Original Article

Systemic blood pressure at exercise in hypoxia in hypertensive and normotensive patients

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Objectives: The current study aimed to determine whether acute hypoxia exposure in laboratory conditions associated with exercise induces an increase in systemic blood pressure (BP) in normotensive and hypertensive patients, and whether hypertensive patients are more prone to develop severe acute mountain sickness (sAMS). Finally, to determine if BP changes at exercise in acute hypoxia in hypertensive patients are predictive factors for sAMS.

Methods: From 2012 to 2015, 852 normotensive and 106 hypertensive patients went through an acute hypoxia exercise test before a sojourn at high altitude. A subgroup of 228 normotensive was selected to match age, sex ratio, body weight and BMI and compared with the hypertensive group.

Results: In normotensive and hypertensive patients, for a given workload, BP was higher in hypoxia than in normoxia, whereas, for a given heart rate, it was lower in hypoxia than in normoxia. Hypertensive patients treated by beta-blockers showed lower arterial oxygen saturation (vs. other treatments) and blunted cardiac and ventilatory responses to hypoxia at exercise. Based on questionnaires filled out at high altitude, hypertensive patients were not more prone than normotensive patients to develop sAMS. During the laboratory acute hypoxic exercise test, hypertensive patients suffering from sAMS, although taking acetazolamide showed similar BP than hypertensive patients without sAMS and without acetazolamide.

Discussion and conclusion: We hypothesize that acute hypoxia with exercise in laboratory conditions induces a peripheral vasodilation that balances vasoconstriction and tachycardia centrally induced through the adrenergic system. Hypertensive and normotensive patients behave similarly during exercise in acute hypoxia. Acute hypoxia does not exacerbate the exercise-induced increase in BP. BP variation, during the acute hypoxia exercise test, is not a useful predictor of intolerance to high altitude. Based on laboratory tests in acute hypoxia, hypertensive patients may not be at higher risk to develop sAMS at high altitude.

Keywords: acute mountain sickness, altitude, exercise, hypoxia

Abbreviations: ACZ, acetazolamide; AMS, acute mountain sickness; DAP, diastolic arterial pressure; HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema; HCR, cardiac response to hypoxia; HR, heart rate; HVR, ventilatory response to hypoxia; LLS, Lake Louise Score; MAP, mean arterial pressure; sAMS, severe AMS; SAP, systolic arterial pressure; SHAI, severe high altitude illness

INTRODUCTION

A large number of sea-level natives with chronic cardiovascular diseases may travel to areas above 4000 m. As they are unacclimatized, they may suffer as healthy people from severe high-altitude illness [SHAI is a collective term for severe acute mountain sickness (AMS), high-altitude pulmonary (HAPE) and cerebral edema (HACE)] [1].

Several risk factors for SHAI have already been identified and a risk prediction score for SHAI has been proposed, based on clinical and physiological variables. The main risk factor is the chemosensitivity to hypoxia (evaluated by the ventilatory response to a hypoxic challenge at moderate exercise). Other risk factors are young age, female sex, regular physical activity, speed of ascent (>400 m/day) in the acclimatization period, previous history of SHAI, migraine and geographical location [1]. Systemic blood pressure (BP) has never been evaluated as a potential risk factor for SHAI, although it was suggested by Ledderhos *et al.*[2], and a significant relation was found between AMS and mean arterial pressure (MAP) by Liu *et al.* [3]. In our previous studies, no information was available about this potential risk and BP was not measured during exercise [1,4]. Although there is no clear scientific evidence of high BP being a risk factor for SHAI, some field doctors continue to use BP values to allow or forbid ascent for climbers [5].

During a short hypoxic exposure, systemic BP either stays stable or slightly increases [6,7]. The direct effect of hypoxia on microcirculation causes vasodilation at the peripheral level and vasoconstriction at the pulmonary

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level. In the same time, hypoxia leads to a central activation of the adrenergic system, which induces vasoconstriction and tachycardia [8–10]. This vasoconstriction is overridden by locally induced vasodilation, especially during exercise, and has been described as 'functional sympatholysis' resulting in no or small changes in BP and a decrease in peripheral resistance in acute hypoxia [11–15].

The risk of exacerbating a preexisting hypertension at high altitude, and changes in arterial BP are depending on the duration of exposure and the method of pressure evaluation [9,16–19]. In normotensive patients, no change in mean BP, and a decrease in peripheral resistance was observed during a laboratory hypobaric hypoxia test at rest for a maximum of 40 h [20]. A slight increase in systolic but no change in diastolic pressure was found in hypertensive patients at high-altitude exercise [21,22]. Liu *et al*. [3] found an increase in MAP and diastolic arterial pressure (DAP) in acute high-altitude hypoxia. When BP is assessed in ambulatory conditions in hypobaric hypoxia at high altitude, a consistent increase in 24-h BP was observed [7,23,24]. Besides, there are few studies about hypertensive patients and antihypertensive treatments in altitude hypoxia [7,10,23,24].

ECG changes during an acute hypoxic exercise in laboratory conditions in healthy normotensive individuals have already been documented, but hypoxia-induced ECG changes do not predict the susceptibility to SHAI [25]. However, heart rate (HR) response to acute hypoxia at exercise takes part in the prediction score for SHAI [1,4]. We could suspect that hypertension could modify the ECG changes induced by hypoxia. However, to our knowledge, no study has ever described ECG changes in response to hypoxia at exercise in hypertensive patients.

Our objectives were to determine whether acute hypoxia associated with exercise induces an increase in systemic BP in normotensive and hypertensive patients; to determine if hypertensive patients are more prone to develop SHAI at high altitude; to determine if BP at exercise in acute hypoxia in hypertensive patients is a predictive factor for SHAI.

METHODS

Patients

From 2012 to 2015, 1113 sea-level natives (271 in 2012, 234 in 2013, 340 in 2014 and 268 in 2015) went through a hypoxia exercise test at an outpatient mountain medicine consultation before a sojourn at high altitude, which can lead to a preventive prescription of acetazolamide (ACZ). Patients were included when they planed to spend at least 3 days above 4000 m with one night above 3500 m.

Hypertensive patients were previously diagnosed by their family physician when systolic arterial pressure (SAP) was at least 140 mmHg and/or DAP was at least 90 mmHg, with mild-to-moderate stabilized essential hypertension with no change of medication in the 3 preceding months. Drugs used by hypertensive patients were beta-blockers (19%), angiotensin II receptor blockers (40%), angiotensin-converting enzyme inhibitor (ACE inhibitor) (23%), diuretics (21%) and calcium channel-blockers (29%). Normotensive patients taking these drugs for other diseases than high BP [angina, heart failure, rhythm disorders (atrial fibrillation, atrial flutter, Bouveret syndrome and ventricular tachycardia)] were excluded of the study. A proportion of 51% of the hypertensive patients were treated by monotherapy, 25% by bitherapy, 4% by tritherapy and 3% by quadritherapy; they were 17% without oral treatment.

TABLE 1. Characteristics of hypertensive and normotensive patients in the overall cohort

	Normotensive, $n = 852$	Hypertensive, $n = 106$	*P* value*
Female sex, *n* (%)	390 (45.8)	44 (41.5)	0.41
Age (years)	44.7 ± 15.2	60.1 ± 9.0	0.001**
Height (cm)	171.6 ± 9.4	170.2 ± 8.6	0.15
Body weight (kg)	68.7 ± 13.5	73.7 ± 15.0	0.001**
BMI (kg/m^2)	23.2 ± 3.2	25.3 ± 3.9	0.001**
Regular endurance training, *n* (%)	233 (27.3)	16 (15.1)	0.007**

Values are mean ± SD or number (%) when appropriate.
*Student *t* test for quantitative variables, Pearson's χ^2 for qualitative variables.
**Significant ($P < 0.05$).

Initially, 958 patients were included in the study, with 106 hypertensive and 852 normotensive patients, so that the prevalence of hypertension in our outpatient mountain medicine consultation was 11%. Preliminary results showed that normotensive and hypertensive patients differed for age, body weight, BMI and endurance training (Table 1). As those variables might be important in determining the tolerance to hypoxia, we sorted from the total cohort a subgroup of normotensive patients that matched to the hypertensive one for all these variables. Finally, data from 264 normotensive and 106 hypertensive patients were further analyzed.

This study is based on a retrospective use of clinical and physiological data obtained during an acute hypoxia exercise test, which can lead to a preventive prescription of ACZ. Before the inclusion in the testing process, each patient was informed and signed consent documents. The acute hypoxia exercise test, part of a routine evaluation of patients going to high altitude, has been approved by the Ethics Committee of Paris Ile-de-France II [1,4,26].

Protocol

Laboratory testing

As explained in previous studies [1,4,25], patients performed an exercise test consisting of five successive phases: first, rest in normoxia; second, rest in hypoxia (fraction of inspired oxygen 0.115 equivalent to 4800 m altitude); third, exercise in hypoxia at 30% of maximal normoxic power output (EH), fourth, exercise in normoxia with the same power output as in exercise in hypoxia; fifth, exercise in normoxia with the same HR achieved during exercise in hypoxia (EN+). The power output used during the exercise in hypoxia and the exercise in normoxia phases was fixed to approximately 30% of maximal aerobic power, which equals to 40–50% of HR reserve based on the value of theoretical maximal HR [27]. Room air temperature was maintained at 22 °C. The exercise was performed on an electrically braked cycloergometer (ER 900; Jaeger, Wuerzburg, Germany). Minute ventilation (l/min) was measured through a metabograph (V_{max} Encore; CareFusion; SensorMedics, Yorba Linda, California, USA) and arterial O_2 saturation (SaO_2, %) by transcutaneous oximetry (Nellcor

N-595; Nellcor, Pleasanton, California, USA). SAP and DAP were measured with a manual sphygmomanometer and a stethoscope. From a continuous 12-lead ECG recording (Cardiosoft; GE Healthcare, Milwaukee, Wisconsin, USA), manual analysis of ECG recordings for the same HR in both normoxia and hypoxia was available in 185 patients (130 normotensive and 55 hypertensive). They were analyzed in standard and precordial derivations by a trained physician, with an accuracy of 0.5 mm and 0.03 s for voltages and durations, respectively. Ventilatory (HVR, 1/min per kg) and cardiac (HCR, bpm/%) responses to hypoxia and the ratio of the decrease in exercise power output induced by hypoxia for the same HR over the decrease in O_2 saturation (ΔPower/ΔSaE, W/%) were calculated as explained in previous articles [4,27]. A SHAI score and probability were calculated using the clinical and physiological risk factors as previously described [1,26].

Clinical evaluation at high altitude

During their sojourn at high altitude, patients were asked to fill out a daily questionnaire about their medication use, daily level and gain in altitude, sleep altitude, activities, medical consultation, cardiovascular or respiratory complains, symptoms of SHAI based on Lake Louise Score (LLS), HAPE [clinical signs of respiratory distress (dyspnea, cyanosis and rales) later confirmed by a thorax radiograph] and HACE (clinical signs of neurological deficit: ataxia, mental confusion). The LLS is a self-questionnaire based on the most frequent symptoms of AMS: headache, gastrointestinal symptoms (anorexia, nausea or vomiting), weakness and/or fatigue, dizziness/light-headedness and sleeping difficulty [28]. Every item is marked from 0 to 3. LLS score has a minimum of 0 and a maximum of 15. As results showed that no patient suffered from pure HAPE and HACE, either hypertensive or normotensive, we restricted the analysis to severe AMS (sAMS) to deal with a homogeneous group of patients who were included in the sAMS+ group patients with sAMS as defined by the LLS questionnaire (headache and LLS ≥ 6) [1,4].

A large proportion of patients (41%) took preventive ACZ during their sojourn as this prescription takes part of our decisional tree in case of high SHAI probability [1,26]. Two specific groups were compared in each normotensive and hypertensive category: patients who experienced sAMS although taking ACZ (patients particularly intolerant to high altitude) and patients who did not suffer from SHAI while they did not take preventive ACZ (patients particularly tolerant to high altitude).

Statistical analysis

In the whole population, we compared hypertensive and normotensive patients for all anthropometrical, clinical, physiological and ECG variables. In the hypertensive group, we compared patients treated by beta-blockers with patients without beta-blockers. In the normotensive and hypertensive subgroups, for which we had the feedback about their tolerance/intolerance to sAMS, we compared patients depending on having experienced sAMS with ACZ or having not experienced sAMS without ACZ.

For each comparison, we used Student t tests for quantitative variables and Pearson's χ^2 test or Fisher exact test (when <5 patients in any condition) for qualitative variables. Changes in BPs induced by exercise or hypoxia were compared using a paired Student t test.

The differences were considered statistically significant when P less than 0.05. Quantitative variables were reported as mean ± SD and qualitative variables as n (%). Statistical analysis was performed by using STATA software version 14 (Stata Inc., College Station, Texas, USA).

RESULTS

Hypertensive vs. normotensive patients in laboratory conditions

Anthropometrical, clinical and physiological variables

When comparing hypertensive and normotensive patients matched for sex ratio, age, body weight, BMI and regular endurance training, history of angina and hypercholesterolemia were more frequent in the hypertensive group (Table 2). The planned altitude was slightly lower in hypertensive than normotensive patients. HCR exercise and ΔPower/ΔSaE were significantly lower in hypertensive patients. There was no difference in SHAI score and probability between hypertensive and normotensive patients.

When the normotensive group ($n = 264$) was compared with hypertensive patients not taking beta-blockers ($n = 86$), similar results were found, except that, as expected, exercise HCR was no longer lower in hypertensive patients (results not shown).

Blood pressure and ECG

Variations of SAP and DAP during the acute hypoxic exercise test for hypertensive and normotensive patients are presented in Fig. 1 and Table 2. Arterial pressures were higher in hypertensive patients than in normotensive patients in all conditions. SAP at exercise was higher in hypoxia than in normoxia for the same power output but lower than in normoxia for the same HR (EN+), in both groups ($P < 0.001$). DAP was higher in hypoxia than in normoxia for the same power output in both groups ($P < 0.001$) but similar to normoxia for the same HR (EN+) in both groups. It is important to note that there was no significant difference between hypertensive and normotensive groups in the hypoxia-induced changes (EH−EN+) in BP.

Comparing ECG characteristics of hypertensive and normotensive patients in exercise in acute hypoxiaand exercise in normoxia (EN+), no significant difference was found (results not shown), except that during exercise, hypertensive patients had a lower HR ($P = 0.02$) and a lower slope of the ST segment in V_6 ($P = 0.02$) than normotensive patients.

Hypertensive patients with and without beta-blockers in laboratory conditions

Anthropometrical, clinical and physiological variables

Among the hypertensive patients, 20 patients (18.9%) were treated by beta-blockers (Table 3). They had more rhythm or conduction disorder history than hypertensive patients without beta-blocker treatment. As expected, at each phase

TABLE 2. Anthropometrical, clinical and physiological variables in hypertensive and normotensive patients

	Normotensive, $n = 264$	Hypertensive, $n = 106$	*P* value*
Female sex, *n* (%)	110 (41.7)	44 (41.5)	0.41
Age (years)	59.0 ± 9.8	60.1 ± 9.0	0.31
Height (cm)	170.3 ± 9.4	170.2 ± 8.6	0.90
Body weight (kg)	73.6 ± 14.9	73.7 ± 15.0	0.91
BMI (kg/m^2)	25.2 ± 3.4	25.3 ± 3.9	0.61
History of angina, *n* (%)	5 (1.9)	7 (6.6)	0.02**
Rhythm or conduction disorder, *n* (%)	31 (11.7)	8 (7.5)	0.25
Hypercholesterolemia, *n* (%)	66 (25.0)	42 (39.6)	0.005**
History of migraine, *n* (%)	28 (10.6)	9 (8.4)	0.62
Postmenopausal women, *n* (% in female)	96 (88.9)	39 (88.6)	0.95
Smokers, *n* (%)	28 (10.6)	8 (7.5)	0.35
History of obstructive sleep apneas, *n* (%)	11 (4.9)	9 (8.5)	0.12
Regular endurance training, *n* (%)	49 (18.6)	16 (15.1)	0.45
History of severe AMS, *n* (%)	22 (8.3)	6 (5.7)	0.41
Mountaineers, *n* (%)	4 (1.5)	1 (0.9)	0.72
Tourists, *n* (%)	69 (26.1)	34 (32.1)	0.27
Workers, *n* (%)	28 (10.6)	7 (6.6)	0.23
Trekkers, *n* (%)	163 (61.7)	64 (60.4)	0.85
Planned altitude (m)	4923 ± 843	4710 ± 793	0.03**
SAP RN (mmHg)	128.4 ± 14.1	136.3 ± 17.7	0.001**
DAP RN (mmHg)	77.8 ± 9.0	81.2 ± 9.6	0.001**
SAP EH (mmHg)	156.9 ± 22.4	168.0 ± 22.9	0.001**
DAP EH (mmHg)	83.1 ± 13.6	89.1 ± 14.9	0.001**
SAP EN (mmHg)	150.3 ± 21.7	161.7 ± 21.4	0.001**
DAP EN (mmHg)	79.6 ± 13.0	84.6 ± 13.4	0.001**
SAP EN+ (mmHg)	164.4 ± 23.4	173.3 ± 23.3	0.001**
DAP EN+ (mmHg)	84.0 ± 13.0	89.0 ± 14.9	0.002**
ΔSAP EH-EN+ (mmHg)	−7.5 ± 11.7	−5.7 ± 12.0	0.20
ΔDAP EH-EN+ (mmHg)	−0.8 ± 10.2	−0.1 ± 9.6	0.53
ΔSaR (%)	8.6 ± 2.5	8.5 ± 2.5	0.63
ΔSaE (%)	18.7 ± 4.5	18.2 ± 4.5	0.29
HCR exercise (bpm/%)	0.81 ± 0.35	0.72 ± 0.39	0.023**
HVR exercise (1/min per kg)	0.94 ± 0.35	0.95 ± 0.36	0.88
ΔPower/ΔSaE (W/%)	2.3 ± 1.0	1.9 ± 0.9	0.001**
SHAI score	4.6 ± 1.9	4.7 ± 1.9	0.43
SHAI probability (%)	31.6 ± 29.6	32.9 ± 30.6	0.56

Values are mean ± SD or number (%) when appropriate. ΔSaE, desaturation at exercise; ΔSaR, desaturation at rest; AMS, acute mountain sickness; DAP, diastolic arterial pressure; EH, exercise in hypoxia; EN+, exercise in normoxia with the same HR achieved during EH; HCR, cardiac response to hypoxia; HVR, ventilatory response to hypoxia; RN, rest in normoxia; SAP, systolic arterial pressure; SHAI, severe high-altitude illness.
*Student *t* test for quantitative variables, Pearson's χ^2 or Fisher exact test (when <5 patients in any condition) for qualitative variables.
**Significant ($P < 0.05$).

of the hypoxia exercise test, HR was lower in patients treated by beta-blockers. Hypertensive patients treated by beta-blockers had a lower SaO_2 in all conditions. Desaturation at rest (ΔSaR) and exercise (ΔSaE) were higher in hypertensive patients treated by beta-blockers. Cardiac and ventilatory responses to hypoxia at exercise were lower in hypertensive patients treated by beta-blockers.

Blood pressure and ECG

SAP in hypertensive patients with beta-blockers at exercise in normoxia (EN+) was lower than in hypertensive patients without beta-blockers.

Hypertensive patients with beta-blockers had a lower HR at exercise in hypoxia and EN+ ($P = 0.02$) and a lower slope of the ST segment in V_6 at EN+ ($P = 0.005$) than hypertensive patients without beta-blockers (results not shown).

Daily high-altitude questionnaires analysis compared with laboratory testing

The daily questionnaire was sent back by 182 patients (49.2%). A comparison of basal physiological and clinical characteristics of patients who sent back or not the questionnaire showed a significant difference only in BMI of normotensive patients (responders: 24.4 ± 3.1 vs. nonresponders: 25.9 ± 3.6 kg/m^2). According to the LLS, 40 (22%) patients of the overall population suffered from sAMS during their sojourn at high altitude (Table 4). Proportion of patients who experienced sAMS was identical (22%) in hypertensive and normotensive groups. A total of 74 patients took ACZ as a preventive treatment during their sojourn at high altitude (41%). None of the patients reported any cardiovascular incident (myocardial infarction, cerebral stroke, arrhythmia).

Characteristics of the particularly intolerant (sAMS+/ACZ+) and tolerant (sAMS−/ACZ−) groups in both normotensive ($n = 75$) and hypertensive ($n = 37$) group are presented in Table 5. As expected, SHAI score and probability were higher in the intolerant group compared with the tolerant group, either in hypertensive or normotensive patients.

In the normotensive group, intolerant patients were younger and mostly female (nonmenopaused) and tended to have a more frequent history of migraine than the

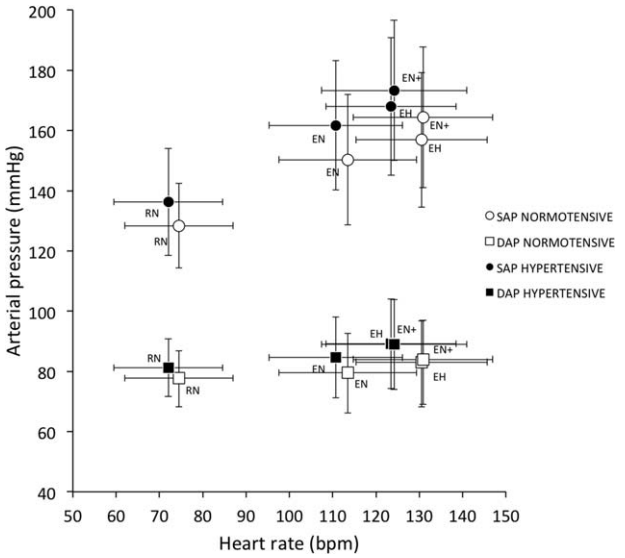

FIGURE 1 Systemic blood pressure (mmHg) in hypertensive and normotensive patients during the hypoxia exercise test as a function of heart rate (bpm). Bars indicate SD. DAP, diastolic arterial pressure; EH, exercise in hypoxia; EN, exercise in normoxia; EN+, exercise in normoxia with the same HR achieved during EH; RN, rest in normoxia; SAP, systolic arterial pressure.

tolerant group. Significantly, systolic pressure was lower in the intolerant group. However, changes induced by acute hypoxia at exercise were similar in the two groups. As expected, desaturation at rest (ΔSaR) and exercise (ΔSaE) was higher, and HVR exercise and ΔPower/ΔSaE were lower in the intolerant vs. tolerant group.

In hypertensive patients, there was more history of hypercholesterolemia in the intolerant than in the tolerant group. Differences in ΔSaE and HVR between tolerant and intolerant patients were similar to the normotensive group, but did not reach significance. No significant differences were found in arterial pressures. Hypoxia-induced ECG changes were similar between groups (results not shown).

DISCUSSION

This is the first study to describe changes in systemic arterial pressure during exercise in acute hypoxia in a large cohort of 370 patients. It is also one of the first studies to focus on hypertensive patients at high altitude [2,7,10,16,23,24,29]. We did not evidence any acute hypoxia-induced increase in systemic BP in healthy patients during exercise (for the same HR) contrary to Liu *et al.* [3]. Arterial pressures of hypertensive patients were always higher than those of normotensive patients at rest and exercise, but the hypoxia-induced changes in pressure were similar in the two groups, similarly to what was found in hypertensive trekkers [16]. From the altitude questionnaires, we demonstrated that the proportion of sAMS in hypertensive patients was similar to that of normotensive ones. Arterial pressures and ECG characteristics during the hypoxia exercise test were similar between hypertensive patients who were intolerant to high altitude (sAMS with ACZ) and those who were tolerant to high altitude (no sAMS, no ACZ). Systolic pressures were slightly lower in intolerant patients, probably, because they were younger than tolerant ones.

The use of a fifth phase (EN+) in our hypoxic exercise test allows us to differentiate the effects of the adrenergic drive and of hypoxia at exercise, realizing a 'functional adrenergic clamp'. When passing from exercise in hypoxia to exercise in normoxia (keeping the same power output), HR and cardiac output (*CO*) decrease and arterial pressures as well. Then, when augmenting power output in normoxia (EN+) to reach the same level of HR than in exercise in hypoxia, the difference in arterial pressures is only due to a difference in vascular resistance, assuming that changes in *CO* follow changes in HR. In a recent review, Siebenmann and Lundby [15] suggest that in acute hypoxia, *CO* is increased by an acceleration of HR, whereas stroke volume (SV) remains unchanged. Lador *et al.* nicely showed that in acute hypoxia, SV was not modified at exercise at 50 and 100 W. Moreover, their results are in line with our hypothesis, as they clearly show that, in hypoxia, *CO* is unchanged, MAP decreases, as well as peripheral resistance [14]. From a preliminary study performed on a subgroup ($n = 10$) of the present cohort, *CO* was continuously measured during the test by impedance plethysmography [30]. It appeared that SV was not modified by hypoxia, either at rest or at exercise, so that changes in *CO* were directly related to changes in HR.

In fact, in the current study, systolic arterial pressure decreases in exercise in normoxia vs. exercise in hypoxia, but increases in EN+ vs. exercise in hypoxia. Altogether, variations of BP at exercise between normoxia and hypoxia are not significantly different between hypertensive and normotensive patients.

An interesting observation was the effect of beta-blockers on SaO_2. Both at rest and exercise, in normoxia and hypoxia, SaO_2 was lower in hypertensive patients treated by beta-blockers than with other drugs. The observed decrease in HCR at exercise is not surprising, whereas the decrease in HVR at exercise in hypertensive patients treated by beta-blockers is more challenging, although a similar effect was already found at rest in hypoxia [24]. Moreover, it was suggested that beta-blockers reduce ventilatory response during exercise in hypoxia possibly by reducing peripheral chemoreflex sensitivity [31]. The analysis of the pharmacological effects of beta-blockers during exercise in hypoxia deserves further investigation by distinguishing different classes of beta-blockers [32]. In fact, quite different results can be obtained, at least at rest, by administering a beta-1 selective or a non-beta-1 selective blocker [33]. In fact, the majority of our hypertensive patients were treated with cardioselective first generation beta-blockers [34]. As expected, ST slope in V_6 was lower in the hypertensive group than in the normotensive group, due to the slower HR of patients treated by beta-blockers.

The prevalence of hypertension in the population coming to our outdoor mountain medicine consultation (11%) was clearly lower than in a general adult French population, as evaluated in a group of 4825 persons in which 47% of men and 35% of women were found hypertensive [35]. This difference might be due to the specific profile of patients aiming for a sojourn at high altitude for leisure or tourism, with a probable higher physical activity and a healthier lifestyle. For example, the mean BMI of our hypertensive population is 25.3 kg/m^2, whereas in a Finish study of 2004,

TABLE 3. Anthropometrical, clinical and physiological variables in hypertensive patients with and without beta-blocker treatment

	Hypertensive beta-blocker−, $n=86$	Hypertensive beta-blocker+, $n=20$	*P* value*
Female sex, *n* (%)	34 (39.5)	10 (50)	0.39
Age (years)	59.5 ± 9.1	62.6 ± 8.7	0.17
Height (cm)	170.3 ± 8.7	169.6 ± 8,2	0.74
Body weight (kg)	73.2 ± 15.5	76.0 ± 12.9	0.47
BMI (kg/m^2)	25.1 ± 4.0	26.3 ± 3.4	0.21
History of angina, *n* (%)	5 (5.8)	2 (10)	0.49
Rhythm or conduction disorder, *n* (%)	4 (4.7)	4 (20)	0.019**
Hypercholesterolemia, *n* (%)	32 (37.2)	20 (100)	0.29
History of migraine, *n* (%)	8 (9.3)	1 (5)	0.53
Postmenopausal women, *n* (% of women)	29 (33.7)	10 (50)	0.51
Smokers, *n* (%)	6 (7.0)	2 (10)	0.65
History of obstructive sleep apneas, *n* (%)	7 (8.1)	2 (10)	0.79
Regular endurance training, *n* (%)	13 (15.1)	3 (15)	0.74
History of severe AMS, *n* (%)	7 (8.1)	1 (5)	0.06
Mountaineers, *n* (%)	1 (1.2)	0 (0)	0.08
Tourists, *n* (%)	23 (26.7)	11 (55)	0.08
Workers, *n* (%)	7 (8.1)	0 (0)	0.08
Trekkers, *n* (%)	55 (64.0)	9 (45)	0.08
SAP RN (mmHg)	136.3 ± 18.1	136.3 ± 16.5	0.99
DAP RN (mmHg)	81.1 ± 9.7	81.6 ± 8.9	0.85
Sa RN (%)	97.8 ± 1.1	97.1 ± 1.0	0.006**
HR RN (bpm)	77.0 ± 13.6	68.5 ± 9.8	0.009**
Sa RH (%)	89.6 ± 2.9	87.6 ± 2.5	0.008**
HR RH (bpm)	83.6 ± 14.4	74.2 ± 9.3	0.008**
SAP EH (mmHg)	169.4 ± 23.7	162 ± 18.2	0.19
DAP EH (mmHg)	88.6 ± 15.0	91.3 ± 14.3	0.48
Sa EH (%)	79.3 ± 4.9	76.3 ± 5.3	0.01**
HR EH (bpm)	125.7 ± 14.4	114.3 ± 14.3	0.002**
SAP EN+ (mmHg)	175.8 ± 23.7	162.6 ± 17.9	0.025**
DAP EN+ (mmHg)	88.7 ± 15.6	90.0 ± 12.0	0.74
Sa EN+ (%)	97.1 ± 1.3	96.4 ± 1.6	0.040**
HR EN+ (bpm)	126.5 ± 16.4	114.4 ± 15.2	0.003**
ΔSAP EH-EN+ (mmHg)	−6.8 ± 12.1	−1.1 ± 10.7	0.06
ΔDAP EH-EN+ (mmHg)	−0.3 ± 10.0	0.8 ± 8.0	0.66
ΔSaR (%)	8.25 ± 2.52	9.53 ± 1.92	0.04**
ΔSaE (%)	17.7 ± 4.4	20.3 ± 4.3	0.018**
HCR exercise (bpm/%)	0.76 ± 0.39	0.51 ± 0.35	0.010**
HVR exercise (1/min per kg)	0.98 ± 0.35	0.79 ± 0.35	0.030**
ΔPower/ΔSaE (W/%)	1.98 ± 0.98	1.62 ± 0.74	0.13
SHAI score	3.36 ± 2.16	4.23 ± 2.29	0.21
SHAI probability (%)	19.46 ± 25.89	32.13 ± 33.01	0.15

Values are mean ± SD or number (%) when appropriate. ΔSaE, desaturation at exercise; ΔSaR, desaturation at rest; AMS, acute mountain sickness; DAP, diastolic arterial pressure; EH, exercise in hypoxia; EN+, exercise in normoxia with the same HR achieved during EH; HCR, cardiac response to hypoxia; HVR, ventilatory response to hypoxia; Hypertensive beta-blocker +, patients affected by hypertension treated by beta-blocker; Hypertensive beta-blocker−, patients affected by hypertension not treated by beta-blocker; RN, rest in normoxia; SAP, systolic arterial pressure; SHAI, severe high-altitude illness.
*Student *t* test for quantitative variables, Pearson's χ^2 or Fisher exact test (when <5 patients in any condition) for qualitative variables.
**Significant ($P<0.05$).

TABLE 4. Distributions of patients who responded to the questionnaire at high altitude

Total	182	Normotensive	123	sAMS−	96	ACZ−	61
						ACZ+	35
				sAMS+	27	ACZ−	13
						ACZ+	14
		Hypertensive	59	sAMS−	46	ACZ−	29
						ACZ+	17
				sAMS+	13	ACZ−	5
						ACZ+	8

ACZ−, patients who did not take preventive acetazolamide treatment; ACZ+, patients who took preventive acetazolamide treatment; sAMS−, patients not affected by severe acute mountain sickness; sAMS+, patients affected by severe acute mountain sickness.

mean BMI of hypertensive men was 27.0 kg/m^2 and of women 26.3 kg/m^2 [36].

Stabilized hypertensive patients seem to have no more risks to develop sAMS than normotensive patients at high altitude. They do not increase more their arterial pressures during moderate exercise in acute hypoxia than normotensive patients. Being hypertensive or not had no impact on the objective in terms of maximal altitude reached. Then it

TABLE 5. Anthropometrical, clinical and physiological variables in hypertensive and normotensive patients depending on being affected by severe acute mountain sickness with acetazolamide preventive treatment or being not affected by severe acute mountain sickness without acetazolamide treatment

	Normotensive, $n = 75$		Hypertensive, $n = 37$	
	sAMS+/ACZ+, $n = 14$	sAMS−/ACZ−, $n = 61$	sAMS+/ACZ+, $n = 8$	sAMS−/ACZ−, $n = 29$
Female sex, *n* (%)	11 (79)	21 (34)*	4 (36)	11 (38)
Age (years)	53.4 ± 10.6	60.2 ± 8.6*	56.6 ± 8.7	60.4 ± 10.0
Height (cm)	166.9 ± 7.8	170.9 ± 9.3	168.9 ± 8.1	170.1 ± 8.6
Body weight (kg)	66.1 ± 8.0	72.1 ± 14.1	76.4 ± 17.0	72.8 ± 12.1
BMI (kg/m^2)	23.7 ± 2.5	24.6 ± 3.0	26.6 ± 5.0	25.1 ± 3.0
History of angina, *n* (%)	0 (0)	2 (3)	0 (0)	1 (3.4)
Rhythm or conduction disorder, *n* (%)	2 (14)	4 (7)	0 (0)	1 (3.4)
Hypercholesterolemia, *n* (%)	2 (14)	19 (31)	6 (75)	10 (34.5)*
History of migraine, *n* (%)	3 (21)	4 (7)	1 (12.5)	3 (10.3)
Postmenopausal women, *n* (%)	6 (55)	19 (95)*	3 (37.5)	9 (31.0)
Smokers, *n* (%)	1 (5.6)	7 (7)	0 (0)	2 (6.9)
History of obstructive sleep apneas, *n* (%)	1 (5.6)	3 (3)	1 (12.5)	2 (6.9)
Snorers, *n* (%)	1 (7)	5 (8)	1 (12.5)	19 (65.5)
Regular endurance training, *n* (%)	1 (7)	12 (20)	1 (12.5)	3 (10.3)
History of severe AMS, *n* (%)	1 (7)	2 (3)	1 (12.5)	1 (3.4)
Mountaineers, *n* (%)	0 (0)	2 (3)	0 (0)	0 (0)
Tourists, *n* (%)	5 (36)	16 (26)	1 (12.5)	13 (44.8)
Workers, *n* (%)	0 (0)	6 (10)	1 (12.5)	0 (0)
Trekkers, *n* (%)	9 (64)	37 (61)	6 (75)	16 (55.2)
Maximal altitude planned (m)	5083 ± 781	4931 ± 934	4601 ± 451	4870 ± 541
Maximal altitude reached (m)	4980 ± 678	4843 ± 930	4869 ± 386	4888 ± 602
SAP RN (mmHg)	121.5 ± 11.8	130.2 ± 14.8*	133.8 ± 21.1	137.4 ± 22.2
DAP RN (mmHg)	74.9 ± 6.4	79.4 ± 9.1	85.6 ± 6.2	82.1 ± 11.2
SAP EH (mmHg)	143.9 ± 12.0	158.4 ± 18.7*	164.4 ± 24.4	162.2 ± 24.6
DAP EH (mmHg)	77.1 ± 12.0	84.4 ± 13.6	90.6 ± 11.8	86.2 ± 12.6
SAP EN+ (mmHg)	150.8 ± 20.2	166.9 ± 20.7*	163.8 ± 23.3	169.1 ± 26.0
DAP EN+ (mmHg)	78.5 ± 10.9	82.9 ± 12.0	88.8 ± 18.3	83.9 ± 14.6
ΔSAP EH-EN+ (mmHg)	−7.3 ± 11.5	−8.8 ± 12.0	0.6 ± 13.7	−7.3 ± 11.7
ΔDAP EH-EN+ (mmHg)	−0.8 ± 12.1	1.5 ± 11.5	1.9 ± 13.1	1.8 ± 10.1
ΔSaR (%)	10.0 ± 2.2	7.7 ± 1.9*	7.4 ± 1.7	7.9 ± 1.9
ΔSaE (%)	21.6 ± 3.4	17.4 ± 4.2*	17.3 ± 5.3	16.7 ± 3.8
HCR exercise (bpm/%)	0.78 ± 0.36	0.86 ± 0.33	0.65 ± 0.28	0.69 ± 0.43
HVR exercise (1/min per kg)	0.69 ± 0.25	1.10 ± 0.37*	0.81 ± 0.15	1.02 ± 0.34
ΔPower/ΔSaE (W/%)	1.8 ± 0.7	2.6 ± 1.0*	2.2 ± 0.9	2.0 ± 1.1
SHAI score	6.4 ± 1.6	3.8 ± 1.5*	4.9 ± 2.1	2.6 ± 1.7*
SHAI probability (%)	61.3 ± 28.7	20.2 ± 22.3*	39.3 ± 28.7	11.1 ± 19.3*

Values are mean ± SD or number (%) when appropriate. Student *t* test for quantitative variables, Pearson's χ^2 or Fisher exact test (when <5 patients in any condition) for qualitative variables. ΔSaR, desaturation at rest; ΔSaE, desaturation at exercise; ACZ−, patients who did not take preventive acetazolamide; ACZ+, patients who took preventive acetazolamide; AMS, acute mountain sickness; DAP, diastolic arterial pressure; EH, exercise in hypoxia; EN+, exercise in normoxia with the same HR achieved during EH; HCR, cardiac response to hypoxia; HVR, ventilatory response to hypoxia; RN, rest in normoxia; sAMS−, patients not affected by severe acute mountain sickness; sAMS+, patients affected by severe acute mountain sickness; SAP, systolic arterial pressure; SHAI, severe high-altitude illness.
*Significant ($P < 0.05$), compared with sAMS+/ACZ+ group.

appears useless to measure arterial pressure at the arrival at an altitude base camp as a predictive factor for sAMS [5]. Moreover, no hypertensive subject reported angina, heart failure, rhythm or conduction disorder at high altitude, even if ischemic events at high altitude can be asymptomatic [37]. Nevertheless, our results concerning tolerant and intolerant patients confirm the efficiency of an outpatient medicine consultation associated with a hypoxia exercise test, leading to the calculation of a SHAI predictive score before a sojourn at high altitude, either in normotensive or hypertensive patients [26,38].

Limitations

The relatively small number of patients who suffered from sAMS ($n = 13$) could limit the relevance about susceptibility of this population to sAMS.

The heterogeneity of antihypertensive medications associated or not with a beta-blocker represents a confounding factor for analyzing the isolated effects of a beta-blocker in hypertensive patients during the hypoxia exercise test and at high altitude. This heterogeneity is an important limitation when considering the effects of hypoxia and exercise on BP in hypertensive patients. However, this diversity of treatment is a common fact in hypertension. Acetazolamide [ACZ, 250 mg twice daily (b.i.d.)] has shown a slight hypotensive effect at rest [39]. However, in the current study and like in most cases nowadays, ACZ was prescribed at 125 mg b.i.d., which has very little effect on BP at rest [40], especially when patients are asked to drink abundantly when taking this medication, although it has been recently shown to induce a slight but sustained reduction in BP during submaximal exercise [41]. In any case, we analyzed two separate groups, taking or not ACZ,

and the proportion of patients taking ACZ was the same in normotensive and hypertensive groups (Normotensive: 40%; Hypertensive: 42%, from Table 4).

As none of the patients experienced overt cerebral or pulmonary edema, we cannot conclude about the importance of BP measurements in these rare (less than 2%) but severe pathological conditions [4].

We cannot exclude that each phase might be influenced by the previous phase and especially that the normoxic exercise phase can be influenced by the hypoxic phases.

Perspectives

The current study, comparing two groups of hypertensive and normotensive patients matched for age, sex and BMI, who performed a hypoxia exercise test at an outpatient medicine consultation before a sojourn at high altitude, shows that acute hypoxia induced an increase in systemic arterial pressure when exercise is performed at the same power output but a decrease in pressure when HR is controlled. Arterial pressures of 106 hypertensive patients behaved like normotensive patients during exercise in acute hypoxia, there was no exacerbation of preexisting hypertension. Beta-blockers might have a deleterious effect on cardiac and ventilatory response to hypoxia, leading to a more pronounced desaturation at rest and exercise. Hypertensive patients are not more prone to develop sAMS than normotensive patients. Tolerant and intolerant patients, either normotensive or hypertensive, differ by the same physiological characteristics determined by a hypoxia-exercise test. Analysis of systemic arterial pressure and ECG characteristics should not be considered as useful to detect intolerant patients.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Reviewer 1

Strengths: reasoning physiologically sound coming from a highly experienced laboratory; large cohort of healthy subjects and hypertensive subjects undergoing exercise test in normoxia and hypoxia in laboratory conditions at sea level before exposure to high-altitude hypoxia.

Weakness: results related to exercise responses at "hyper-acute" normobaric hypoxia exposure (few minutes) in laboratory conditions, not necessarily reflecting cardiovascular adaptation in real life high-altitude hypoxia exposure; reasoning based on the assumption (data not available) that at a same heart rate in normoxic and hypoxic condition during exercise stroke volume would be the same.