Physiol. Res. 66: 467-479, 2017

Baseline Values of Cardiovascular and Respiratory Parameters Predict Response to Acute Hypoxia in Young Healthy Men

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Received February 20, 2016
Accepted October 21, 2016
On-line February 28, 2017

Summary

The majority of the available works have studied distinct hypoxic responses of respiratory and cardiovascular systems. This study examines how these systems interact while responding to hypoxia and whether baseline metrics moderate reactions to a hypoxic challenge. Central hemodynamic, aortic wave reflection, and gas exchange parameters were measured in 27 trained young men before and after 10-min normobaric isocapnic hypoxia (10 % O2). Associations were assessed by correlation and multiple regression analyses. Hypoxic changes in the parameters of pulse wave analysis such as augmentation index (-114 %, p=0.007), pulse pressure amplification (+6 %, p=0.020), time to aortic reflection wave (+21 %, p<0.001) report on the increase in arterial distensibility. Specifically, initially compliant arteries blunt the positive cardiac chronotropic response to hypoxia and facilitate the myocardial workload. The degree of blood oxygen desaturation is directly correlated with both baseline values and hypoxic responses of aortic and peripheral blood pressures. The hypoxia-induced gain in ventilation (VE), while controlling for basal VE and heart rate (HR), is inversely associated with ∆HR and ∆systolic blood pressure. The study suggests that cardiovascular and respiratory systems mutually supplement each other when responding to hypoxic challenge.

Key words

Pulse wave analysis • Central hemodynamics • Stiffness • Gas exchange • Hypoxia

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Introduction

Although many researchers have studied the influence of both high altitude hypobaric and experimental normobaric hypoxia on respiratory and cardiovascular functions in humans, the existed literature provides contradictory data. On the one hand, hypoxia has been found to increase peripheral blood flow (Leuenberger *et al.* 1999) and dilate muscular arteries (Thomson *et al.* 2006) by reducing their stiffness (Vedam *et al.* 2009) despite an increase in muscle sympathetic vasoconstrictor nerve activity (Xie *et al.* 2001). However, this is not a general phenomenon since it is not observed in aorta (Boos *et al.* 2012) or renal arteries (Sharkey *et al.* 1998). Acute hypoxia diminished forearm skin blood flow in skiers and increased it in swimmers (Krivoschekov *et al.* 2013). While in humans an acute hypoxia increased HR (Divert *et al.* 2015), in anesthetized rats it elicited no or even negative cardiac chronotropic effects (Donina *et al.* 2015).

The modern recommendations for identifying individuals with health or physiological contraindications for an activity involving hypoxia mainly refer to mountaineers or to patients suffering from cardiovascular or respiratory insufficiencies (Rimoldi *et al.* 2010). However, there are a number of life situations in which people are occasionally exposed to professional or

PHYSIOLOGICAL RESEARCH • ISSN 0862-8408 (print) • ISSN 1802-9973 (online)

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environmental hypoxia (i.e. air passengers, divers, sportsmen, firefighters, miners, military). Based on the theoretical consideration of cross-adaptation mechanisms, it seems likely that hypoxic challenge testing could be useful for determining the resistance to other entropic factors.

Data concerning the basal and post-stimulus relations in cardiac and respiratory interactions during hypoxia have infrequently been considered in the research literature. Consequently, the objective of this study was to evaluate whether cardiovascular and respiratory responses to hypoxia depend upon basal parameters and, if so, how strong the any associations might be. Identification of such parameters or relationships would allow the choosing of individuals resistant to hypoxia without or before testing physiological responses to hypoxic challenge.

We hypothesized that there would be predominantly inverse quantitative and timing inter-relations between cardiovascular and respiratory systems in response to a hypoxic challenge – the cardiac reaction precedes the ventilator response and the enhanced responsiveness of one system relates to a diminished response in the other. Evidence consistent with this hypothesis is found in the data of Lhuissier *et al.* (2012a) who have documented an enhanced respiratory response to hypoxia but a reduced cardiac reaction in an older sample. Similarly, Calbet *et al.* (2008) have shown that an increase of heart rate and cardiac output during exercise in hypoxia impairs pulmonary gas exchange by reducing the time available for alveolar-end capillary diffusion equilibration. The current report examines the associations between these two systems in a sample of young, healthy men.

Methods

Participants

Twenty-seven healthy nonsmoking male students aged 17-24 years participated in the study. Their height, weight and body mass index were 181.0±5.8 cm, 69.6±8.6 kg, 21.2±1.8 kg/m^2. Participants were selected on the basis that they were normotensive or pre-hypertensive (<140/90 mm Hg), and had no cardiovascular, respiratory or metabolic diseases. They were trained in an exclusive aerobic exercise modality (viz. middle distance running and skiing) and were participating in a regular training program 4-6 days a week. All provided written consent and the Institute's Ethics Committee approved the study protocol.

Protocol

Participants were asked to abstain from alcohol and caffeine for the 24 h before the study and the laboratory temperature was maintained at 23-25 °C throughout the study. After a 15-min adaptation to laboratory conditions, subjects went through an acute 10-min hypoxia (10 % O_2). Immediately before the test and at the 10th minute, gas exchange and pulse wave characteristics were measured in the seating position. All tests were performed in winter at the same time of day in the morning and by the same observer.

Physiological evaluation

The respiratory parameters were assessed using the Oxycon Pro ergospirometry system (Erich Jaeger, Germany) combined with the BCI Autocorr Pulse Oximeter (Smith Medical PM, Inc., USA). A transcutaneous sensor was placed on an ear lobe. The hypoxic gas mixture was prepared by using a New Life medical oxygen concentrator (AirStep, USA) that was converted to a hypoxycator with a controlled output oxygen concentration ranging from 18 to 9 % in a mixture with atmospheric nitrogen. Gas exchange was recorded breath-by-breath, using a facemask connected to a Y system fixation with a double valve, which ensures separate pathways between inspired and expired flows. An inspiratory valve, connected to a gas mixer, allowed the subjects to inhale a hypoxic mixture of ambient air.

The following parameters were measured at 5-s intervals during the hypoxic period: blood oxygen saturation (SpO_2, %), pulmonary ventilation (VE, l/min), breathing frequency (BF, 1/min), oxygen consumption rate ($\dot{V}O_2$, ml/min), carbon dioxide production rate ($\dot{V}CO_2$, ml/min), respiratory exchange (gas exchange) ratio (RER, $\dot{V}CO_2/\dot{V}O_2$), mean O_2 and CO_2 concentrations in expired air (FeO_2, $FeCO_2$, %).

The assessment of arterial wave characteristics was performed using the SphygmoCor Pulse Wave Analysis (PWA) Px system (AtCor Medical, Australia) (Korpas *et al.* 2009). After recording the blood pressure in the brachial artery with an automated oscillometric method (MT-4, MediTech USA), the applanation tonometer was positioned over the radial artery and the pulse was continuously recorded. Using a previously validated generalized transfer function (Pauka *et al.* 2001) the system software calculates an averaged radial artery waveform, calibrated with brachial systolic and diastolic pressure, and derives a corresponding aortic pressure waveform (Fig. 1).

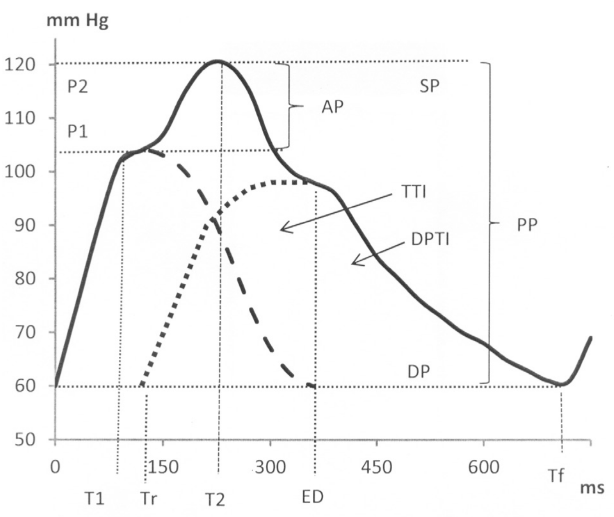

Fig. 1. Aortic pressure profile as a result of pulse wave analysis. X-axis represents the time of cardiac cycle. DP – diastolic blood pressure; SP – systolic pressure; P1 – pressure at T1; P2 – peak pressure as a result of superposition of primary and reflection waves; PP – pulse pressure; AP – augmentation pressure; T1 – time to the first shoulder; Tr – time to return of the reflection wave; T2 – time to the pressure peak; ED – ejection duration; Tf – the end time of aortic waveform; TTI – tension time index, area left to the point ED; DPTI – diastolic pressure time index, area right to ED.

The augmentation pressure is determined as a rise in pressure predominantly due to the reflected wave, $AP=P_2 - P_1$, mm Hg. In young individuals, it is common to see no augmentation or a negative one. The latter situation occurs if the reflected pressure wave comes to the aorta after the systolic peak, $P_2<P_1$. The augmentation index (AIx, standardized for a heart rate of 75 bpm) is defined as the percentage of AP-to-pulse pressure ratio. The extent of augmentation is known to increase as the arteries stiffen (Wilkinson *et al.* 1998). The left ventricular ejection duration (ED) is the systolic time. Using the point of ED, the areas under the systolic and diastolic parts of the pulse curve are then calculated. The first parameter, commonly known as Tension Time Index (TTI), has been shown to relate to the contractile work of the heart and to its oxygen consumption. The diastolic part (diastolic pressure time index, DPTI) is associated with the time for coronary perfusion and characterizes energy supply. The ratio is termed as subendocardial viability ratio (SEVR=DPTI / TTI) and characterizes the balance between the energy supply and demand on the heart. Time to reflection, Tr, reflects the time at the onset of the reflected wave. It correlates with pulse wave velocity (Wilkinson *et al.* 2002, Sharman *et al.* 2005) and is a proxy of the arterial compliance: the reflected pressure wave arrives earlier at the ascending aorta from rigid peripheral arteries compared to compliant ones. Vedam *et al.* (2009) provided evidence to support the suggestion that hypoxic change in AIx represents muscular arteries stiffness whereas Tr characterizes mainly the aortic elasticity.

The pulse pressure amplification from the aorta to radial artery was calculated according to formula $Ampl=PP_r / PP_a$. This parameter has been shown to represent the arterial stiffness in hypertensive patients (Avolio *et al.* 2009, Hashimoto and Ito 2010).

For the purposes of comparison and correlation analysis, the relative hypoxic response of each variable was determined as that corresponding to 1 percent of blood desaturation and was computed according to formulae $\Delta Var=(Var_{hyp} - Var_{bl}) / (SpO_{bl} - SpO_{hyp})$. In order to make associations of negatively responding variables, like SpO_2, intuitively understandable and clear, the magnitude of their responses were inverted and calculated as $\Delta Var_{in}=Var_{bl} - Var_{hyp}$. Since the amplitude and particularly timing parameters of pulse curve substantially depend upon HR (Wilkinson *et al.* 2000, Lantelme *et al.* 2002) correlations for cardiovascular variables were computed after controlling for the effects of HR_{bl}, HR_{hyp} or ΔHR, as appropriate.

Statistical analysis

All the continuous variables were tested for Gaussian distribution with the Kolmogorov-Smirnov criterion. A comparison between initial and hypoxic values was made with paired t-test or Wilcoxon's test. The calculation of paired or partial coefficients of Spearman's or Pearson's correlations, as appropriate, assessed linear associations among variables. In order to evaluate comparative contributions of known predictors to cardio-vascular-respiratory responses, the General Linear Model (GLM) procedure in SPSS-19 was used. The approach provides regression analysis and analysis of variance for one dependent variable examining the distinct effects of covariates and fixed factors as well as any interactions between them. All tests were 2-tailed, and $p \leq 0.05$ was considered significant. However, $p \leq 0.1$ is also indicated in order to mark a tendency in a difference or association. Values are Means ± SDs.

Results

Parameters at baseline (Table 1)

Respiratory characteristics. Persons with high ventilation rate also manifest an elevated value of oxygen consumption (r=0.42, p=0.043).

Cardiovascular parameters. Augmentation pressure and index are both negative as it is usually observed in young persons with good arterial flexibility. The left ventricular ejection duration comprises 30 % of the cardiac cycle. Pulse pressure in radial artery is 1.7 times higher compared to aortic PP due to the greater peripheral SBP. The high value of PP amplification is strongly associated with low augmentation pressure and augmentation index (r=-0.95) while the absolute timing variables, Tr and ejection duration, are obviously associated with Tf (directly) and HR (inversely).

Table 1. Cardiovascular and respiratory parameters before and after acute hypoxia (10 min, 10 %) and ranges of individual hypoxia-induced responses (n=27).

Parameter	Baseline		Hypoxia		p	$\Delta Var = Var_{hyp} - Var_{bl}$		
	Mean	± SD	Mean	± SD		Min	Mean	Max
SpO_2 (%)	97.70	1.10	73.80	5.06	<0.001	-15.00	-24.00	-43.00
VE ($l \times min^{-1}$)	9.78	1.93	11.15	2.89	0.021	-2.42	1.30	8.28
BF ($1 \times min^{-1}$)	14.20	4.60	13.60	4.50	NS	-6.10	-0.60	3.20
$\dot{V}O_2$ ($ml \times min^{-1} \times kg^{-1}$)	3.86	0.72	3.41	0.71	0.015	-1.51	-0.44	2.25
$\dot{V}CO_2$ ($ml \times min^{-1} \times kg^{-1}$)	3.57	0.74	3.62	0.75	NS	-1.21	0.05	1.10
RER	0.91	0.09	1.13	0.12	<0.001	0.03	0.20	0.50
FeO_2 (%)	17.80	0.70	8.20	0.80	<0.001	-11.30	-9.50	-7.30
$FeCO_2$ (%)	2.94	0.48	2.73	0.53	0.013	-0.74	-0.20	1.03
HR ($beat \times min^{-1}$)	63.10	10.00	79.30	13.00	<0.001	-9.10	16.00	37.30
r-SBP (mm Hg)	128.90	9.60	132.00	14.40	NS	-27.20	3.10	29.40
r-DBP (mm Hg)	77.80	8.50	76.80	10.30	NS	-15.00	-1.10	7.50
r-PP (mm Hg)	51.10	8.90	54.40	10.60	0.098	-13.20	3.20	24.00
r-MBP (mm Hg)	92.00	7.30	91.90	10.10	NS	-16.40	-0.20	12.10
r-T2 (%Tf)	23.00	3.30	28.50	3.80	<0.001	-2.30	5.30	8.90
a-SBP (mm Hg)	108.30	7.40	108.70	10.80	NS	-21.00	0.20	17.30
a-DBP (mm Hg)	78.90	8.60	78.40	10.40	NS	-14.70	-0.30	8.60
a-PBP (mm Hg)	29.50	5.30	29.50	7.00	NS	-25.40	±0.00	12.40
a-T2 (% Tf)	20.20	3.50	23.70	4.30	<0.001	-2.10	3.70	12.80
Tr (% Tf)	16.40	3.10	19.80	3.10	<0.001	-1.50	3.20	6.90
ED (% Tf)	30.10	4.10	35.10	6.40	<0.001	-6.00	5.20	13.10
DD (% Tf)	69.80	4.10	64.80	6.30	<0.001	-12.50	-5.00	5.90
Ampl (r-PP/a-PP)	1.74	0.11	1.80	0.09	0.002	-0.07	0.07	0.33
AP (mm Hg)	-1.56	3.20	-4.00	3.26	0.002	-15.03	-2.50	4.18
AIx (%)	-5.90	10.20	-12.60	12.60	0.007	-38.20	-7.00	24.10
SEVR (%)	206.00	40.00	170.00	52.00	0.002	-111.00	-34.00	84.00

p – Student paired t-test or Wilcoxon test, NS – nonsignificant, VE – ventilation, BF – breathing frequency, $\dot{V}O_2$ – oxygen consumption rate, $\dot{V}CO_2$ – carbon dioxide production rate, FeO_2 – mean oxygen concentration in exhaled air, $FeCO_2$ – carbon dioxide concentration in exhaled air, HR – heart rate, SBP, DBP, MBP – systolic, diastolic, and mean blood pressures, PP – pulse pressure, T2 – time to maximum systolic pressure, Tr – time to reflection, Tf – length of cardiac cycle, ED – left ventricular ejection duration, DD – diastole duration, Ampl – PP amplification, AP – augmentation pressure, AIx – augmentation index, SEVR – subendocardial viability ratio, a-, aortic, r-, radial.

Respiratory/cardiovascular relations. When HR was controlled, there was a slight positive partial correlation of breath frequency with aortic time to reflection (r=0.47, p=0.025) but inverse correlations with pulse pressure in *a. radialis* (r=-0.44) and aorta (r=-0.42) due to the direct association of BF with diastolic blood pressure (r=0.40, p=0.037). The high ventilation rate is associated with lower peripheral and aortic pulse pressures (r=-0.44 and r=-0.45).

Table 2. Results of the univariate analysis of variance and multiple regression (GLM) between inter-relating physiological characteristics.

Source of variation	Mean sum of squares	p	Partial Eta squared	Regression coefficient, b
(A) Dependent variable: baseline FeO_2				
Corrected model	7562.00	<0.001	0.99	-
PP $Ampl_{bl}$	198.50	<0.001	0.97	9.80
Tr_{bl}	40.10	<0.001	0.87	1.42
Ampl × Tr	32.40	<0.001	0.84	-0.79
(B) Dependent variable: $\Delta HR/\Delta SpO_2$				
(B1) Corrected model	1.90	<0.001	0.80	-
Intercept	0.50	0.013	0.26	2.50
HR_{hyp}	5.20	<0.001	0.79	0.04
Tr_{bl}	2.30	<0.001	0.62	-0.11
$Ampl_{bl}$	0.80	0.002	0.36	-1.83
(B2) Corrected model	1.80	<0.001	0.64	-
Intercept	5.00	<0.001	0.71	3.79
VE_{bl}	3.50	<0.001	0.64	0.30
$\Delta VE/\Delta SpO_2$	1.20	0.003	0.37	-2.52
(C) Dependent variable: $\Delta ED/\Delta SpO_2$				
Corrected model	0.46	<0.001	0.57	-
Intercept	0.62	<0.001	0.47	-1.021
HR_{hyp}	0.91	<0.001	0.57	0.016
AIx_{bl}	0.24	0.011	0.26	0.011
(D) Dependent variable: $\Delta SEVR_{in}=(SEVR_{bl}-SEVR_{hyp})/\Delta SpO_2$				
(D1) Corrected model	21.70	0.008	0.36	-
Intercept	21.40	0.022	0.22	-5.994
HR_{hyp}	35.60	0.004	0.31	0.100
AIx_{bl}	25.90	0.013	0.25	0.111
(D2) Corrected model	17.50	0.007	0.43	-
Intercept	8.10	0.130	0.11	-4.090
HR_{hyp}	14.10	0.050	0.17	0.072
AIx_{bl}	16.60	0.035	0.20	0.413
HR × AIx	9.30	0.107	0.12	0.004

The regression analysis yielded the most robust relations between FeO_2, PP Ampl, and Tr. The regression model including the latter two variables as covariates explains 99 % of total variation of FeO_2 (Table 2A). Both parameters are thus highly reliable predictors of partial oxygen concentration in exhaled air: the greater the Ampl and Tr (i.e. the more compliant arteries), the higher the FeO_2 and, most likely, the lower the oxygen demand. A comparison of sums of squares for both independent variables reports on almost 5-time preponderance of PP amplification over Tr. The negative interaction term shows that both predictors blunt the each other's positive effect upon FeO_2.

The oxygen consumption rate increases with increasing arterial compliance. The partial correlation coefficients, adjusted for the basal HR, of $\dot{V}O_2$ with AP and PP Ampl are -0.41 (p=0.050) and 0.46 (p=0.029), respectively.

Response to hypoxia (Table 1)

Respiratory characteristics. Since the O_2 concentration in the air decreases, so do the SpO_2 and FeO_2 as parameters which primarily and directly depend on the partial oxygen content in inspired air. Hypoxia slightly increases VE but not BF. The fall in oxygen consumption (-24 %) is observed on the ground of unchanged $\dot{V}CO_2$.

Cardiovascular parameters. In this sample, the hypoxia elicited a positive cardiac chronotropic effect markedly shortening the cardiac cycle. The relative ejection duration increases at the expense of decreasing diastole duration. The SEVR therefore falls. This pattern suggests an elevation of the cardiac contractile load and worsening conditions for myocardial afterload perfusion. The inhaling hypoxic mixture notably elongates relative time to reflection Tr.

Hypoxia causes no changes in BPs regardless of marked increases in HR. However, there is a tendency toward an increase in radial PP that favors aortic-to-radial PP amplification. The decrease in augmentation pressure and augmentation index together with the rise in PP amplification and Tr illustrate the diminished stiffness of large muscular arteries that is a likely reason for the lack of hypertensive reaction during hypoxia.

The figures in the two right columns of the Table 1 highlight the remarkable individual variability of hypoxic physiological responses. Only SpO_2, FeO_2, and RER demonstrate unidirectional responses across all participants whereas other parameters show both positive and negative individual variation. So, for example, $\dot{V}O_2$ decreased in 22 and increased in five persons.

To summarize the effects of acute short-lasting normobaric hypoxia, the responses consist of an increase of pulmonary ventilation, heart rate, aortic-to-peripheral pulse pressure amplification, cardiac ejection duration, and a decrease of augmentation pressure. The substantial shortening of diastole and fall in SEVR worsen the cardiac afterload perfusion and oxygen demand/supply ratio.

Associations among initial values and hypoxia-induced responses

The next questions to be answered were as follows: are there and what are the parameters at baseline that relate to hypoxic reactions. After the preliminary paired correlation analysis, related variables were tested with regressions testing for interactions among several predictors and evaluating their comparative contribution to response magnitudes. The significant regression models are presented in Table 2.

Respiratory parameters. Although the average group response of breathing frequency is close to zero, its relative value calculated per percent of desaturation depends upon baseline ventilation (r=-0.49, p=0.021): low VE predicts a greater gain in breathing frequency.

Cardiovascular characteristics. We then tested a hypothesis regarding whether compliant arteries facilitate the contractile cardiac work and hence abolish the hypoxia-induced increase in heart rate. The regression model (Table 2B1) for ΔHR combining hypoxic value of HR and two baseline stiffness characters (Ampl and wave reflection time Tr, the latter adjusted for Tf), explains 80 % of the total variation in the dependent variable (per η^2). All three predictors exert a consistent influence on the ΔHR. The impact of Tr is 3 times greater than that of Ampl as it follows from the comparison of sum of squares. The negative regression coefficients demonstrate the inverse association: the greater the baseline values of Ampl and Tr (i.e. the greater the arterial compliance), the smaller the hypoxic rise in HR. Similarly, an initially high value of Aix (i.e. high arterial stiffness), is associated with greater hypoxia-induced increases in ejection duration (Table 2C) and, converse decreases in SEVR (Table 2, D1). The nonsignificant interaction between the two predictors (Table 2, D2) means that their effects are independent. Thus, the effects of stiffness parameters are distinct from the changes attributable to HR, meaning that stiff arteries stress the heart and worsen myocardial perfusion during short-term hypoxia.

Respiratory/cardiovascular relations. The next question to be considered regarded the predictors of desaturation. The level of ΔSpO_2 magnitude linearly increases with baseline blood pressures at least within the limits observed in the selected population. The slight correlations (r=0.37 – 0.44, p<0.05) show that desaturation is greater among participants with high initial systolic and diastolic blood pressures: the higher the pressure the less saturation falls.

The AP and AIx levels become progressively less negative during the hypoxic test (i.e. changes in arterial resilience become less pronounced, with increasing individual RER at baseline). Thus, AP_{hyp} is equal to -6.33±2.06 mm Hg among those participants having lower than median RER (0.92) and AP_{hyp}=-2.08±2.97 mm Hg among those where RER ≥0.92 (p=0.001). The respective difference for AIx corresponds to p-value of 0.006. Therefore, persons with a low initial $\dot{V}CO_2$-to-$\dot{V}O_2$ ratio show a greater hypoxic decrease in arterial stiffness than those with high RER. After controlling for ΔHR, the partial correlation between hypoxic augmentation pressure drop (ΔAP_{in}) and RER_{bl} is -0.45, p=0.033, while the respective coefficient for ΔAIx_{in} is -0.50, p=0.016.

The high initial ventilation and its enhanced hypoxic reaction blunt the positive cardiac chronotropic response (Table 2, B2). Similarly, the VE_{bl} tends to be inversely correlated with hypoxia-induced gain in Ampl (r=-0.34, p=0.075, ΔHR=const.). Although the mechanisms underlying the latter association are unclear, the link may reflect the relations between VE and blood pressures. Thus, the correlation coefficients are -0.46 (p=0.025) for ΔrDBP and -0.48 (p=0.019) for ΔaDBP. The linear regression models using PP as a predictor are as follows:

$$VE=9.7 + 0.051 \text{ (95 \% CL, -0.001, 0.104)} \times \Delta rPP$$

for radial artery (p_{model}=0.056; r=0.38, p_r=0.028) and

$$VE=9.9 + 0.090 \text{ (95 \% CL, 0.007, 0.173)} \times \Delta aPP$$

for aortic pulse pressure (p_{model}=0.035; r=0.43, p_r=0.017). Although the difference among regression coefficients (p=0.097) is small given the influence of VE upon the degree of radial and aortic pulse pressure, the gains seems to be sufficient to detect a correlation between baseline ventilation rate and central-to-peripheral PP amplification.

Although ΔAP, ΔAix, ΔED, and ΔSEVR do not relate to $\dot{V}O_2$ or $\dot{V}CO_2$ values, they are associated with baseline values of RER: the respective coefficients of partial correlation after controlling for ΔHR are as follows: 0.40 (p=0.062), 0.45 (p=0.032), 0.58 (p=0.003), and -0.46 (p=0.025).

The high initial values of VE, BF, HR, diastolic pressure, and PP amplification predict a greater decrement of oxygen uptake ($\Delta\dot{V}O_2$): the correlation coefficients ranges from 0.33 (p=0.1) for VE to 0.63 (p=0.009) for Ampl. However, these associations are completely attributable to basal HR as the correlations disappear once the cardiac effect is statistically controlled. The only exception to this general pattern is the influence of baseline PP amplification which remains reliable after controlling for HR. The participants having the great PP amplification and thus the resilient peripheral arteries demonstrate the greatest reduction in oxygen consumption.

For each variable associated with hypoxia, robust inverse correlations with r=-0.70 – -0.90 between baseline value and the response magnitude are found.

Inter-relations between hypoxic responses of physiological variables

The degree of desaturation is inversely correlated with hypoxic RER gain (r=-0.51, p=0.007) but not with the magnitudes of distinct $\dot{V}O_2$ and $\dot{V}CO_2$ changes. The HR increment increases with increasing $\dot{V}O_2$ and $\dot{V}CO_2$ decrement (r=0.45 for both cases) and does so independently of ΔRER.

The hypoxic augmentation of Tr is strongly correlated with ΔRER (r=0.72, p<0.001, ΔHR=const.) but is not associated with changes in either $\dot{V}O_2$ or $\dot{V}CO_2$. Both ΔED and ΔSEVR are associated with ΔFeO_2 (r=-0.62, p=0.001 and r=0.52, p=0.008, respectively).

The last step of the analysis consisted in verifying the hypothesis of the contradictive cardio-pulmonary interaction in their contribution to hypoxic adaptation. After adjustment for baseline HR and VE, the hypoxia-induced gain in VE, relative to the extent of desaturation, is inversely correlated with ΔHR and ΔrSBP (Fig. 2). Closer associations are found between ΔHR and $\Delta\dot{V}O_2$ (r=-0.62, p=0.003) and $\Delta\dot{V}CO_2$ (r=-0.56, p=0.009). The multiple regression model combining VE_{bl} and ΔVE (Table 2, B2) explains 64 % of total variation of ΔHR with independent negative effects for both predictors. The value of mean sum of squares and hence the contribution of baseline VE is almost three times higher than that for ΔVE. These results provide evidence consistent with our hypothesis: the high reaction of one system is associated with a lowered contribution from the other.

Discussion

The results of our study based on the AP, AIx, Ampl, and Tr alterations are consistent with the conclusion of previous studies demonstrating that acute hypoxia increases arterial resilience outside of the changes attributable to HR. The relative duration of left ventricular systole becomes longer and therefore the SEVR decreases and myocardial perfusion worsens. Regardless of the activation of left ventricular function the blood pressures do not change due to dilation of large arteries. These changes occur even within 10 min and hence cannot be resulted from alterations in arterial wall structure and more likely concern functional regulation of the vessel's tone. The hypoxia increases ventilation rate due to enhanced depth of respiration and does not alter breath frequency. The oxygen concentration in the expired gas falls because of hypoxemia. The current report demonstrates a generally inverse relationship between respiratory and cardiovascular systems under hypoxic conditions in young men and shows that baseline values modulate responding under these conditions.

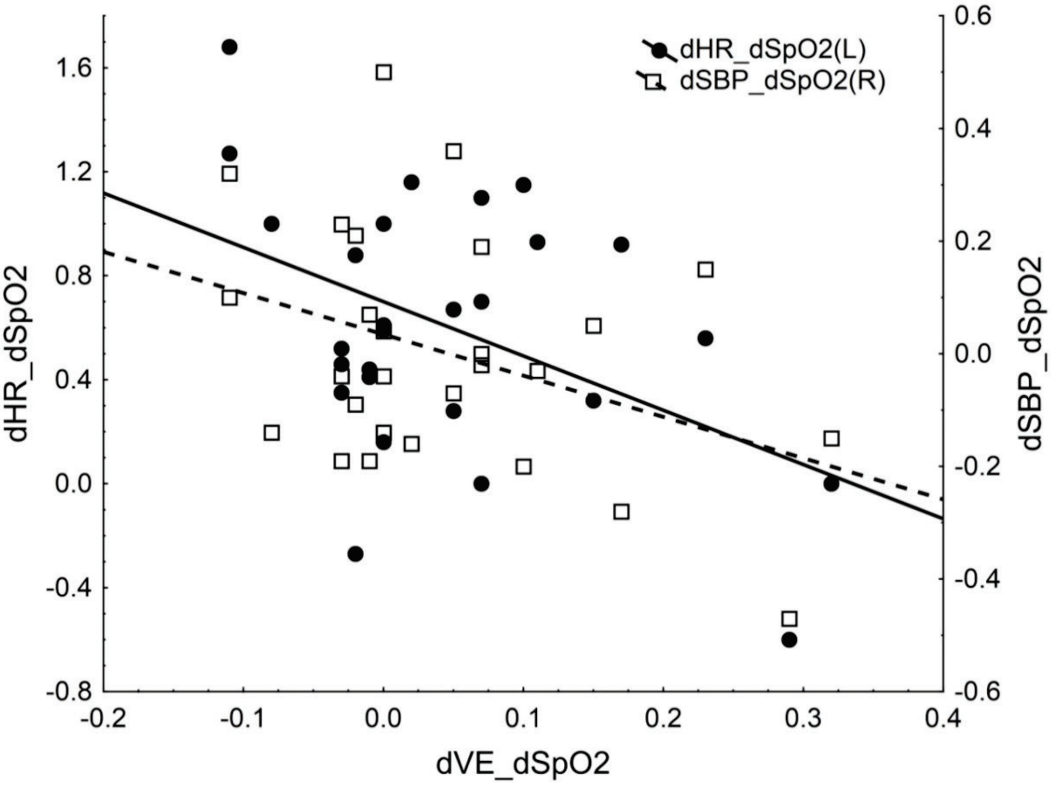

Fig. 2. Scatterplots and linear regression lines of hypoxia-induced changes in heart rate and aortic systolic blood pressure against changes of ventilation. dHR_dSpO2 / dVE_dSpO2: $y=0.7 – 2.1* x$; $r=-0.45$, $p=0.017$, $r^2=0.21$. dSBP_dSpO2 / dVE_dSpO2: $y=0.03 – 0.73 * x$; $r=-0.38$, $p=0.053$, $r^2=0.14$.

Prior studies have shown that acute hypoxia increases the compliance of large peripheral muscle arteries (Thomson *et al.* 2006) but not of elastic aorta (Vedam *et al.* 2009, Boos *et al.* 2012, Lefferts *et al.* 2016). The dilative effect is consistent with data on the contrasting impact of exogenous hyperoxemia which results in dose-dependent linear decreases in arterial resilience (Rossi and Boussuges 2005), muscle blood flow (Rousseau *et al.* 2005), left ventricular stroke volume, and end-diastolic area with no changes in HR, mean BP, and $\dot{V}CO_2$ (Bak *et al.* 2007). Stiff arteries are known to impair cardiovascular responsiveness to breathe holding in both healthy individuals (Zavoreo and Danarin 2010) and among patients with coronary heart disease (Rucka *et al.* 2015). Compared to hypercapnia, hypoxia has been found to cause a greater reduction in total peripheral vascular resistance and a higher increase in heart rate and cardiac output (Steinback *et al.* 2009). The authors conclude that hypoxia affects cardiovagal rather than sympathetic baroreflex gain and the pressure set-point in a manner not related to ventilatory chemoreflex sensitivity.

Conversely, Krnic *et al.* (2011) have reported an unusual hypoxia-induced elevation of AIx and hence an increase in arterial stiffness. Inconsistent findings across different studies can be explained, first, by the pronounced individual variability in cardiovascular responsiveness, a pattern also evident in the present study which specifically employed young, healthy men. Second, this variability depends on the contribution of two principal contradistinctive factors considered responsible for cardiovascular reactions to hypoxia. Positive blood pressure responses are primarily caused by the carotid chemoreceptor reflex and followed by sympathetically mediated vasoconstriction in the peripheral vascular bed and by enhanced cardiac output (Marshall 1994, Dinenno *et al.* 2003). On the other hand, this pressor effect is opposed by vasodilation due to direct impact of hypoxia on local tissue and endothelial vasodepressor agents in arterial wall such as nitric oxide (Blitzer *et al.* 1996, Vedam *et al.* 2009, Jouner and Casey 2014). The net hemodynamic effect is thus determined by a dynamic balance between these factors. Hypoxic signaling events and vasodilation are attributed, at least partly, to a reduction in nitrite anions to nitric oxide instead of oxidation to nitrate anions if local oxygen level decreases in tissues (van Faassen *et al.* 2009).

Our finding of a significant increase in Tr is, however, in contrast to Vedam *et al.* (2009) who reported no change in Tr under the influence of 20-min hypoxia at the level of 80 % oxyhemoglobin saturation. These authors concluded that this exposure does not affect aortic stiffness as they considered Tr just a proxy of aortic distensibility, although it is worth noting that mean desaturation was greater in the current report (74 %).

A gradual rise in heart rate, but not in cardiac output, has previously been observed over 8 h of moderate hypoxia (Clar *et al.* 2000). Acute stimulus did not alter BF, BP (Iwasaki *et al.* 2007), and blood flow velocity in middle cerebral artery (Ainslie *et al.* 2008). Due to decreased peripheral vascular resistance (Creager *et al.* 1990) and hypoxic vasodilation of large arteries described elsewhere (Marshall 2000), several studies similar to our own (Thomson *et al.* 2006, Momen *et al.* 2009, Lefferts *et al.* 2016), have reported no marked changes in systolic, diastolic, and mean arterial pressures during hypoxia regardless of remarkable tachycardia. One exception is a study in which intermittent 7-day exposure (Katayama *et al.* 2001) and high altitude hypoxia (Parati *et al.* 2014) were found to elicit a pronounced hypertensive effect. Such discrepancies may reflect variations in experimental conditions such as extent, duration, and repeatability of hypoxic exposures or, again, specific characteristics of the sample.

Specifically, it is already known that individuals with stiff arteries have low basal oxygen consumption. In turn, physical fitness is known to influence parameters such as hypoxia-induced blood desaturation (Lhuissier *et al.* 2012b), vasodilation (McAllister *et al.* 2008), arterial stiffness (Phillips *et al.* 2012), basal metabolic rate (Drenowatz *et al.* 2013, Burt *et al.* 2014), and maximum oxygen consumption (Keadle *et al.* 2014). Thus, it may be that respiratory and/or cardiovascular responses to hypoxia are different among fit, or highly trained young men than they are in other groups (Divert *et al.* 2015).

Only one paper in the modern literature describes SEVR in hypoxia (Lefferts *et al.* 2016). The authors did not find any alterations but concluded that acute normobaric hypoxic exposure (11.6 % O_2, 105 min) unloads the left ventricular due to a reduction in reflective wave magnitude without disturbing myocardial oxygen supply-to-demand ratio (ΔSEVR≈0). In our work, the 10-min test substantially decreases SEVR as a diastole/systole ratio and thus worsens the myocardial afterload perfusion. However, a 5-min hypoxic test has been shown to increase coronary blood velocity (Momen *et al.* 2009) without effects on blood pressure. The cardiac vasodilation in the face of shorten diastole is likely due to sympathetic activation and could be considered a compensatory mechanism acting to meet the myocardial oxygen demand increased by a physiological stressor.

A second major contribution of the current report lies in demonstrating that all of the characteristics investigated here demonstrate robust inverse associations between the initial value of a parameter and its hypoxic value – responses are consistently modulated. This general pattern is consistent with Wilder's basimetric 'law of initial value' (1931, 1962), although he was originally concerned with biological rhythms. According to this rule, a low baseline value for a physiological variable is usually associated with a high positive response to a stimulus and *vice versa*. That is, a parameter with high initial activity has low reserves for further elevation compared to instances with a low baseline value.

Since hypoxia stimulates ventilation (Easton *et al.* 1986), this potential confounding effect must be considered insofar as some hypoxic cardiovascular responses that might be attributed to alterations in oxygen tension could, in fact, be caused by secondary changes in respiratory function. The high baseline ventilation rate seems likely to be a contraindication for work and activities associated with acute hypoxemia. Thus, high baseline ventilation reduces the positive cardiac chronotropic response to hypoxia and blunts the gain in PP amplification.

In our experiment, the hypoxia-induced response of pulmonary characteristics is less pronounced compared to the changes seen in cardiovascular parameters. This difference may reflect a greater energy cost to breathing activation than for changes in the more economical cardiac and, especially, vascular responses. It seems likely that the energy economy requiring the involvement of different physiological mechanisms becomes a critical consideration during hypoxia. Again, however, this may or may not be a general phenomenon and may more accurately characterize young men. The opposite pattern has been reported by Lhuissier and co-authors (2012a) who have described in men, but not women, a decrease in heart rate to acute hypoxia and an increase in the ventilatory reaction with aging especially in trained individuals.

Some limitations of the work are to be acknowledged. First, there is no special control group breathing ambient air through the mask, meaning effects may also reflect the laboratory context and apparatus rather than hypoxia *per se*. However, in a preliminary study, we evaluated the additional resistance of the mask to breathing and found it negligible. Second, the duration of hypoxic test is comparatively short although evidence suggests the duration was sufficient to produce quite pronounced physiological responses. This noted, it is unclear whether these data are specific to hypoxic challenge or whether similar patterns might arise in response to different types of stressors. Equally, it is not yet clear whether and/or how physiological systems will adapt to longer periods of hypoxia. Third, the gas exchange was measured at rest under conditions of low oxygen demand. Under such conditions, reserves of cardio-pulmonary functions usually cover the organism's energy requirements even in low blood oxygen saturation that is not followed by functional impairments at the cellular level.

Conclusions

This study evaluates the associations between respiratory and cardiovascular parameters under hypoxic conditions with an emphasis on assessing the characteristics of arterial stiffness in a sample of physically trained young men.

Analyses provide clear evidence for two key findings. First, they show that the physiological responses to acute hypoxia are associated with baseline characteristics: the higher the initial value of a parameter, the lower the response to hypoxia. This suggests that even short-term hypoxic exposure decreases arterial stiffness and may be an important underlying mechanism explaining the protective effects of hypoxic training in cardiovascular patients. Second, analysis consistently reveals an inverse association between cardiovascular and respiratory systems and a comparison of their contributions suggests a mutually substitutional interaction under hypoxic conditions: the lower the response of one system the higher the answer of the other. The initially compliant arteries blunt the incremental HR response and facilitate the hypoxia-induced enhanced cardiac workload through increasing SEVR. In practical terms, physiological evaluation at rest before performing a hypoxic test, going to high altitude, or selecting athletes for oxygen-sensitive sports competitions may be helpful to identify persons with poorer or more energetically expensive physiological reactions.

Conflict of Interest

There is no conflict of interest.

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