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Exercise-Induced Cardiac Fatigue after a 45-min Bout of High-Intensity Running Exercise Is Not Altered under Hypoxia

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Background: Acute exercise promotes transient exercise-induced cardiac fatigue, which affects the right ventricle and to a lesser extent the left ventricle. Hypoxic exposure induces an additional increase in right ventricular (RV) afterload. Therefore, exercise in hypoxia may differently affect both ventricles. The aim of this study was to investigate the acute effects of a bout of high-intensity exercise under hypoxia versus normoxia in healthy individuals on right- and left-sided cardiac function and mechanics.

Methods: Twenty-one healthy individuals (mean age, 22.2 ± 0.6 years; 14 men) performed 45-min high-intensity running exercise under hypoxia (fraction of inspired oxygen 14.5%) and normoxia (fraction of inspired oxygen 20.9%) in a randomized order. Pre- and post-exercise echocardiography, at rest and during low-to-moderate intensity recumbent exercise (''stress''), was performed to assess RV and left ventricular (LV) cardiac function and mechanics. RV structure, function, and mechanics were assessed using conventional two-dimensional, Doppler, tissue Doppler, speckle-tracking echocardiographic, and novel strain-area loops.

Results: Indices of RV systolic function (RV fractional area change, Tricuspid annular plane systolic excursion, RV s′, and RV free wall strain) and LV function (LV ejection fraction and LV global longitudinal strain) were significantly reduced after high-intensity running exercise ($P < .01$). These exercise-induced changes were more pronounced when echocardiography was examined during stress compared with baseline. These responses in RV and LV indices were not altered under hypoxia ($P > .05$).

Conclusions: There was no impact of hypoxia on the magnitude of exercise-induced cardiac fatigue in the right and left ventricles after a 45-min bout of high-intensity exercise. This finding suggests that any potential increase in loading conditions does not automatically exacerbate exercise-induced cardiac fatigue in this setting. (J Am Soc Echocardiogr 2021;■:■-■.)

Keywords: Athlete's heart, Exercise-induced cardiac fatigue, Hypoxia, Echocardiography, Speckle-tracking echocardiography

It is well established that exercise is associated with potent cardioprotective effects,[1-3] but acute exercise can lead to a paradoxical short-term increase in cardiac events.[4-6] One potential explanation is that exercise performed under demanding conditions (i.e., exercise at high intensity and/or of prolonged duration) may lead to an acute reduction in cardiac function.[7-13] This transient decline in cardiac function after strenuous exercise is typically referred to as exercise-induced cardiac fatigue (EICF). EICF may affect both the left and right

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Conflicts of interest: None.

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Abbreviations

BP = Blood pressure

EICF = Exercise-induced cardiac fatigue

FiO_2 = Fraction of inspired oxygen

HR = Heart rate

ICC = Intraclass correlation coefficient

LOA = Limits of agreement

LV = Left ventricular

PAH = Pulmonary arterial hypertension

PAP = Pulmonary artery pressure

PAT = Pulmonary acceleration time

PVR = Pulmonary vascular resistance

RV = Right ventricular

Vo_2max = Maximal oxygen consumption

ventricles, with possibly a larger impact on the right ventricle because of the disproportionately higher wall stress experienced by the right ventricle relative to the left ventricle during exercise.[11,14,15]

Previous studies have demonstrated that hypoxia increases the demands on the cardiovascular system.[16] Specifically, acute exposure to hypoxia induces a decrease in systemic vascular resistance at rest, which may contribute to a decrease in left ventricular (LV) afterload.[17,18] In contrast, hypoxia leads to a resting increase in pulmonary artery resistance and subsequently to an increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP).[19] Exercise in normoxic conditions results in additional load challenges and increased PAP secondary to the mismatch of elevated stroke volume to inadequate pulmonary vascular distension.[20] This is exacerbated when exercising in hypoxic conditions, leading to even greater PAP and right ventricular (RV) wall stress and potentially further increasing the risk for RV EICF.[19-23]

To non-invasively examine right heart hemodynamics, investigators have examined conventional and Doppler-based echocardiographic indices at rest and during exercise.[24-26] Recently, the strain-area loop has been introduced, simultaneously assessing structure and strain across the cardiac cycle.[5] Previously, we found that RV loop characteristics relate to PVR in patients with pulmonary arterial hypertension (PAH) while also demonstrating value in the assessment of EICF.[27,28] Therefore, these non-invasive characteristics may provide additional insight in understanding exercise-induced changes in hypoxia.

In view of this, the aim of this study was to investigate the acute effects of a bout of high-intensity exercise under hypoxia versus normoxia in healthy individuals on right- and left-sided cardiac function and mechanics (i.e., longitudinal strain and strain-area loops). On the basis of the presumed higher workload of the right ventricle during hypoxic versus normoxic exercise, we hypothesized that exercise under hypoxia exaggerates the right ventricle to a greater extent than the left ventricle compared with exercise under normoxia. To investigate EICF, we examined pre- and post-exercise echocardiography at rest but also during a standardized low-to-moderate intensity recumbent exercise challenge ("stress"). As the post-exercise recovery period is associated with persistent sympathoexcitation and peripheral vasodilation,[17,18] evaluation of EICF could be confounded when evaluated solely at rest. Therefore, evaluation during stress echocardiography might better reflect cardiac function during exercise and offsets the key limitation of (para)sympathetic imbalance associated with echocardiographic assessment in recovery.[14]

METHODS

Study Population

Twenty-one participants (mean age, 22.2 ± 0.6 years; 14 men; mean body mass index, 24.0 ± 0.6 kg/m^2; mean maximal oxygen consumption [Vo_2max] per kilogram, 52.4 ± 1.8 mL/min/kg) completed the study. Baseline characteristics are shown in Table 1. Participants were eligible to take part in this study if they were able to run on a treadmill and if they had trained <2 hours a week at moderate to high intensity for the previous 6 months. Exclusion criteria were body mass index <18 or >30 kg/m^2, active smoking, any possibility of pregnancy, personal history of cardiovascular disease, positive family history of cardiovascular death (at <55 years of age), exercise-limiting respiratory disease, physical (i.e., musculoskeletal) symptoms making completion of a bout of high-intensity running exercise impossible, abnormalities on resting 12-lead electrocardiography, and abnormalities on resting transthoracic echocardiography. The procedures were in accordance with institutional guidelines and conformed to the Declaration of Helsinki. The study was approved by the ethics research committee of Liverpool John Moores University (18/SPS/065). Participants gave full written and verbal informed consent before participation.

Study Design

In this randomized crossover trial, participants attended the laboratory on three separate occasions (Figure 1). During the first visit, medical screening was performed to determine the eligibility of potential participants. After participants provided informed consent, baseline measurements were performed. The second and third visits included performance of a 45-min bout of high-intensity running exercise under normobaric hypoxia or normoxia, performed in a randomized order. Participants were blinded to the order of test days and abstained

Table 1 Subject characteristics

Variables	Value
Sex, male/female	14/7
Age, y	22.2 ± 0.6
Height, cm	170 ± 2
Body mass, kg	70 ± 2
BMI, kg/m^2	24.0 ± 0.6
BSA, m^2	1.8 ± 0.04
Resting HR, beats/min	65 ± 2
Resting SBP, mm Hg	119 ± 1
Resting DBP, mm Hg	69 ± 2
Resting MAP, mm Hg	85 ± 1
Resting SpO_2, %	98.4 ± 0.3
Vo_2max, L/min	3.6 ± 0.1
Vo_2max/kg, mL/min/kg	52 ± 2
VE, L/min	138 ± 6
HRmax, beats/min	199 ± 2

BMI, Body mass index; *BSA*, body surface area; *DBP*, diastolic BP; *HR*, heart rate; *HRmax*, maximal heart rate; *MAP*, mean arterial pressure; *SBP*, systolic BP; *SpO_2*, oxygen saturation; *VE*, ventilation. Data are expressed as number or as mean ± SEM.

HIGHLIGHTS

- High-intensity exercise for 45 min induces right- and left-sided cardiac fatigue.
- EICF is more pronounced during stress echocardiography.
- Exercise under hypoxia does not exaggerate EICF.

from exercise for a minimum of 48 hours and from alcohol and caffeine consumption 24 hours before the test days.

Baseline Measurements. Participants were examined for height (SECA stadiometer; SECA, Hamburg, Germany), weight (SECA scale; SECA), oxygen saturation (pulse oximetry; Ana Pulse 100, Ana Wiz, Addlestone, United Kingdom), 12-lead electrocardiography (Cardiovit MS-2010; Schiller, Baar, Switzerland) and V_{O_2}max. Resting heart rate (HR; Polar, Kempele, Finland) and resting blood pressure (BP; Dinamap V100; GE Vingmed Ultrasound, Horten, Norway) were determined at the end of 10-min quiet rest in a supine position. A standardized maximal cardiopulmonary exercise test (Oxycon pro; CareFusion, San Diego, CA) for V_{O_2}max assessment was conducted on a motorized treadmill (H/P/Cosmos Sports & Medical, Nussdorf-Traunstein, Germany) after a 10-min warmup and familiarization. V_{O_2}max was defined as the highest value of a 30-sec average,[29] and attainment was verified according to previously recommended criteria.[30]

Test Days. Figure 1 outlines the details of a single test day. One of the test days was performed at normoxia (sea level, equivalent to fraction of inspired oxygen [FiO_2] 20.9%) and the other at normobaric hypoxia (FiO_2 14.5%, equivalent to a simulated altitude of 3,000 m), separated by ≥48 hours of rest. Participants were subjected to 30-min acclimation in a seated position followed by 45-min high-intensity (85% of maximum achieved HR during cardiopulmonary exercise testing) endurance running exercise on a motorized treadmill and 60-min recovery in a seated position. HR was measured continuously throughout, and rate of perceived exertion was monitored during the 45-min high-intensity running exercise.[31]

In total, four echocardiographic assessments were performed per test day. After acclimation and before the 45-min exercise, echocardiography was performed under resting conditions ("rest") and during recumbent cycling to elevate HR to directly assess cardiac function during exercise ("stress"; target HR 110–120 beats/min). "Stress" echocardiography was repeated directly after the 45-min exercise to prevent sympathetic withdrawal (i.e., decreases in BP and HR).[32] Finally, images were obtained at the end of the 60-min of recovery in a resting state. During every echocardiographic assessment, BP measurements were performed. Measurements were performed at the same time on both days to control for diurnal variation. Fluid intake was controlled by providing the same amount of water to participants during both testing days.

Environmental Chamber and Safety. All exercise tests were conducted in an environmental chamber (TIS Services, Alton, United Kingdom; Sporting Edge, Basingstoke, United Kingdom). Normobaric hypoxia was achieved using a nitrogen dilution technique. Ambient temperature, carbon dioxide and oxygen levels were controlled in all sessions (20°C, FiO_2 14.5%, carbon dioxide 0.03%), while a Servomex gas analysis system (Servomex MiniMP 5200; Servomex, Crowborough, United Kingdom) was used inside the chamber to provide the researcher continuous information regarding oxygen and carbon dioxide levels. Acute mountain sickness symptoms (measured using the Lake Louise score[33]) were monitored during testing and training sessions every 20 min. The subject was removed from the environmental chamber if oxygen saturation levels dropped below 80% or severe acute mountain sickness was suspected (Lake Louise score ≥ 6).

Echocardiographic Measurements

Rest and stress echocardiography were performed in the left lateral decubitus position on a supine cycle ergometer (Lode, Groningen, the

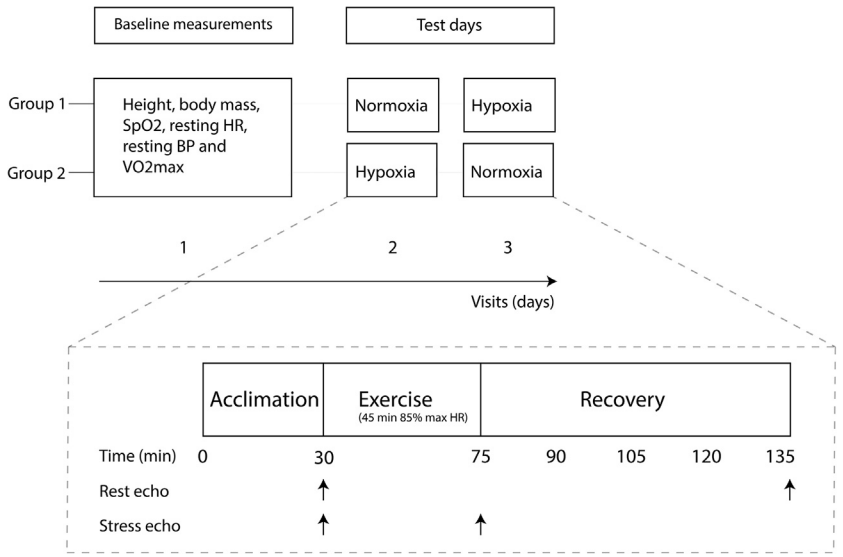

Figure 1 Overview of study design. The *dotted panel* highlights visits 2 and 3 (test days). *SpO_2*, Oxygen saturation.

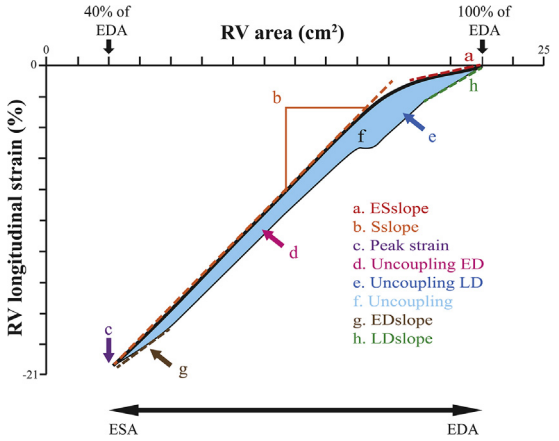

Figure 2 Schematic overview of the RV strain-area loop and the derived characteristics. The *black line* represents the strain-area loop; the *thick part* represents the systolic phase and the *thin part* the systolic phase. *ED*, End-diastolic, *EDA*, end-diastolic area; *ESA*, end-systolic area; *LD*, late diastolic.

Netherlands) by one highly experienced sonographer (D.L.O.) using a Vivid E95 ultrasound machine (GE Vingmed Ultrasound) equipped with a 1.5- to 4.5-MHz transducer. Images were stored in raw Digital Imaging and Communications in Medicine format and were exported to an offline workstation (EchoPAC version 203; GE Vingmed Ultrasound). Data analysis, from three stored cycles, was performed by a single observer with experience in echocardiography (G.K.) using commercially available software (EchoPAC version 203). The observer was blinded for the timing (before vs after exercise) and condition (normoxia vs hypoxia) under which echocardiography was performed. For stress echocardiography, low-to-moderate intensity (target HR 110–120 beats/min) exercise consisted of recumbent cycling at a cadence of about 60 rpm, with watts manually adjusted to stabilize at the target HR.

Conventional Measurements. Cardiac structural and functional measurements were made according to the current guidelines for cardiac chamber quantification.[34] Regarding the right heart, we examined the following structural and functional indices: basal and midcavity end-diastolic diameters, RV end-diastolic area, RV end-systolic area, RV outflow tract diameter at the proximal level in the parasternal long-axis and parasternal short-axis views, right atrial area, RV fractional area change, tricuspid annular plane systolic excursion, Doppler tissue imaging of the tricuspid annulus (RV s′, e′, and a′), and pulmonary acceleration time (PAT). Tricuspid regurgitation velocity was not obtainable in the majority of participants and therefore could not be assessed in this study.

Regarding the left heart, the following structural and functional indices were determined: LV end-diastolic volume, LV end-systolic volume, left atrial diameter, left atrial volume, modified Simpson's LV ejection fraction, Doppler tissue imaging of the mitral annulus (LV s′, e′, and a′) and, transmitral Doppler (E, A, and E/A ratio). Doppler A and RV and LV Doppler tissue imaging a′ were not measurable, because of e′/a′ and E/A fusion during stress echocardiography at higher HRs.

Mechanics. Images were acquired and optimized for speckle-tracking echocardiography. This involved maintaining frame rates between 40 and 90 frames/sec, depth to ensure adequate imaging of the chamber of interest, and compression and reject to ensure endocardial delineation. The RV-focused and the apical two-chamber, four-chamber, and long-axis views were used for RV and LV global longitudinal strain, respectively. Pulmonary and aortic valve closure times were determined from the respective pulsed-wave Doppler signals. For both the RV and LV views, the myocardium was manually traced to include the septum and adjusted so that the region of interest incorporated all of the wall thickness while avoiding the pericardium.[35,36] The region of interest was divided into six myocardial segments, providing segmental strain curves and a longitudinal strain curve as an average of all six segments for the LV views and as an average of the three segments of the RV free wall. LV global longitudinal strain was obtained by averaging the single strain measurements of the three separate apical LV views. If inappropriate tracking of segments was observed visually or detected by the system, retracing was performed until all segments were considered acceptable.

RV Strain-Area Loops. The longitudinal strain-area relationship (for detailed methods of derivation, see Supplemental 1, Oxborough *et al*,[5] and Hulshof *et al*[37]) was assessed using the following parameters (Figure 2): (1) the linear strain-area slope (Sslope) and early strain-area slope during the first 5% of volume ejection in systole (ESslope); (2) end-systolic peak longitudinal strain (peak strain); (3) the early linear strain-area slope during the first 5% (EDslope) and late linear strain-area slope (LDslope) during the last 5% of volume increase in diastole; and (4) diastolic uncoupling (i.e., the difference in strain between systole and diastole at any given area), divided into uncoupling during early and late diastole.[5,28] On the basis of previous work from our laboratory, we found that patients with PAH with higher PVR had lower Sslope and decreased late diastolic uncoupling. Therefore, these may serve as markers of increased PVR and consequently PAP.[28]

To assess intraobserver variability, strain-area loops were reanalyzed for 20 randomly selected echocardiograms ($n = 10$ rest, $n = 10$ stress). For all strain-area loop characteristics, analyses of intraclass correlation coefficients (ICCs) and Bland-Altman limits of agreement (LOA) were performed.[38]

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 25 (SPSS, Chicago, IL). All parameters were visually inspected for normality and tested using Shapiro-Wilk normality tests. Continuous variables are reported as mean ± SEM and categorical variables as proportions. Linear mixed-models analysis for repeated measurements were performed to test the acute effects of a 45-min bout of high-intensity exercise on cardiac function and mechanics (exercise) and whether this effect was influenced when echocardiography was performed at rest or during stress (exercise × stress). Furthermore, linear mixed models were used to test the effect of hypoxia versus normoxia (hypoxia) and the effect of rest versus stress echocardiography (stress) on cardiac structure and function. To examine our primary objective, linear mixed-models analysis was used to examine whether hypoxia influenced the effect of exercise on cardiac function (exercise × hypoxia) and how this was affected

Table 2 RV function and mechanics during rest and stress before and after exercise under normoxia and hypoxia

	Rest echocardiography				Stress echocardiography									
	Normoxia		Hypoxia		Normoxia		Hypoxia			*P* values				
Variables	Pre	Post	Pre	Post	Pre	Post	Pre	Post	H	E	S	H*E	E*S	E*H*S
Structure														
RV basal diameter, mm	36.8 ± 0.9	37.4 ± 0.7	36.9 ± 0.7	37.8 ± 0.7	36.4 ± 0.7	35.6 ± 0.8	36.9 ± .7	37.1 ± 0.6	.13	.45	**.03**	.25	.10	.36
RV midcavity diameter, cm	28.9 ± 0.8	29.4 ± 0.6	29.4 ± 0.9	29.9 ± 0.7	28.8 ± 0.7	28.2 ± 0.8	28.9 ± .7	28.8 ± 0.8	.19	.9	.07	.61	.22	.65
RVEDA, cm^2	20.4 ± 0.7	20.3 ± 0.6	20.7 ± 0.7	21.4 ± 0.7	19.9 ± 0.6	19.7 ± 0.8	20.3 ± 0.6	20.3 ± 0.7	**.01**	.56	**.01**	.14	.38	.46
RVESA, cm^2	10.8 ± 0.5	11.2 ± 0.4	11.0 ± 0.4	11.8 ± 0.4	9.8 ± 0.3	10.3 ± 0.5	9.9 ± 0.4	10.8 ± 0.5	.14	**.001**	**<.001**	.14	.65	.99
$RVOT_{PLAX}$, mm	24.0 ± 0.7	24.4 ± 0.8	25.5 ± 0.6	25.6 ± 0.5	24.2 ± 0.7	23.0 ± 0.7	24.6 ± 0.7	24.1 ± 0.7	.07	.22	**.006**	.55	**.04**	.21
$RVOT1_{PSAX}$, mm	24.8 ± 0.8	25.6 ± 0.7	26.1 ± 0.7	25.9 ± 0.6	25.2 ± 0.6	24.2 ± 0.6	25.9 ± 0.9	25.1 ± 0.7	.15	.34	.15	.36	.08	.11
$RVOT2_{PSAX}$, mm	16.6 ± 0.4	16.7 ± 0.4	17.3 ± 0.4	16.8 ± 0.4	17.0 ± 0.5	16.6 ± 0.5	17.1 ± 0.4	17.0 ± 0.5	.17	.28	.62	.75	.82	.21
RA area, cm^2	14.5 ± 0.5	13.8 ± 0.5	14.8 ± 0.6	14.4 ± 0.6	13.4 ± 0.4	13.1 ± 0.5	14.0 ± 0.5	13.4 ± 0.4	**.04**	**.001**	**.001**	.98	.8	.28
Function and mechanics														
RVFAC, %	47 ± 1	45 ± 1	47 ± 1	45 ± 1	50 ± 1	48 ± 1	51 ± 1	47 ± 1	.93	**.007**	**<.001**	.49	.43	.36
TAPSE, cm	27 ± 1	26 ± 1	28 ± 1	26 ± 1	30 ± 1	28 ± 1	30 ± 1	28 ± 1	.89	**<.001**	**<.001**	.52	.20	.9
DTI s′, cm/sec	15 ± 1	14 ± 1	15 ± 1	15 ± 1	19 ± 1	17 ± 1	20 ± 1	18 ± 1	**.02**	**.002**	**<.001**	.55	.11	.73
DTI e′, cm/sec	17 ± 1	16 ± 1	18 ± 1	17 ± 1	28 ± 1	28 ± 1	29 ± 1	27 ± 1	.20	**.02**	**<.001**	.45	.61	.45
DTI a′, cm/sec	13 ± 1	12 ± 1	13 ± 1	13 ± 1	—	—	—	—	.19	.33	—	.24	—	—
RV free wall strain, %	−28.0 ± 1	−27 ± 1	−28 ± 1	−28 ± 1	−33 ± 1	−30 ± 1	−32 ± 1	−30 ± 1	.90	**<.001**	**<.001**	.58	**.01**	.86
RV time of peak, sec	0.36 ± 0.01	0.37 ± 0.01	0.37 ± 0.01	0.36 ± 0.01	0.28 ± 0.01	0.32 ± 0.01	0.29 ± 0.01	0.31 ± 0.01	.51	**<.001**	**<.001**	.09	**.004**	.57
PAT, msec	152 ± 3	151 ± 3	139 ± 4	134 ± 3	122 ± 4	120 ± 3	106 ± 4	105 ± 3	**<.001**	.008	**<.001**	.60	.36	.30
Strain-area loop characteristics														
Uncoupling, %	2.0 ± 0.2	1.0 ± 0.4	1.4 ± 0.3	0.6 ± 0.4	1.4 ± 0.5	1.2 ± 0.5	0.7 ± 0.4	0.3 ± 0.5	.07	.05	.32	.99	.23	.66
Uncoupling ED, %	2.0 ± 0.3	1.0 ± 0.4	1.4 ± 0.3	0.6 ± 0.4	1.4 ± 0.5	1.3 ± 0.5	0.7 ± 0.5	0.4 ± 0.6	.10	.10	.40	.92	.14	.7
Uncoupling LD, %	2.0 ± 0.2	1.1 ± 0.3	1.3 ± 0.3	0.6 ± 0.4	1.5 ± 0.4	1.0 ± 0.5	0.8 ± 0.4	0.1 ± 0.5	**.04**	**.01**	.22	.96	.67	.62
Sslope, %/cm^2	2.5 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	.07	.53	**.003**	.8	.35	.33
ESslope, %/cm^2	2.4 ± 0.2	2.6 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	2.9 ± 0.2	2.7 ± 0.2	2.9 ± 0.2	2.7 ± 0.2	.85	.97	**.05**	.87	**.04**	.88
EDslope, %/cm^2	1.4 ± 0.1	1.9 ± 0.2	1.7 ± 0.1	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	2.2 ± 0.3	.41	.08	.29	.73	.82	**.03**
LDslope, %/cm^2	3.3 ± 0.2	3.0 ± 0.2	3.1 ± 0.2	2.8 ± 0.2	3.6 ± 0.3	3.5 ± 0.3	3.4 ± 0.3	3.1 ± 0.3	.11	.18	**.02**	.77	.73	.34

DTI, Doppler tissue imaging; *ED*, Early diastole; *LD*, late diastole; *PAT*, pulmonary acceleration time; *PLAX*, parasternal long-axis view; *PSAX*, parasternal short-axis view; *RA*, right atrial; *RVEDA*, RV end-diastolic area; *RVESA*, RV end-systolic area; *RVFAC*, RV fractional area change; *RVOT*, RV outflow tract; *TAPSE*, tricuspid annular plane systolic excursion.
Linear mixed-models factors: *H*, hypoxia (comparison between all echocardiographic measurements performed under hypoxic vs normoxic conditions); *E*, exercise (comparison between all echocardiographic measurements performed before vs after 45-min high-intensity exercise); *S*, stress (comparison between all echocardiographic measurements performed during rest vs during stress); *E*S*, exercise × stress (comparison whether the change before vs after exercise is different measured during rest vs stress echocardiography); *H*E*, hypoxia × exercise (comparison whether the change before vs after exercise [EICF] is different during hypoxic vs normoxic conditions); *E*H*S*, exercise × hypoxia × stress (comparison whether the change before vs after exercise under hypoxic vs normoxic conditions was different when observed using rest vs stress echocardiography).
Data are expressed as means ± SEM.

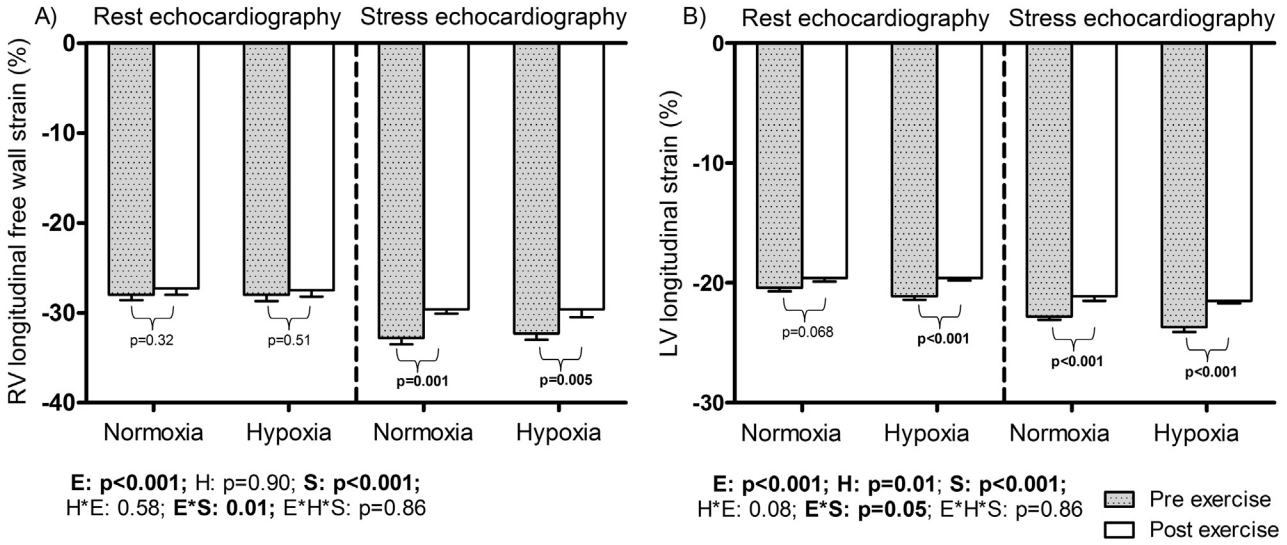

Figure 3 RV longitudinal strain **(A)** and LV longitudinal strain **(B)** before and after 45-min high-intensity running exercise. Error bars reflect SEM. Linear mixed-models factors: *H*, hypoxia (comparison between all echocardiographic measurements performed under hypoxic vs normoxic conditions); *E*, exercise (comparison between all echocardiographic measurements performed before vs after 45-min high-intensity exercise); *S*, stress (comparison between all echocardiographic measurements performed during rest vs during stress); *E*S*, exercise × stress (comparison whether the change before vs after exercise is different measured during rest vs stress echocardiography); *H*E*, hypoxia × exercise (comparison whether the change before vs after exercise [EICF] is different during hypoxic vs normoxic conditions); *E*H*S*, exercise × hypoxia × stress (comparison whether the change before vs after exercise under hypoxic vs normoxic conditions was different when observed using rest vs stress echocardiography).

by testing condition rest versus stress (exercise × hypoxia × stress). For all tests, we assumed statistical significance at $P < .05$.

RESULTS

Both the right and left heart had normal geometry, and all structural measurements were within normal ranges (Table 2). There were no abnormal 12-lead electrocardiographic findings.

Exercise Characteristics

HR during exercise was matched between exercise under hypoxia and normoxia (172 ± 1 and 173 ± 2 beats/min, respectively, $P = .23$). Body mass loss (hypoxia, −410 ± 70 g; normoxia, −410 ± 43 g; $P = .99$) and water intake (hypoxia, 373 ± 60 mL; normoxia, 336 ± 44 ml; $P = .24$) during exercise did not differ between testing sessions. Mean distance covered during exercise was significantly higher in normoxia (6,655 ± 351 m) compared with hypoxia (5,797 ± 308 m; $P < .001$), while there was no significant difference in subjective ratings of perceived exertion (rate of perceived exertion under normoxia 12.5 ± 0.3, rate of perceived exertion under hypoxia 13.3 ± 0.3; $P = .07$). Oxygen saturation during exercise was significantly lower in hypoxia (82 ± 0.8%) compared with normoxia (95 ± 0.4%).

RV Structure, Function, and Mechanics

All RV structural, functional, and mechanical indices before and after 45-min high-intensity running exercise are displayed in Table 2. Indices of RV systolic function (RV fractional area change, tricuspid annular plane systolic excursion, RV s′, and RV free wall strain; Figure 3A) were significantly reduced following 45-min high-intensity exercise (exercise: $P < .01$). The declines in indices of RV function and mechanics after exercise were not different between rest and stress echocardiography, except for a more pronounced reduction in RV free wall strain during stress (exercise × stress: $P = .01$; Table 2, Figure 3A). Related to the strain-area loop, following 45-min high-intensity exercise, there were reductions in RV longitudinal strain, uncoupling, and late diastolic uncoupling (exercise: $P < .05$) without a rightward shift (RV end-diastolic area exercise: $P > .05$; Table 2 Figure 4A and B).

Exercise under Hypoxia. Under hypoxia, PAT was significantly shorter, right atrial size significantly larger, and late diastolic uncoupling significantly lower, and a trend was found for a lower systolic slope (Sslope) compared with normoxic conditions (hypoxia: $P = .04$, $P = .04$, $P < .001$, and $P = .07$, respectively; Table 2, Figure 4A and B). Importantly, hypoxia did not alter the impact of exercise and/or stress on indices of RV function (hypoxia × exercise and exercise × hypoxia × stress: $P > .05$ for all; Table 2).

Intraobserver Variability. ICCs and LOA for RV strain-area loop characteristics were as follows: RV free wall strain: ICC = 0.95 (95% CI, 0.89 to 0.98), LOA = 0.33 (95% CI, −1.55 to 2.21); Sslope: ICC = 0.91 (95% CI, 0.80 to 0.97), LOA = −0.05 (95% CI, −0.30 to 0.20); ESslope: ICC = 0.60 (95% CI, 0.23 to 0.82), LOA = 0.17 (95% CI, −1.20 = 0.86); EDslope: ICC = 0.93 (95% CI, 0.84 to 0.97), LOA = 0.19 (95% CI, −0.37 to 0.75); LDslope: ICC = 0.95 (95% CI, 0.87 to 0.98), LOA = −0.30 (95% CI, −0.93 to 0.32); uncoupling: ICC = 0.88 (95% CI, 0.73 to 0.95), LOA = −0.27 (95% CI, −2.36 to 1.81); early diastolic uncoupling: ICC = 0.86 (95% CI, 0.68 to 0.94), LOA = −0.31 (95% CI, −2.63 to 2.01); and late diastolic uncoupling: ICC = 0.88 (95% CI, 0.72 to 0.95), LOA = −0.20 (95% CI, −2.25 to 1.86).

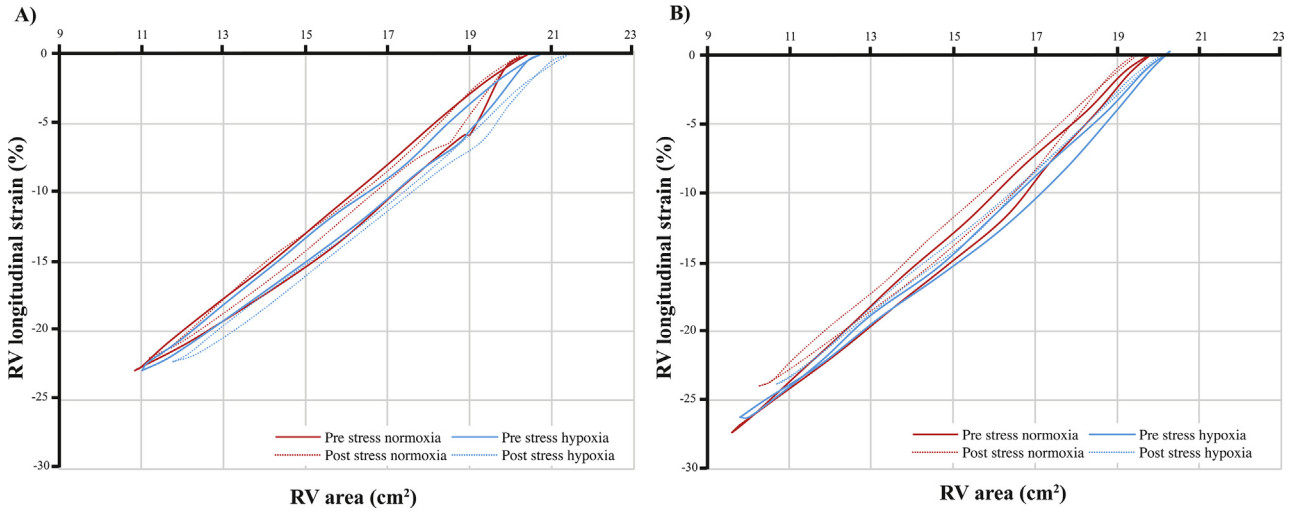

Figure 4 RV strain-area loops before and after 45-min high-intensity running exercise during rest **(A)** and stress **(B)**. *Red* and *blue lines* indicate normoxic and hypoxic exercise, respectively. *Solid* and *dotted lines* indicate before and after exercise, respectively.

LV Structure, Function and Mechanics

All LV structural, functional, and mechanical indices before and after 45-min high-intensity running exercise are displayed in Table 3. With the exception of LV s′ (exercise: $P = .78$), indices of LV systolic function (LV ejection fraction and LV global longitudinal strain) were significantly reduced following high-intensity exercise (exercise: $P < .001$). The reductions in LV ejection fraction and LV global longitudinal strain were more pronounced during stress versus rest echocardiography (exercise × stress: $P < .05$ for both; Figure 3B).

Exercise under Hypoxia. Changes in LV indices in response to exercise, examined at rest and/or during stress, were not different when performed under hypoxic conditions (hypoxia × exercise and exercise × hypoxia × stress: $P > .05$; Table 3). BP response patterns did not significantly differ between hypoxic and normoxic conditions (hypoxia and hypoxia × exercise: $P > .05$ for all; Table 3).

DISCUSSION

The aim of our study was to investigate the impact of a bout of high-intensity exercise under hypoxia versus normoxia on EICF on both ventricles. The main findings were as follows: (1) a 45-min bout of high-intensity exercise induced reductions in functional indices of right- and left-sided cardiac function and mechanics in healthy individuals; (2) the reductions in right- and left-sided cardiac function were more pronounced when echocardiography was performed during a standardized low-to-moderate intensity recumbent exercise challenge; and (3) there was no impact of hypoxia on exercise-induced reductions in right- and left-sided cardiac function and mechanics, either under rest or under stress. Taken together, these data indicate that EICF after short-term high-intensity exercise is not exaggerated under hypoxia, suggesting that an additional cardiac load (induced by hypoxia) on the right ventricle does not necessarily relate to exaggerated EICF in this setting.

High-Intensity Exercise–Induced Cardiac Fatigue

A 45-min bout of high-intensity running exercise induced reductions of both RV and LV function indicative of EICF, which were expressed mainly during a low-to-moderate intensity exercise challenge ("stress") compared with resting conditions. Earlier studies primarily investigated EICF after prolonged exercise (>180-min),[4,27] but recent research has revealed a dose-response relationship between EICF and the duration and intensity of exercise.[14,39] Our study adds the novel knowledge that EICF also occurs after relatively short periods of high-intensity exercise in both the right and left ventricles. Interestingly, in contrast to other short-term high-intensity EICF studies,[10,14,39] we also showed marked reductions in LV function, which may be due to the different type of exercise (running vs cycling). An explanation for our ability to detect EICF after a relatively short duration of exercise may relate to the post-exercise assessment of cardiac function during "stress" (i.e., low-to-moderate intensity exercise). Indeed, some of the indices of systolic function were primarily or only reduced when echocardiography was performed during the low-to-moderate intensity exercise challenge. For example, a reduction in RV longitudinal strain after exercise was apparent only during the low-to moderate-intensity exercise challenge (Figure 4A). We believe that echocardiographic assessment under low-to-moderate intensity exercise is more likely to detect EICF. The recovery phase after exercise is associated with a change in autonomic tone and vasodilation, which may result in post-exercise tachycardia and hypotension, respectively. These (para)sympathetic imbalance factors likely influence cardiac function measurements such as strain and therefore potentially mask the presence of EICF. Evaluation of cardiac function during high-intensity exercise, therefore, is preferred. However, one should consider the practical aspects (e.g., echocardiography is impossible during running) and that reliable speckle-tracking is extremely challenging with higher HRs (i.e., 70% of maximum HR).[40] Low-to-moderate intensity cycling exercise on a semirecumbent bicycle is both feasible and reliable and makes it possible to examine cardiac function during exercise. Using this approach, our data indicate that

Table 3 Hemodynamics and LV function and mechanics during rest and stress before and after exercise under normoxia and hypoxia

	Rest echocardiography				Stress echocardiography									
	Normoxia		Hypoxia		Normoxia		Hypoxia			*P* values				
Variables	Pre	Post	Pre	Post	Pre	Post	Pre	Post	H	E	S	H*E	E*S	E*H*S
Hemodynamics														
HR, bpm	68 ± 2	71 ± 3	74 ± 2	79 ± 3	113 ± 1	112 ± 1	111 ± 1	113 ± 1	.03	.07	**<.001**	.18	.10	.41
Systolic BP, mm Hg	121 ± 2	118 ± 2	124 ± 2	117 ± 2	143 ± 3	120 ± 3	141 ± 4	125 ± 3	.38	**<.001**	**<.001**	.56	**<.001**	.03
Diastolic BP, mm Hg	70 ± 2	69 ± 2	70 ± 2	67 ± 2	75 ± 2	60 ± 1	73 ± 2	60 ± 1	.47	**<.001**	.16	.98	**<.001**	.19
Mean arterial pressure, mm Hg	87 ± 1	85 ± 2	88 ± 2	84 ± 2	98 ± 2	80 ± 2	96 ± 2	82 ± 1	.99	**<.001**	.08	.75	**<.001**	**.04**
SpO_2, %	98 ± 0.2	98 ± 0.3	90 ± 0.5	90 ± 0.7	94 ± 0.8	95 ± 0.6	82 ± 1.0	83 ± 0.9	**<.001**	.17	**<.001**	.36	.86	.68
Structure														
LVEDV, mL	120 ± 7	113 ± 7	123 ± 6	113 ± 6	114 ± 6	109 ± 6	117 ± 7	110 ± 6	.30	**<.001**	.004	.46	.55	1.0
LVESV, mL	50 ± 2	52 ± 3	50 ± 3	49 ± 3	42 ± 2	45 ± 2	42 ± 2	43 ± 2	.24	.06	**<.001**	.17	.12	.76
LA diameter, mm	30 ± 1	29 ± 1	30 ± 1	28 ± 1	31 ± 1	27 ± 1	30 ± 1	27 ± 1	.79	**<.001**	.34	.72	.06	.25
LA volume, mL	38 ± 2	34 ± 0.3	39 ± 2	34 ± 2	38 ± 1	35 ± 1	39 ± 1	36 ± 1	.21	**<.001**	.18	.13	.12	.50
Function and mechanics														
Biplane LVEF, %	58 ± 1	56 ± 1	59 ± 1	56 ± 1	63 ± 1	58 ± 1	65 ± 1	60 ± 1	.008	**<.001**	**<.001**	.69	.005	.44
DTI s′, cm/sec	10 ± 0.4	11 ± 0.4	11 ± 0.3	11 ± 0.4	14 ± 0.5	13 ± 0.5	14 ± 0.4	14 ± 0.4	.04	.78	**<.001**	.98	.24	.19
DTI e′, cm/sec	18 ± 0.5	17 ± 0.6	19 ± 0.4	16 ± 0.4	22 ± 1.1	19 ± 0.7	21 ± 0.6	20 ± 0.5	.89	**<.001**	**<.001**	.45	.52	.09
DTI a′, cm/sec	8 ± 0.4	9 ± 0.3	9 ± 0.3	10 ± 0.3	—	—	—	—	.001	.054	—	.60	—	—
E, cm/sec	1.02 ± 0.03	0.85 ± 0.04	1.06 ± 0.03	0.86 ± 0.03	1.28 ± 0.05	1.14 ± 0.03	1.32 ± 0.04	1.16 ± 0.04	.09	**<.001**	<.001	.30	.37	.80
A, cm/sec	0.56 ± 0.02	0.57 ± 0.02	0.55 ± 0.02	0.62 ± 0.03	—	—	—	—	.004	.39	—	.18	—	—
E/A ratio	1.86 ± 0.06	1.6 ± 0.10	1.83 ± 0.07	1.41 ± 0.06	—	—	—	—	.048	**<.001**	—	.15	—	—
LV longitudinal strain, %	−20 ± 0.3	−20 ± 0.3	−21 ± 0.3	−20 ± 0.2	−23 ± 0.3	−21 ± 0.4	−24 ± 0.4	−22 ± 0.2	.01	**<.001**	<.001	.08	.05	.86
LV time of peak, sec	0.36 ± 0.01	0.36 ± 0.01	0.35 ± .01	0.34 ± 0.01	0.28 ± 0.01	0.29 ± 0.01	0.28 ± 0.01	0.29 ± 0.01	.14	**.03**	**<.001**	.22	**<.001**	.88

DTI, Doppler tissue imaging; *LA*, left atrium; *LVEDV*, LV end-diastolic volume; *LVEF*, LV ejection fraction; *LVESA*, LV end-systolic volume; *SpO_2*, oxygen saturation.
Linear mixed-models factors: *H*, hypoxia (comparison between all echocardiographic measurements performed under hypoxic vs normoxic conditions); *E*, exercise (comparison between all echocardiographic measurements performed before vs after 45-min high-intensity exercise); *S*, stress (comparison between all echocardiographic measurements performed during rest vs during stress); *E*S*, exercise × stress (comparison whether the change before vs after exercise is different measured during rest vs stress echocardiography); *H*E*, hypoxia × exercise (comparison whether the change before vs after exercise [EICF] is different during hypoxic vs normoxic conditions); *E*H*S*, exercise × hypoxia × stress (comparison whether the change before vs after exercise under hypoxic vs normoxic conditions was different when observed using rest vs stress echocardiography).
Data are expressed as mean ± SEM.

with short durations of high-intensity exercise, EICF occurs when assessment of cardiac function is performed during an exercise challenge.

Impact of Exercise under Hypoxia

Under hypoxic conditions, less oxygen is bound to hemoglobin and will therefore increase the demand on the cardiovascular system. In our population, this was reflected by higher resting HRs under hypoxia than under normoxia and the shorter distance covered under hypoxia than under normoxia during exercise, despite its being matched for relative intensity. More important, hypoxia has been shown to induce vasoconstriction of the pulmonary vasculature, leading to higher relative PVR, resulting in a higher PAP and consequently higher RV wall stress. Elevated PAP has been previously demonstrated at 3000-m altitude.[23] Although we were unable to directly measure PAP, we demonstrated shorter PAT and larger right atrial size, which indirectly supports the presence of an increase in PAP and therefore potentially wall stress. Also, the strain-area loop showed less uncoupling in late diastole and a trend toward a less steep systolic slope under hypoxia. In line with a previous study in patients with PAH, these changes are associated with higher PVR at rest.[28] Although we adopted a noninvasive approach and one should consider alternative explanations (i.e., related to the assessment), these findings support the presence of an elevated wall stress in our study under hypoxia. That aside, our hypothesis was rejected, as the 45-min high-intensity running exercise under hypoxia did not exaggerate RV EICF compared with exercise under normoxia. This suggests that changing cardiac workload does not necessarily change the magnitude of RV EICF and may not be the principal mechanism of RV EICF. One potential explanation for the lack of an impact of hypoxia on EICF may be that the exaggerated loading conditions under hypoxia were not sufficient enough at 3,000 m of simulated altitude, and/or the exposure time to the raised afterload of the right ventricle was not long enough to contribute to the EICF magnitude. There are also indications that hypoxia itself may induce cardiac dysfunction due to sustained low oxygen availability, but this seems to occur mainly during prolonged exposure.[41]

Our hypothesis originated from the accepted phenomenon of disproportionately higher relative wall stress in the right ventricle compared with the left ventricle during exercise but was also based on observations suggesting a larger magnitude of EICF in the right ventricle compared with the left ventricle.[11,14,15] For example, Stewart *et al*[10] examined the influence of high-intensity exercise on RV free wall and segmental LV strain EICF following 90 min of cycling[10] and found that the reduction in strain was more profound in the right ventricle than in the left ventricle. In their study, they demonstrated a relative reduction in RV strain of −17.5%, compared with −9.8% in our study, which supports a dose-response relationship. Our study is the first to our knowledge to directly compare the influence of normoxic and hypoxic conditions on EICF and demonstrated similar changes in both the right and left ventricles. Although mechanical changes in the right and left ventricles are independent of each other[27] and likely differ during exercise, our work suggests that (after)load dependency may be a less contributory factor to EICF as previously suggested. Alternatively, intrinsic myocardial factors such as β-adrenergic receptor desensitization[7,42] and oxidative stress[43] may play a more substantial role. Our study, however, is unable to provide further insight into these other possible mechanisms.

It is also of interest that following the 45-min high-intensity exercise, this study showed a lack of any RV dilation (no rightward shift of strain-area loop; Figure 4), as previously demonstrated following prolonged exercise.[27] Previous studies have demonstrated a serial and parallel impact from ventricular interdependence on LV filling secondary to RV volume and pressure overload.[27,44] This finding is consistent with those of other studies of high-intensity exercise of relative short durations compared with EICF studies of prolonged exercise, highlighting a possible dose response related to both intensity and duration.[10,14,27] In the shorter duration exercise intervention studies, the reduction in LV size occurs irrespective of changes in RV size, which provides additional support for an intrinsic mechanism independent of both the right and left sides of the heart. Moreover, the decreased uncoupling in the strain-area loop (Figure 4), indicating less longitudinal contribution to area change, in combination with a lack of RV dilatation, supports that the reduction in peak longitudinal strain after exercise (i.e., EICF) is more likely representative of intrinsic dysfunction.

Perspectives

The mechanisms underlying EICF are likely multifactorial and importantly may differ between the right and left ventricles. Previous researchers have proposed several influencing factors, including β-adrenergic receptor desensitization, oxidative stress, impaired calcium metabolism, and altered post-exercise loading. The influence of afterload conditions on RV EICF has rarely been explored. This study demonstrated that under hypoxic conditions at 3,000-m altitude (FiO_2 14.5%), the magnitude of EICF is not augmented, and thus it may be less likely that a role for elevated RV wall stress is relevant. Although knowledge about the clinical long-term consequences of these temporary post-exercise reductions in cardiac function is lacking, it has been hypothesized that this may be associated with myocardial damage and worse clinical outcomes. The absence of an effect in EICF between exercising at sea level (normoxia) and 3,000-m altitude (hypoxia) is interesting, but long-term studies that link these findings to prolonged follow-up are needed to better understand these findings. The novel strain-area loop, introduced to assess hemodynamics noninvasively, provided substantial added value in this study, as it was sensitive enough to detect changes due to hypoxia. This novel technique seems promising in providing physiologic and pathophysiologic insight and might be of added value in clinical practice.[5,27,28,37,45-48]

Limitations

We implemented a standardized exercise challenge to prevent a pre- and post-exercise (para)sympathetic imbalance during echocardiographic evaluation. In contrast to the methodology of Stewart *et al*[14] (aiming at 100 beats/min), we set our target HR at 110 to 120 beats/min during the exercise challenge, to better mimic cardiac function during exercise. This higher HR may impede speckle-tracking quality. With current frame rates used, we experienced that tracking was still good to excellent for LV global longitudinal strain and RV free wall strain.

A further limitation is that we did not obtain direct measures of RV wall stress, as this would require invasive procedures. Alternatively, we used only noninvasive echocardiographic, indirect measures to estimate any potential difference in RV wall stress under hypoxia compared with normoxia. When considering these indirect indices, some studies have demonstrated value of PAT during stress to estimate PAP in patients with PAH, whereas others have questioned the outside of the normal HR range (<60 or >100 beats/min).[24,26] It is clear that a more robust assessment of PAP would provide added

support to the well-established physiologic concepts and understanding of hypoxia and pulmonary hemodynamics. Previous studies have applied strain-area loops to patients with PAH and demonstrated an association between PVR and late diastolic uncoupling and Sslope during rest only.[28] Further work should aim to validate the strain-area loops during stress.

Finally, for technical reasons we evaluated only right heart function and hemodynamics during low-to-moderate stress echocardiography rather than during the high-intensity running exercise.

CONCLUSION

There was no impact of hypoxia on the magnitude of EICF in the right and left ventricles after a 45-min bout of high-intensity exercise. This finding suggests that any potential increase in loading conditions does not automatically exacerbate EICF in this setting.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2020.12.003.

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