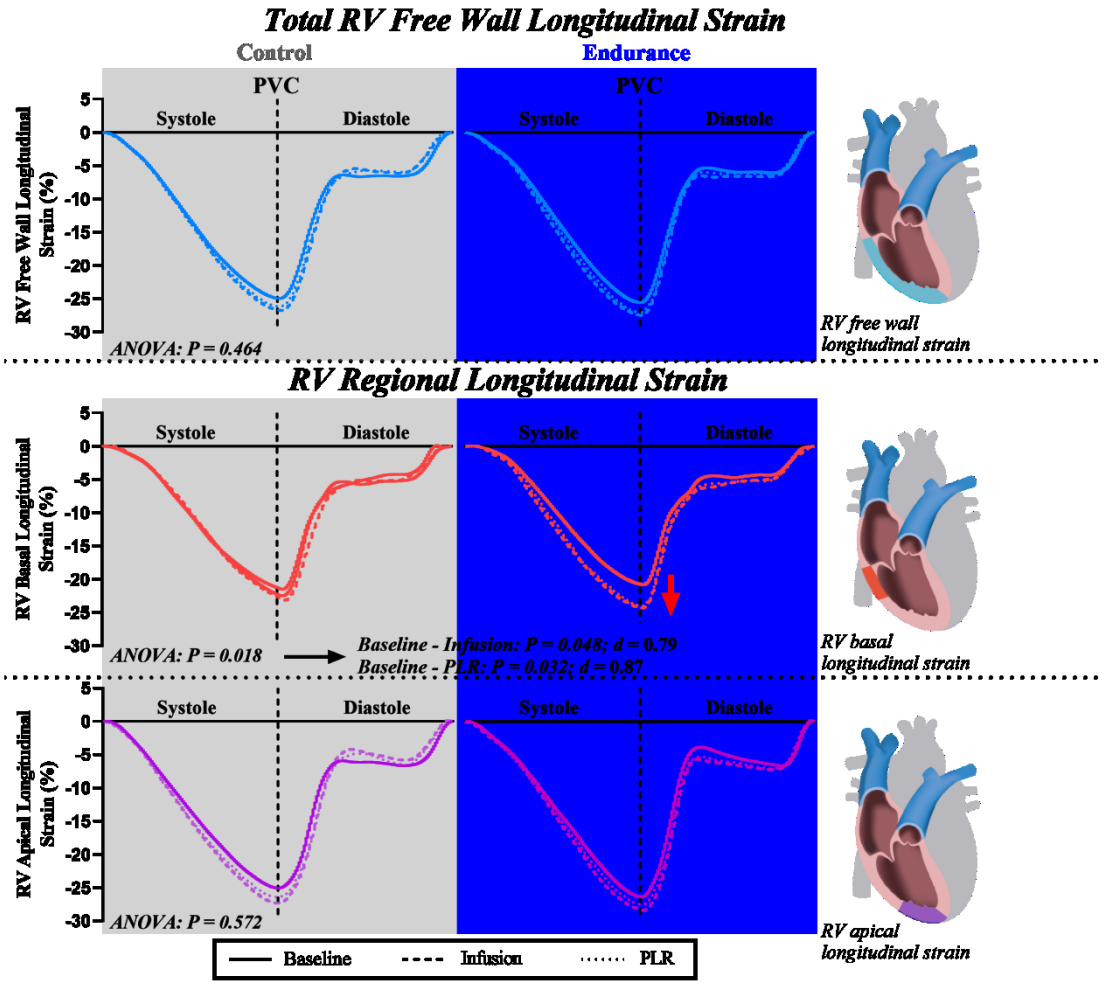

Figure 1. Right ventricular free wall strain among endurance-trained (right panel) and control participants (left panel) before (solid line) and after 7 ml·kg-1 intravenous Gelofusine infusion (dashed line) and subsequent passive leg-raise (PLR; dotted line).

Blue Red arrow illustrates statistical significance of between-subjects effects, as assessed from a two-way analysis of variance of the delta change (%). Cohen's d effect sizes also reported.

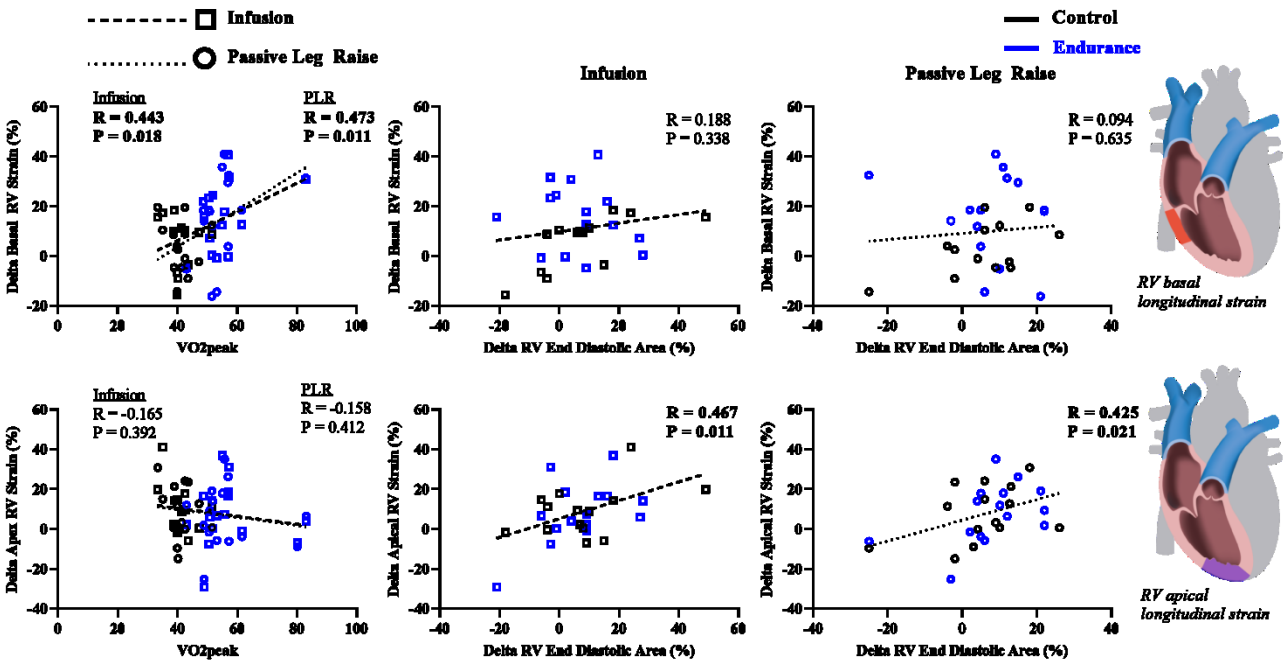

Figure 2. Delta regional strain values from baseline to post infusion are reflected by squares whilst delta regional strain values from baseline to passive leg raise (PLR) are reflected by circles. Endurance-trained individuals are represented in blue whilst non-athletic controls are represented in black.