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ORIGINAL ARTICLE

Effects of exercise in normobaric hypoxia on hemodynamics during muscle metaboreflex activation in normoxia

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Abstract

Purpose Little is known about the cardiovascular effects of the transition from exercise in hypoxia (EH) to normoxia. This investigation aimed to assess hemodynamics during the metaboreflex elicited in normoxia after EH.

Methods Ten trained athletes (four females and six males, age 35.6 ± 8.4 years) completed a cardiopulmonary test to determine the workload at anaerobic threshold (AT). On separate days, participants performed three randomly assigned exercise sessions (10 min pedalling at 80% of AT): (1) one in normoxia (EN); (2) one in normobaric hypoxia with FiO_2 15.5% (EH15.5%); and (3) one in normobaric hypoxia with FiO_2 13.5% (EH13.5%). After each session, the following protocol was randomly assigned: either (1) post-exercise muscle ischemia after cycling for 3 min, to study the metaboreflex, or (2) a control exercise recovery (CER) session, without any metaboreflex stimulation.

Results The main result were that both EH15.5% and EH13.5% impaired ($p < 0.05$) the ventricular filling rate response during the metaboreflex (− 18 ± 32 and − 20 ± 27 ml s^{-1}), when compared to EN (+ 29 ± 32 ml s^{-1}), thereby causing a reduction in stroke volume response (− 9.1 ± 3.2, − 10.6 ± 8.7, and + 5 ± 5.7 ml for EH15.5%, EH13.5% and EN test, respectively, $p < 0.05$). Moreover, systemic vascular resistance was increased after the EH15.5% and the EH13.5% in comparison with the EN test.

Conclusions These data demonstrate that moderate exercise in hypoxia impairs the capacity to enhance venous return during the metaboreflex stimulated in normoxia. Overall, there is a functional shift from a flow to vasoconstriction-mediated mechanism for maintaining the target blood pressure during the metaboreflex.

Keywords Cardiac pre-load · Venous return · Stroke volume · Cardiac output · Blood pressure

Abbreviations

AT	Anaerobic threshold
CER	Control exercise recovery
CO	Cardiac output
COX	Cerebral tissue oxygenation
CPX	Cardiopulmonary test
DBP	Diastolic blood pressure
DT	Diastolic time
EH	Exercise in acute hypoxia
EN	Exercise in normoxia
HR	Heart rate
MAP	Mean blood pressure
NIRS	Near-infrared spectroscopy
NO	Nitric oxide
PEMI	Post-exercise muscle ischemia
PEP	Pre-ejection period
SBP	Systolic blood pressure
SNA	Sympathetic nervous activity
SO_2	Peripheral blood O_2 saturation
SV/VET	Stroke volume/ventricular ejection time ratio
SV	Stroke volume
SVR	Systemic vascular resistance
VER	Mean ventricular ejection rate
VET	Left ventricular ejection time

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VFR	Ventricular filling rate
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}O_{2\,max}$	Maximum oxygen uptake
W_{max}	Maximum workload
Z0	Thoracic impedance

Introduction

Both dynamic exercise and hypoxia are effective stimuli for cardiovascular changes and sympathetic nervous activity (SNA) (Bourdillon et al. 2017; Crisafulli et al. 2015; Fisher et al. 2013; Nobrega et al. 2014; Dinenno 2016; Kara et al. 2003; Marshall 2015) and the effect of their combination has been assessed in a number of studies (Casey and Joyner 2011, 2012; Rowell and Blackmon 1987; Siebenmann and Lundby 2015; Wagner 2000). Collectively, it appears well established that during submaximal exercise in acute hypoxia, muscle blood flow and cardiac output (CO) are greater than in normoxia for a given oxygen uptake. This is due to muscle vasodilation and increased CO arising from an accelerated heart rate HR which is driven by the stimulation of arterial chemoreceptors and a concomitant reduction in arterial baroreflex activity, which together concur to enhance SNA (Bourdillon et al. 2017).

Recently, the development of commercially available normobaric hypoxic chambers, tents, and ventilatory circuits have provided available tools for exercising in normobaric hypoxia without the need to dwell at terrestrial altitude. The rationale is to stimulate, at least theoretically, the same body adaptations observed at altitude, i.e., in hypobaric hypoxia (Millet et al. 2010, 2016; Wilber 2001). These devices expose the subjects to acute hypoxemia, suddenly followed by normoxia, at the cessation of the hypoxic stimulus. The body homeostasis is then continuously disturbed by the transition from hypoxia to normoxia and cardiovascular regulating mechanisms are challenged. This intermittent hypoxia exposure is now extensively used with both pathogenic and beneficial effects, as a "matter of dose" including the severity level of hypoxia (Navarrete-Opazo and Mitchell 2014).

However, little is known about the transition from exercise during acute hypoxia to normoxia in terms of cardiovascular regulation. Exercise in acute hypoxia (EH) is known to increase the production of a variety metabolites, such as nitric oxide (NO), adenosine, and prostaglandin-derived factors (Casey and Joyner 2012). These metabolites exert vasodilating effects and restrain vasoconstriction due to the hypoxemia-induced increase in SNA (Dinenno 2016). These metabolites are also believed to stimulate those nerve endings within muscles that are sensitive to metabolite accumulation. This can trigger the "muscle metaboreflex", which is able to enhance SNA (Amann et al. 2011; Crisafulli et al. 2009, 2011; Marongiu et al. 2013; Milia et al. 2015; O'Leary and Augustyniak 1998; Sala-Mercado et al. 2006; Strange et al. 1993). Thus, in one way these metabolites act as vasodilator, inducing the so-called "compensatory vasodilation", but contrarily may produce vasoconstriction as a result of the increased SNA activity elicited by the metaboreflex.

It should also be taken into consideration that EH induces a reduction in SNA after returning to normoxic conditions (Gujic et al. 2007). This would lower SNA-induced global arteriolar constriction, thus reducing systemic vascular resistance (SVR). Furthermore, it is possible that metabolites accumulated during EH may vasodilate arterial and venous beds, thereby reducing gross vascular resistance and impairing venous return and cardiac pre-load.

Hence, the consequences of EH upon cardiovascular regulation seem complex and multifaceted. Cardiovascular homeostasis can be challenged and cardiovascular events, such as blood pressure drops, may occur.

The cardiovascular response arising from the activation of the muscle metaboreflex is attracting growing interest since it has been demonstrated to play a pivotal role in hemodynamic adjustment to exercise. This reflex provides continuous feedback to the cardiovascular control areas on the metabolic status of contracting muscles (Amann et al. 2011; Crisafulli et al. 2015; Fisher et al. 2013; Nobrega et al. 2014). During the metaboreflex, all the main hemodynamic modulators (i.e., chronotropism, contractility, pre-load and after-load) are recruited (Augustyniak et al. 2001; Crisafulli et al. 2007, 2009; Crisafulli 2017; Magnani et al. 2018; Marongiu et al. 2013; Milia et al. 2015; O'Leary and Augustyniak 1998; Roberto et al. 2012, 2017; Sala-Mercado et al. 2006).

Taking into account that little is known about the cardiovascular effects of the transition from EH to normoxia, the purpose of this investigation was to assess the hemodynamic responses to the metaboreflex elicited during normoxia immediately after EH bouts. Considering that metabolite accumulation during EH may vasodilate arterial and venous beds, we hypothesised that a session of EH led to a reduction in global vascular resistance and blunted the blood pressure change during the metaboreflex recruited following EH. In addition, it was hypothesised that after EH, the capacity to squeeze (i.e., vasoconstrict) the venous bed and propel blood volumes towards the heart was reduced, which would dampen the possibility to reach the target blood pressure by utilising the pre-load and the stroke volume (SV) reserve.

Methods

Participants

Seventeen healthy Caucasian subjects (including 7 females) aged 22–50 years agreed to participate in this

study. All were well-trained athletes regularly involved in endurance competitions (cycling, triathlon, and marathon running) and were considered healthy on the basis of a preliminary medical examination (see experimental design). None had any history of cardiac or respiratory disease or were taking any medication at the time of the experiment. The protocol was not completed by all the subjects as seven of them complained of unbearable fatigue during the EH test. Thus, they were excluded from results, which included the remaining ten subjects (four females and six males). Their age, body mass, and height were 35.6 ± 8.4 years, 66.8 ± 12.6 kg, and 174.6 ± 9.3 cm, respectively. All the subjects were normotensive and nonsmokers and were unaware of the nature of the study. Subjects were asked to refrain from alcoholic beverages and caffeine for at least 24 h before the experimental sessions. The study was performed according to the Declaration of Helsinki and was approved by the ethics committee of the University of Cagliari. Written informed consent was obtained from all the participants included in the study.

Experimental design

Preliminary test

Subjects underwent a general medical visit. Afterward, a cardiopulmonary test (CPX) with a gas analyser (VO2000, MedGraphics St. Paul, MN, USA), calibrated immediately before each CPX, was conducted on a mechanically braked cycle ergometer (Monark 828E, Vansbro, Sweden). The test consisted of a linear increase of workload (30 W min^{-1}), starting at 30 W, at a pedalling frequency of 60 rpm, until exhaustion, which was taken as the point at which the subject was unable to maintain a pedalling rate of at least 50 rpm. During the CPX, anaerobic threshold (AT), maximum workload (W_{max}), and maximum oxygen uptake ($\dot{V}O_{2\,max}$) were measured. Achievement of $\dot{V}O_{2\,max}$ was considered as the attainment of at least two of the following criteria: (1) a plateau in $\dot{V}O_2$ despite increasing workload (< 80 ml min^{-1}); (2) respiratory exchange ratio (RER) above 1.10; and (3) heart rate (HR) ± 10 beats min^{-1} of predicted maximum HR calculated as 220-age (Howley et al. 1995). Anaerobic threshold was determined using the *V*-slope method, which detects AT using a computerised regression analysis of $\dot{V}CO_2$ slopes vs. the carbon dioxide production ($\dot{V}CO_2$) plot during exercise (Beaver et al. 1986). $\dot{V}O_{2\,max}$ was calculated as the average $\dot{V}O_2$ during the final 30 s of the incremental test.

During the preliminary test, participants familiarised with the laboratory equipment and staff. This allowed habituation to the environment and the ergometer that was otherwise identical to the exercise under hypoxia sessions.

Exercise under hypoxia sessions

After the preliminary visit (interval 4–7 days), each subject completed, in separate days (interval 3–5 days), three randomly assigned exercise sessions: (1) an exercise session in normoxia (EN); (2) an exercise session in normobaric hypoxia with a FiO_2 of 15.5% (EH15.5%), which simulated the partial pressure of oxygen at an altitude of 2500 m; (3) and finally, an exercise session in normobaric hypoxia with a FiO_2 of 13.5% (EH13.5%), which simulated an altitude of 3500 m. Exercise sessions were conducted on the same bicycle employed for the CPX test. During each session, the subject exercised for 10 min at 80% of the AT previously assessed during the CPX. Throughout the sessions, the subject was connected with a facemask to an hypoxic gas generator (Everest Summit II Generator, Hypoxico, New York, USA). This device utilises a molecular sieve system that uses zeolites to separate nitrogen from O_2 in the air, and consequently provides a nitrogen-rich gas mixture, to purge the atmosphere within the container. Connected to the container, and in conjunction with a one-way pressure relief valve, the hypoxic generators can reduce the concentration of O_2 up to about 12.5%, which corresponds approximately to the O_2 pressure at 4000 m altitude. The level of oxygen concentration was adjusted by the operator on the basis of an oxygen analyser provided with the device (Maxtec, Handi+, Salt Lake City, UT, USA). The applied generator setting was blinded to the athlete and controlled every minute by the operator. This device is commonly used for training in normobaric hypoxia (Schega et al. 2016). Before commencing sessions, the athlete was connected to the hypoxic generator and rested for 3 min to reach a stable condition in respiratory gas exchange. Throughout sessions, subjects were also monitored for peripheral blood O_2 saturation (SO_2), measured by finger pulse oximetry. To further detect the real presence of body hypoxemia, cerebral tissue oxygenation (COX) was assessed with near-infrared spectroscopy (NIRS) (Nonin, SenSmart X-100, Plymouth, MN, USA). Briefly, one NIRS sensor was placed on the left forehead above the eyebrow. The probe was covered and maintained with a headband and taped to reduce the intrusion of extraneous light. Care was taken to ensure that the attached probe did not constrict the head and did not block the circulation.

Test for metaboreflex function assessment

A brief recovery was allowed after each exercise sessions (10 min). Then (within 15 min), the participants were subjected to the following protocol, randomly assigned to study

the effects of hypoxic exercise on hemodynamic responses during the metaboreflex:

– *Post-exercise muscle ischemia (PEMI)* This session was composed of 3 min of resting, followed by 3 min of exercise, consisting of cycling at mild intensity (30% of W_{max} measured during the CPX) at 60 rpm. The cycling period was followed by 3 min of PEMI on the right leg. Ischemia was induced by rapidly (in less than 3 s) inflating, at the cessation of exercise, a thigh cuff, to 50 mmHg above peak exercise systolic pressure. The cuff was kept inflated for 3 min. A further 3 min of recovery were allowed after the cuff was deflated, for a total of 6 min of recovery. Thus, the total PEMI session duration was 12 min. This protocol, although conducted at mild intensity, has demonstrated the ability to "trap" muscle metabolites in the exercising limb and to stimulate the metaboreceptors (Crisafulli et al. 2008; Scott et al. 2002). PEMI is effective in eliciting substantial hemodynamic responses in terms of cardiac contractility, pre-load, and after-load (Crisafulli et al. 2008; Marongiu et al. 2013; Milia et al. 2015; Roberto et al. 2012; Scott et al. 2002). This response is suggested to be mediated only by the metaboreflex, since in this setting, the central command and mechanoreflex activation are no longer present (Bastos et al. 2000; Crisafulli et al. 2011; Nobrega et al. 2014).

– *Control exercise recovery (CER) session* The same rest-exercise protocol used for PEMI was used, but the recovery was conducted without cuff inflation.

The PEMI and the CER tests were randomised and a recovery was allowed between sessions (approximately 15 min). Recovery was considered complete when HR was not higher than 5 bpm compared with the pre-exercise level.

The study design is summarised by Fig. 1. All experiments were carried out in a temperature-controlled, air-conditioned room (22 °C—relative humidity 50%). To eliminate any potential effect of hormonal changes on hemodynamics, all women were tested in the follicular phase of the menstrual cycle (i.e., within 10 days from the start of menstruation) as self-reported.

Hemodynamic assessment during metaboreflex activation

Throughout sessions of metaboreflex activation, subjects' hemodynamics were collected by impedance cardiography (NCCOM 3, BoMed Inc., Irvine, CA), which has been previously utilised in similar experimental settings (Crisafulli et al. 2008, 2009, 2011). This device allows for continuous, non-invasive, hemodynamic evaluation. The rationale of its use is based on the fact that pulsatile aortic blood flow, due to ventricular systole, induces proportional fluctuation

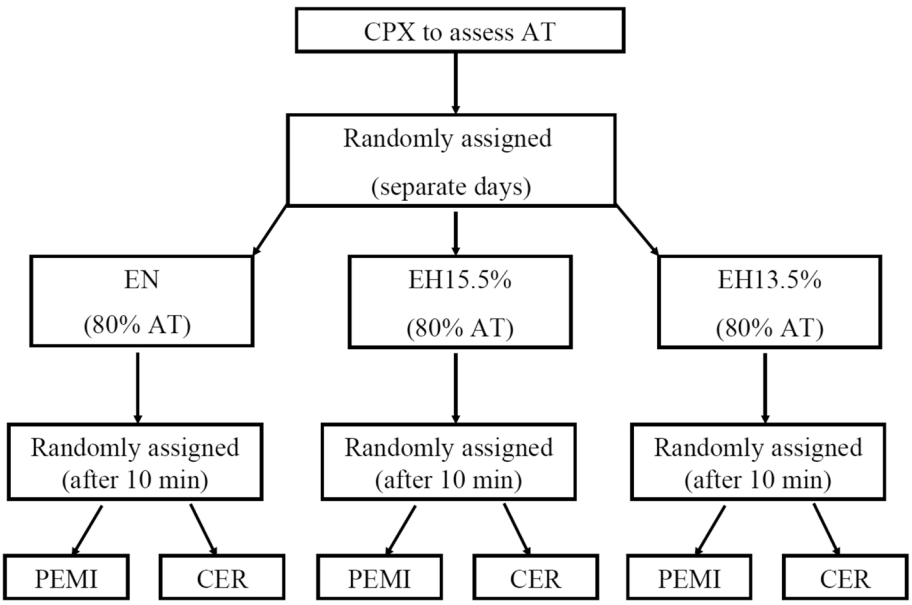

Fig. 1 Study design. After the cardiopulmonary test (CPX, interval 4–7 days), subjects underwent in separate days (interval 3–5 days), three randomly assigned exercise sessions, each lasting 10 min at a workload corresponding to 80% of the AT previously measured during the CPX. (1) Exercise session in normoxia (EN); (2) exercise session in normobaric hypoxia with a FiO_2 of 15.5% (EH15.5%); (3) and finally, an exercise session in normobaric hypoxia with a FiO_2 of 13.5% (EH13.5%). After each exercise session, participants underwent randomly assigned the post-exercise muscle ischemia (PEMI) and the control exercise recovery (CER) test to study the metaboreflex. See text for more details

in electrical conductivity. Therefore, changes in thoracic impedance (Z0) are representative of the blood volume ejected during systole. By employing standard formulas, the SV can be estimated (Bernstein 1986). The data acquisition procedure is described in detail in previous research (Crisafulli et al. 2008, 2009, 2011). Briefly, analogue traces provided by impedance cardiography along with ECG were collected and stored by means of a digital chart recorder (ADInstruments, PowerLab 8sp, Castle Hill, Australia) at a sampling rate of 500 Hz. Z0 and its first derivative were collected, stored, and analysed afterwards offline. Stored traces were also used to calculate beat-to-beat HR, which was estimated as the reciprocal of the electrocardiogram R–R interval. The pre-ejection period (PEP) and the left ventricular ejection time (VET) were also measured from impedance traces, as shown in detail by previous published paper (Sainas et al. 2016). Diastolic time (DT) was measured by subtracting the sum of PEP and VET from the cardiac cycle total period. The ventricular filling rate (VFR), which is a measure of the mean rate of diastolic blood flux, was obtained by dividing SV by DT (Gledhill et al. 1994; Marongiu et al. 2013; Milia et al. 2015). The mean ventricular ejection rate (VER), an index of myocardial performance, was obtained by calculating the SV/VET ratio (Gledhill et al. 1994; Sanna et al. 2017). CO was obtained as a product of SV and HR.

A standard manual sphygmomanometer was employed for systolic (SBP) and diastolic (DBP) blood pressure assessment, which was performed on the non-dominant arm by the same physician throughout all protocol sessions. Mean arterial blood pressure (MAP) was calculated with the formula by Moran et al. (1995) (Sainas et al. 2016), which takes into account changes in the diastolic and systolic time due to exercise-induced tachycardia in calculating MAP. To have a measure of global vascular resistance, SVR was calculated by multiplying the MAP/CO ratio by 80, where 80 is a conversion factor to change units to standard resistance units.

Data analysis

Data are shown as mean ± SD. All collected data were averaged over 1 min. Differences in SO_2 and COX were assessed using a two-way analysis of variance (ANOVA) (factors of time and condition: EN, EH15.5%, and EH13.5%) followed by Bonferroni post hoc where appropriate. Hemodynamic values at rest, at the third minute of exercise, and at the third minute of PEMI (when a steady state in metaboreflex activity was expected to be reached) during the metaboreflex tests were assessed. Two-way ANOVA was utilised to compare hemodynamic data for the effects of test (PEMI and CER) and condition (EN, EH15.5%, and EH13.5% sessions) followed by Bonferroni post hoc when appropriate. To further assess the metaboreflex activity, the following procedure was employed: the difference in the level of variables between the post-exercise ischemia phases of the PEMI and the CER test at the third minute of recovery was calculated. This procedure enabled metaboreflex response to be assessed, i.e., the response due to the metaboreflex activity (Crisafulli et al. 2013; Milia et al. 2015). Differences in measured variables due to metaboreflex response were assessed by means of the one-way repeated measures ANOVA test, followed by Bonferroni post hoc, as appropriate. Statistical analysis was performed by utilising commercially available software (GraphPad Prism). Statistical significance was established as a p value of < 0.05 in all the cases.

Results

Results of the CPX test are shown in Table 1. During exercise sessions, subjects cycled at a workload corresponding to 187.2 ± 3.4 W, i.e., 80% of AT. The time course of SO_2 and COX is illustrated in Fig. 2. There was a progressive reduction in SO_2 throughout the EH15.5% and EH13.5% sessions with respect to EN (panel A). Even though the EH13.5% appeared to induce a stronger SO_2 reduction than the EH15.5% test, no statistical difference was demonstrated between sessions, with the exception of the second minute of exercise. Panel B of Fig. 2 shows that COX (reported as % changes from rest) progressively decreased during the EH15.5% and EH13.5% sessions as compared to EN, without any significant difference between the two exercise sessions conducted in hypoxia.

Table 2 shows the mean values of hemodynamic parameters gathered during rest periods preceding the PEMI and the CER tests. The SV was the only parameter affected by condition, as it was on average reduced by the EH15.5% and the EH13.5% sessions, as compared to EN. Table 3 shows that at the third minute of exercise, preceding the PEMI and the CER manoeuvres, none of the hemodynamic parameters were influenced by test or condition.

Table 1 Metabolic data values at the anaerobic threshold (AT) and at maximum workload (Wmax) collected during cardiopulmonary test

	AT	W_{max}
Workload (W)	234 ± 38	297 ± 58
$\dot{V}O_2$ (ml kg^{-1} min^{-1})	40.1 ± 10.9	45.8 ± 11.9
$\dot{V}O_2$ (ml min^{-1})	2537 ± 556	2903 ± 626
$\dot{V}CO_2$ (ml min^{-1})	2817 ± 650	3697 ± 960
RER	1.11 ± 0.09	1.27 ± 0.14
$\dot{V}E$ (l min^{-1})	68.8 ± 15.5	98.1 ± 27.9
HR (bpm)	155 ± 7	168 ± 6

Values are mean ± SD. $N = 10$

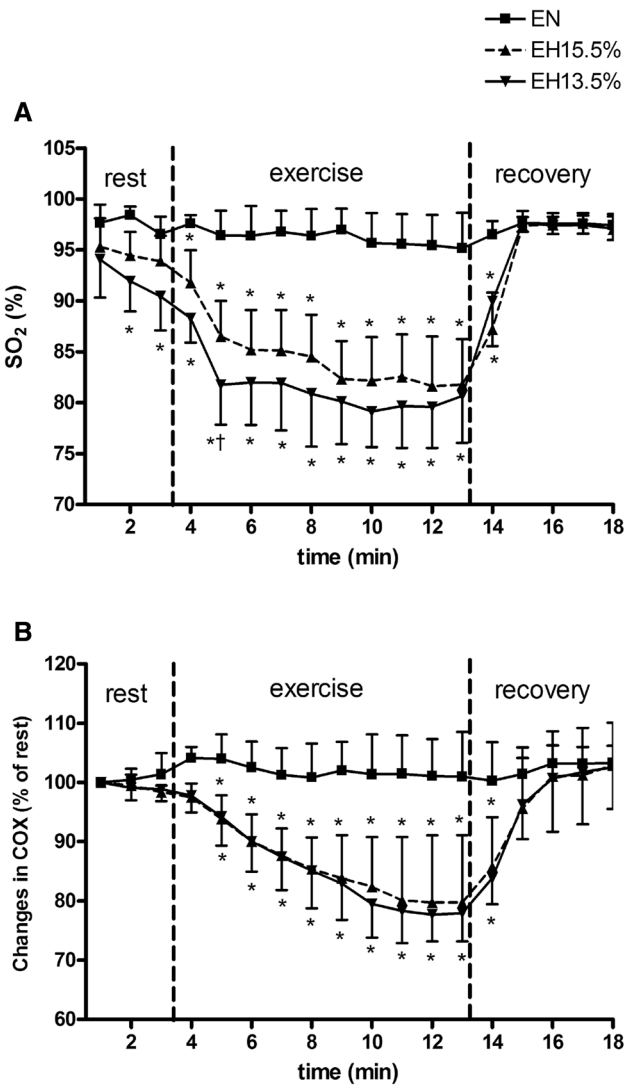

Fig. 2 Changes in the level of peripheral blood O_2 saturation (SO_2, **a** during the sessions of exercise in normoxia (EN), in normobaric hypoxia with a FiO_2 of 15.5% (EH15.5%), and in normobaric hypoxia with FiO_2 of 13.5% (EH13.5%). **b** Shows changes in cerebral oxygenation (COX) during the same tests. Values are mean ± SD. $N = 10$. $^{*}p < 0.05$ vs. EN; $^{\dagger}p < 0.05$ vs. EH15.5%

Figures 3 and 4 depict hemodynamic variables obtained during the third minute of recovery of the PEMI and the CER tests. Panel A of Fig. 3 demonstrates that HR was on average higher after the EH15.5% and EH13.5% sessions, with respect to EN ($p = 0.042$ for condition). No significant difference was found for HR response between conditions (panel B). The SV was significantly reduced by exercise in hypoxia ($p = 0.042$ for condition, panel C). Moreover, exercise in hypoxia significantly reduced SV response (panel D) with respect to EN. The CO was unchanged by exercise in hypoxia, neither in absolute values (panel E), nor in terms of its response (panel F).

Figure 4a illustrates that absolute values of VFR was unaffected by exercise in hypoxia. However, its response was significantly lower after EH15.5% and EH13.5% as compared to EN (panel B). Similarly, VER was not significantly different among treatment with hypoxic gases (panel C), but its response was reduced in EH15.5% and EH13.5% sessions in comparison with EN (panel D). The MAP was significantly influenced by test, as this parameter was higher during the PEMI than during the CER manoeuvres ($p = 0.0005$ for test effect, panel E) without any detectable difference in its response (panel F). Finally, panel G of Fig. 4 demonstrates that the PEMI tests induced higher SVR than the CER tests ($p = 0.039$ for test effect). Furthermore, the response in this parameter was more elevated after both sessions of exercise in hypoxia than in normoxia (panel H).

Discussion

The main aim of the present study was to discover whether a single bout of hypoxic exercise could alter the cardiovascular response during the metaboreflex activated immediately in normoxia after exercise. Our hypothesis was that the capacity to globally vasoconstrict both the arteriolar and the venous beds was impaired due to production of vasodilating metabolites able to restrain the metaboreflex-induced vasoconstriction (Casey and Joyner 2011). It has, in fact, been demonstrated that during the metaboreflex, both arteriolar and venous circulation is constricted by the augmented sympathetic tone (Crisafulli 2017; Marongiu et al. 2013; Nobrega et al. 2014; Sheriff et al. 1998; Shoemaker et al. 2005).

Although no direct measure of venous constriction was gathered, results show that EH led to an impairment in the capacity to enhance venous return, as testified by the reduction in the VFR response. This parameter has already been utilised in recent research on the metaboreflex and has been able to detect reductions in venous return and diastolic functions during the metaboreflex (Crisafulli et al. 2009; Magnani et al. 2018; Marongiu et al. 2013; Mulliri et al. 2016; Roberto et al. 2017). The lack of any VFR response indicates that the capacity to centralise blood volume was negatively affected by EH and that this occurrence led to a reduction in the SV response. Indeed, SV was lower after EH sessions, both in terms of absolute values and of its response. Several researchers have demonstrated that the capacity to increase cardiac pre-load is pivotal to achieving normal hemodynamics during the metaboreflex (Bastos et al. 2000; Crisafulli et al. 2009; Marongiu et al. 2013; Milia et al. 2015). Studies have reported that the capacity to centralise blood volumes, by means of visceral and venous constriction, supports ventricular performance, by recruiting the Frank–Starling mechanism. This allows SV to increase

Table 2 Hemodynamic values during rest periods preceding the post-exercise muscle ischemia (PEMI) and the control exercise recovery (CER) tests in the three conditions: *EN* exercise in normoxia; *EH15.5%* exercise in hypoxia with $FiO_2 = 15.5\%$; and *EH13.5%* exercise in hypoxia with $FiO_2 = 13.5\%$

	EN	EH15.5%	EH13.5%	*p* value condition effect	*p* value test effect
HR (bpm)	PEMI 77 ± 11 CER 81 ± 10	PEMI 84 ± 9 CER 79 ± 8	PEMI 88 ± 9 CER 83 ± 9	0.102	0.338
SV (ml)	PEMI 62.2 ± 12.7 CER 64.5 ± 8.7	PEMI 53.1 ± 10.7 CER 54.8 ± 12.6	PEMI 52.9 ± 9.7 CER 59.0 ± 15.6	0.048	0.327
CO (l min^{-1})	PEMI 4.76 ± 0.9 CER 5.25 ± 1.00	PEMI 4.35 ± 1.13 CER 4.59 ± 1.19	PEMI 4.74 ± 1.15 CER 4.86 ± 1.19	0.306	0.322
VFR (ml s^{-1})	PEMI 161.0 ± 38.7 CER 194.0 ± 56.5	PEMI 174.2 ± 57.5 CER 152.1 ± 52.4	PEMI 177.2 ± 54.4 CER 174.4 ± 49.6	0.636	0.841
VER (ml s^{-1})	PEMI 259.8 ± 59.4 CER 268.9 ± 45.6	PEMI 240.0 ± 45.0 CER 241.8 ± 60.3	PEMI 242.9 ± 52.7 CER 255.7 ± 59.1	0.387	0.573
MAP (mmHg)	PEMI 81.6 ± 9.1 CER 83.1 ± 8.4	PEMI 81.9 ± 7.8 CER 84.6 ± 8.5	PEMI 85.6 ± 7.6 CER 83.5 ± 6.8	0.683	0.735
SVR (dynes s^{-1} cm^{-5})	PEMI 1429.3 ± 379.3 CER 1310.8 ± 282.9	PEMI 1480.9 ± 289.7 CER 1649.6 ± 440.3	PEMI 1530.6 ± 424.2 CER 1474.9 ± 471.4	0.275	0.985

Values are mean ± SD. $N = 10$

Table 3 Hemodynamic values at the third minute of exercise of the post-exercise muscle ischemia (PEMI) and the control exercise recovery (CER) tests in the three conditions: *EN* exercise in normoxia; *EH15.5%* exercise in hypoxia with $FiO_2 = 15.5\%$; and *EH13.5%* exercise in hypoxia with $FiO_2 = 13.5\%$

	EN	EH15.5%	EH13.5%	*p* value condition effect	*p* value test effect
HR (bpm)	PEMI 117 ± 14 CER 119 ± 13	PEMI 117 ± 10 CER 116 ± 10	PEMI 117 ± 10 CER 119 ± 12	0.823	0.831
SV (ml)	PEMI 99.7 ± 32.9 CER 124.4 ± 42.8	PEMI 115.6 ± 35.7 CER 125.3 ± 37.4	PEMI 105.1 ± 27.3 CER 109.7 ± 28.7	0.455	0.134
CO (l min^{-1})	PEMI 11.83 ± 4.3 CER 14.75 ± 4.9	PEMI 13.64 ± 5.06 CER 14.67 ± 5.08	PEMI 12.52 ± 4.30 CER 13.27 ± 4.63	0.694	0.206
VFR (ml s^{-1})	PEMI 488.4 ± 195.8 CER 640.4 ± 204.9	PEMI 556.4 ± 221.6 CER 621.0 ± 240.8	PEMI 531.7 ± 239.7 CER 572.9 ± 221.1	0.869	0.138
VER (ml s^{-1})	PEMI 510.1 ± 180.4 CER 585.8 ± 199	PEMI 572.2 ± 191.7 CER 586.7 ± 169.9	PEMI 513.5 ± 135.8 CER 544.8 ± 149.6	0.650	0.367
MAP (mmHg)	PEMI 97.9 ± 11.7 CER 97.9 ± 9.2	PEMI 96.3 ± 6.3 CER 94.6 ± 5.4	PEMI 95.9 ± 8.6 CER 93.1 ± 7.6	0.522	0.193
SVR (dynes s^{-1} cm^{-5})	PEMI 768.5 ± 432.3 CER 609.3 ± 272.0	PEMI 623.3 ± 193.9 CER 578.6 ± 210.5	PEMI 664.4 ± 176.5 CER 620.6 ± 221.4	0.424	0.492

Values are mean ± SD. $N = 10$

during the metaboreflex (Bastos et al. 2000; Crisafulli et al. 2009; Marongiu et al. 2013; Milia et al. 2015; Sheriff et al. 1998; Shoemaker et al. 2005).

It is to be noted that the impaired SV was not compensated by any HR response. Although HR was on average higher during both the PEMI and the CER test after EH sessions, the response in this variable (i.e., the difference between the PEMI and the CER test) was unaffected by condition. This is in good accordance with the concept that HR does not usually participate in the hemodynamic adjustments during the metaboreflex obtained by PEMI (Crisafulli et al. 2011, 2015; Fisher et al. 2013; Iellamo et al. 1999; Nishiyasu et al. 1994). This finding supports the concept that during PEMI, reductions in cardiac pre-load are compensated mainly by arteriolar constriction, rather than by chronotropic increments (Crisafulli et al. 2011; Mulliri et al. 2016; Roberto et al. 2017).

Another consequence of the impaired VFR response was the reduced capacity to increase VER during the metaboreflex. This parameter is considered to be directly related to myocardial performance and it is sensible to make modifications in both cardiac inotropism and pre-load (Gledhill et al.

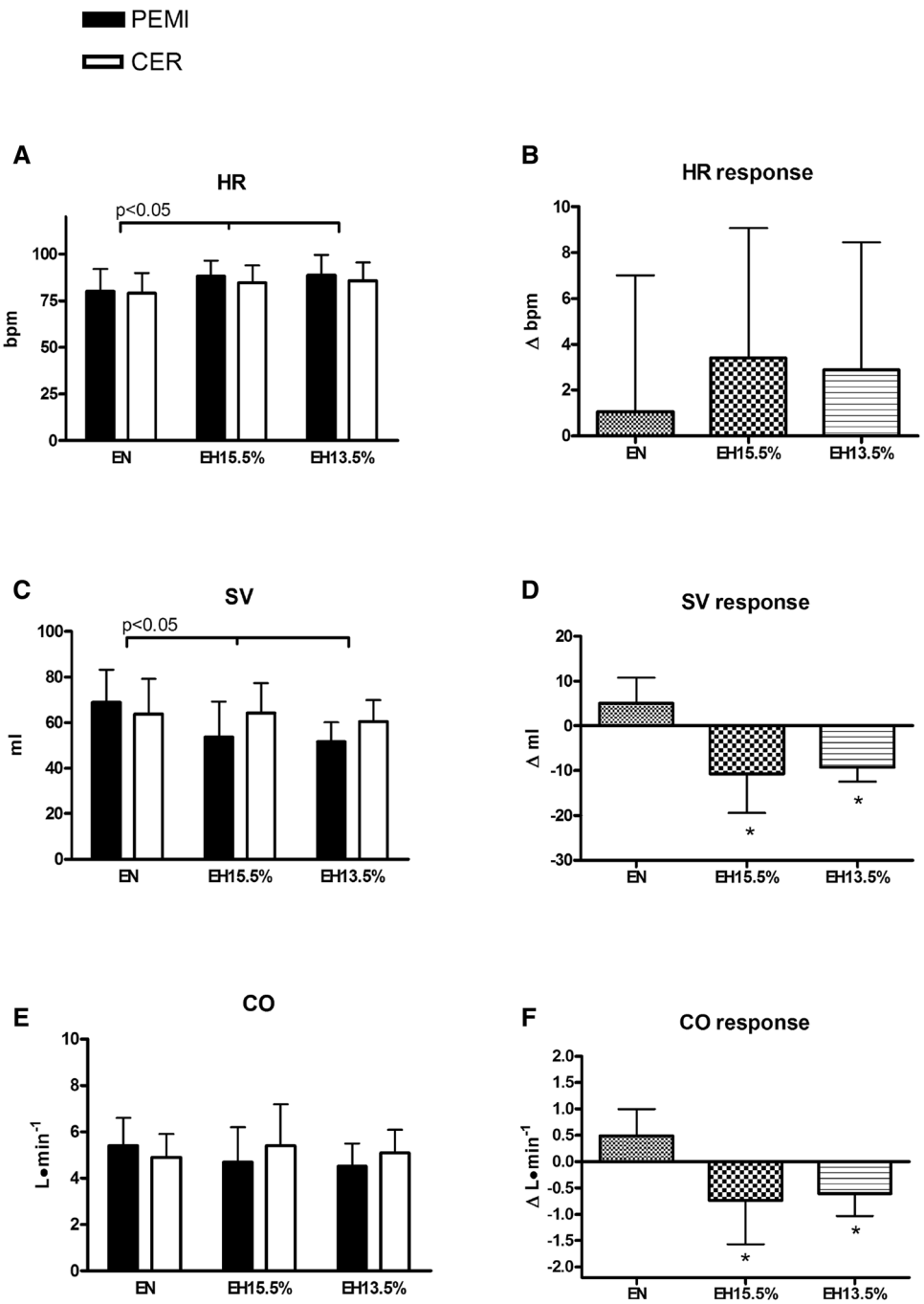

Fig. 3 Absolute values and responses of cardiovascular parameters during the post-exercise muscle ischemia (PEMI) and the control exercise recovery (CER) test, conducted after exercise in normoxia (EN), in normobaric hypoxia with a FiO_2 of 15.5% (EH15.5%), and in normobaric hypoxia with FiO_2 of 13.5% (EH13.5%). *HR* Heart rate (**a, b**), *SV* stroke volume (**c, d**), and *CO* cardiac output (**e, f**). Responses were calculated as the difference between the PEMI and the CER test at the third minute of recovery (see text for further details). Values are mean ± SD. $N = 10$. Horizontal brackets indicate the significant ($p < 0.05$) overall main effect of treatment. There were no interaction effects. *$p < 0.05$ vs. EN

1994; Sanna et al. 2017). Indeed, VER response was on average positive after EN and negative after both sessions of EH.

As far as SVR is concerned, it was increased after the EH15.5% and the EH13.5% tests as compared to the EN test. This indicates that the capacity to vasoconstrict the arteriolar bed was not impaired after EH. Rather, it was enhanced, and this occurrence speaks against our initial hypothesis that EH could reduce gross vascular resistance due to vasodilating metabolite accumulation. A possible explanation for the increased SVR response found after the two sessions of EH may be that the baroreflex activity was effective in counteracting the reduced CO response by recruiting the after-load reserve and inducing arteriolar constriction. This phenomenon explains the unchanged MAP found during the metaboreflex after the two exercise sessions in hypoxia. Hence, the baroreflex successfully maintained the MAP response, despite the reduced SV and CO response.

It remains to be explained why, after the EH sessions, the venous bed was not constricted whereas the arteriolar was. It was likely due to exercise sessions in

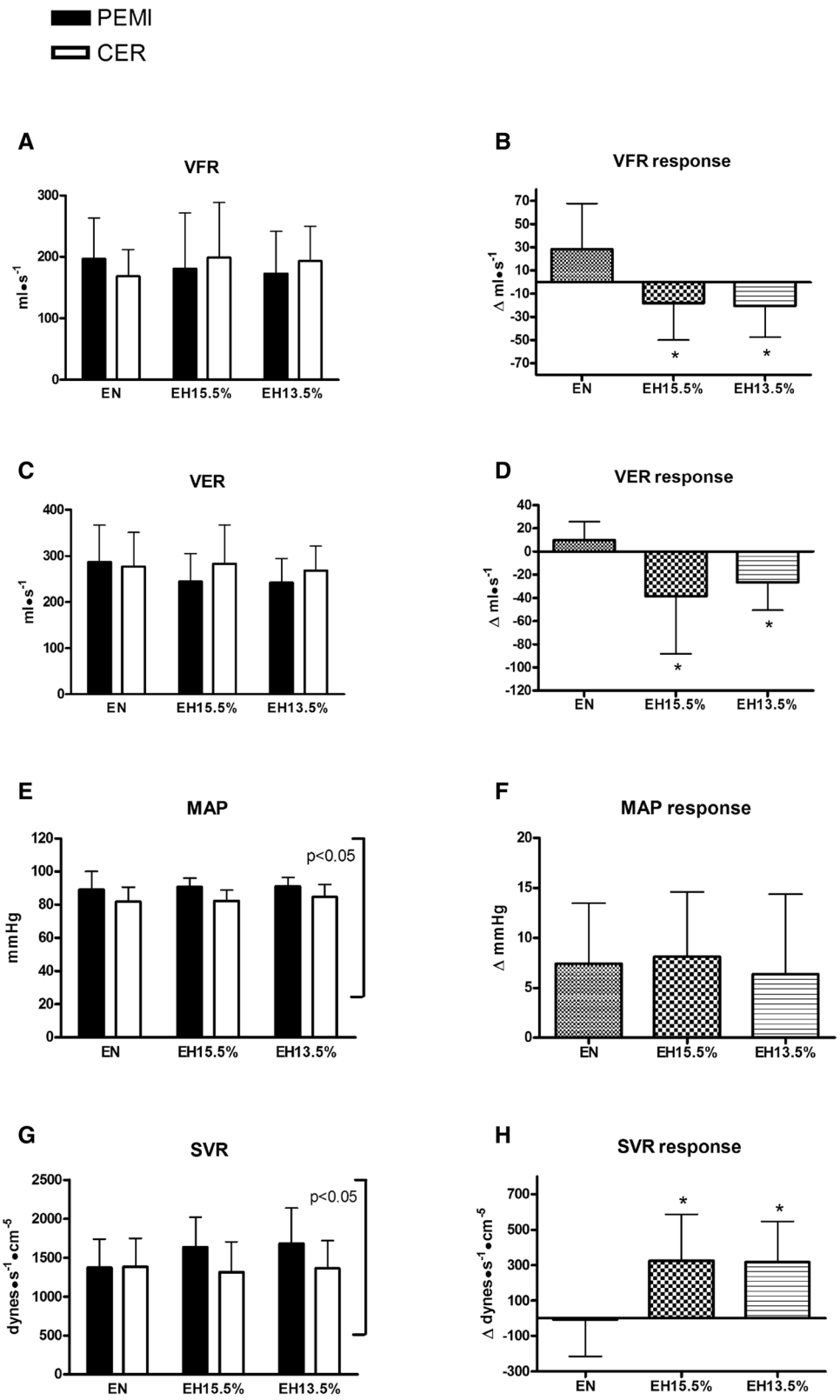

Fig. 4 Absolute values and responses of cardiovascular parameters during the post-exercise muscle ischemia (PEMI) and the control exercise recovery (CER) test conducted after exercise in normoxia (EN), in normobaric hypoxia with a FiO_2 of 15.5% (EH15.5%), and in normobaric hypoxia with FiO_2 of 13.5% (EH13.5%). *VFR* Ventricular filling rate (**a, b**), *VER* ventricular ejection rate (**c, d**), *MAP* mean arterial pressure (**e, f**), and *SVR* systemic vascular resistance (**g, h**). Responses were calculated as the difference between the PEMI and the CER test at the third minute of recovery (see text for further details). Values are mean ± SD. $N = 10$. Vertical brackets indicate the significant ($p < 0.05$) overall main effect of condition. There were no interaction effects. *$p < 0.05$ vs. EN

hypoxia producing a variety of vasodilating metabolites, such as NO, adenosine, and prostaglandin-derived factors (Dinenno 2016; Marshall 2015). In this regard, it is to be noted that oral nitrates were found to exert a venodilator effect with a quantitatively lesser effect on arteriolar resistance vessels. In particular, it has been demonstrated that

the administration of NO-donors before the metaboreflex activation impairs cardiac pre-load by inducing venous dilation, whereas effects on SVR were less evident (Koole et al. 2000; Marongiu et al. 2013). Moreover, recent research showed that preconditioning manoeuvres, able to augment the NO-production, resulted in an impaired possibility to induce venous constriction and to increase SV during the metaboreflex in healthy subjects (Mulliri et al. 2016). It is then possible, in the current study, that the EH increased the production of NO (likely the main vasodilatory contributor) and—to a lesser extent—other metabolites (prostaglandins?) which in turn restrained the sympathetic-induced venous constriction during the metaboreflex (Casey and Joyner 2011). This occurrence prevented the recruitment of the Frank–Starling mechanism and reduced SV response, although it must be acknowledged that this hypothesis remains speculative since the present study did not measure metabolite production.

To summarise, the current study proposed that the EH session induced metabolite production which restrained the sympathetic-induced venous constriction induced by the metaboreflex activation. This resulted in an impaired capacity to recruit the pre-load reserve and, in turn, prevented the possibility to increase SV during the metaboreflex; however, baroreflex activation successfully defended MAP by increasing gross vascular resistance. That is, there was a functional shift from a flow- to a vasoconstriction-mediated mechanism for maintaining the target blood pressure during the metaboreflex.

To the best of our knowledge, the present study is the first to report on the hemodynamics during the metaboreflex elicited immediately after a single bout of hypoxic exercise. In the past, metaboreflex was studied during hypoxia, but without the assessment of central hemodynamics (Gujic et al. 2007; Houssiere et al. 2005, 2006). Instead, only blood pressure and HR were collected along with SNA. Thus, there are no studies with which to compare the present results. The paucity of research dealing with the hemodynamic consequences of intermittent hypoxia is somewhat surprising considering that the use of normobaric hypoxic devices has become popular in athletes and patients (Millet et al. 2016). However, the pros and cons of these practices have yet to be demonstrated. In particular, the transition from EH to normoxia may be critical since the cardiovascular homeostasis is challenged. It should also be considered that mild hypoxia may be protective from ischemic events by inducing the phenomenon known as ischemic preconditioning and by promoting neurogenesis (Marongiu and Crisafulli 2014; Tsai et al. 2013). Hence, the weight of scientific evidence about the effects of EH on the cardiovascular apparatus remains equivocal since both detrimental and positive effects have been reported. Further study on the cardiovascular effects of EH is then warranted.

Limitations of the study

One potential limitation of the present investigation was that we did not measure the production of any metabolite during the two hypoxic tests. This kind of assessment would have been useful as EH is known to induce the production of a variety of vasodilating metabolites, such as NO, adenosine, and prostaglandin-derived factors (Dinenno 2016). Unfortunately, these measurements are complex, expensive, and somewhat invasive. However, results of SO_2 and COX confirm that a substantial hypoxia was induced by EH tests with respect to EN. Inasmuch as EH is known to increase metabolites production (Casey and Joyner 2012), it was then likely that EH bouts induced greater metabolic by-products accumulation than EN. Moreover, we could not measure VO_2 during EH bouts since the gas analyser was not set up to be used simultaneously with the hypoxic gas generator because of technical reasons. Although the mechanical power was the same for all tests (i.e., 80% of AT), we could not verify the metabolic cost was the same.

Another limit was that the rise in MAP found during PEMI could potentially be due to the mechanical effect of the circulatory occlusion and not to metaboreflex activation. However, in our opinion, it is very unlikely that mechanical circulatory occlusion in one leg per se would cause substantial hemodynamic changes. Early as well as more recent findings reported that mechanical occlusion alone in one or two legs/arms could not induce any detectable hemodynamic effect. For example, already in 1976, Rowell and co-workers (1976) reported that total circulatory occlusion of both resting legs for 15 min had little or no effect on HR or MAP. They further concluded that a *work factor* (i.e., metabolites production) seems necessary for any significant cardiovascular response to be generated by muscle ischemia. Therefore, mechanical stimulation of muscle is not a major factor in generating pressor responses. Moreover, in the recent past some experiments conducted in our lab did not discover any hemodynamic effect due to regional circulatory occlusion (in one leg) not preceded by exercise (Crisafulli et al. 2008). Thus, results from these studies do not support the thesis that circulatory occlusion *per se* can cause significant hemodynamic changes.

A final potential limitation of the present investigation was that the study population was limited to young, healthy, Caucasian trained subjects and results can not be extended either to a general population.

In conclusion, data from the present research demonstrated that exercise in acute hypoxia impairs the capacity to enhance venous return during the metaboreflex elicited in normoxia, immediately after EH sessions. The reduced capacity to increase venous return negatively affects SV, which can not participate in the hemodynamic response during the metaboreflex. This in turn causes a functional

shift from a flow- to a vasoconstriction-mediated mechanism by which the target blood pressure is achieved during the metaboreflex. Importantly, the described dys-regulation was successfully counteracted by cardiovascular controlling mechanisms (probably the baroreflex), which maintained MAP notwithstanding the reduced SV.

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Author contributions GM, AD and AC: conceived and designed research, conducted experiments, analysed data, and wrote the manuscript. GS, SM, SR, GG, MM, and VP: conducted experiments and analysed data. SJW and GPM: conceived and designed research, analysed data, and wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards The study was approved by the ethics committee of the University of Cagliari.

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