Changes in Subendocardial Viability Ratio With Acute High-Altitude Exposure and Protective Role of Acetazolamide

Paolo Salvi, Miriam Reversa, Andrea Faini, Andrea Giuliano, Francesca Gregorini, Piergiuseppe Agostoni, Carlos G. Ramos Becerra, Grzegorz Bilo, Carolina Lombardi, Michael F. O’Rourke, Giuseppe Mancia, Gianfranco Parati

Abstract—High-altitude tourism is increasingly frequent, involving also subjects with manifest or subclinical coronary artery disease. Little is known, however, on the effects of altitude exposure on factors affecting coronary perfusion. The aim of our study was to assess myocardial oxygen supply/demand ratio in healthy subjects during acute exposure at high altitude and to evaluate the effect of acetazolamide on this parameter. Forty-four subjects (21 men, age range: 24–59 years) were randomized to double-blind acetazolamide 250 mg bid or placebo. Subendocardial viability ratio and oxygen supply/demand ratio were estimated on carotid artery by means of a validated PulsePen tonometer, at sea level, before and after treatment, and after acute and more prolonged exposure to high altitude (4559 m). On arrival at high altitude, subendocardial viability ratio was reduced in both placebo (from 1.63±0.15 to 1.18±0.17; P<0.001) and acetazolamide (from 1.68±0.25 to 1.35±0.18; P<0.001) groups. Subendocardial viability ratio returned to sea level values (1.65±0.24 after 3 days at high altitude under acetazolamide but remained lower than at sea level under placebo (1.42±0.22; P<0.005 versus baseline). At high altitude, oxygen supply/demand ratio fell both under placebo (from 29.6±4.0 to 17.3±3.0; P<0.001) and acetazolamide (from 32.1±7.0 to 22.3±4.6; P<0.001), its values remaining always higher (P<0.001) on acetazolamide. Administration of acetazolamide may, thus, antagonize the reduction in subendocardial oxygen supply triggered by exposure to hypobaric hypoxia. Further studies involving also subjects with known or subclinical coronary artery disease are needed to confirm a protective action of acetazolamide on myocardial viability under high-altitude exposure. (Hypertension. 2013;61:793-799.) • Online Data Supplement

Key Words: acetazolamide ■ altitude ■ arterial stiffness ■ hypobaric hypoxia ■ myocardial oxygen demand ■ pulse wave analysis

Tourism to high altitude is more and more popular, and this carries the possibility that a significant number of subjects with either manifest or subclinical ischemic heart disease are exposed to acute hypobaric hypoxia and to the potentially adverse cardiovascular effects of ascending several thousand meters above sea level. These effects include an imbalance between myocardial oxygen supply and demand, which, when severe enough, might reduce myocardial perfusion below a critical threshold. This condition, in coronary patients, has been shown to be able to trigger an acute event.

A noninvasive assessment of the degree of myocardial perfusion relative to left-ventricular workload can be obtained through the quantification of subendocardial viability ratio (SEVR). This parameter was introduced by G.D. Buckberg at the beginning of the 1970s, based on hemodynamic studies performed in large animals and in humans. It is computed as the ratio between diastolic pressure–time index (DPTI, an estimate of myocardial oxygen supply based on both coronary driving pressure in diastole and diastolic time) and systolic pressure–time index (SPTI, an estimate of myocardial consumption of oxygen). The advent of reliable noninvasive diagnostic methods, such as transcutaneous arterial tonometry and cardiac ultrasounds, has offered the possibility to make SEVR assessment easier and feasible not only in daily clinical practice but also in challenging conditions, such as high-altitude research. In the latter case, it offers the possibility to at least indirectly explore whether exposure to high-altitude hypobaric hypoxia may indeed influence factors related to myocardial viability.

The aim of our study was, thus, to investigate the supply/demand ratio for myocardial blood flow during acute exposure...
to high altitude and to assess the effect of acetazolamide, a potent carbonic anhydrase inhibitor commonly used for prevention and treatment of acute mountain illness, on this parameter.10-12

Methods

Study Design and Protocol

Forty-four healthy lowlanders were included in a randomized, double-blind, parallel group, placebo-controlled study. Only subjects without known cardiovascular disease, with no chronic cardiovascular therapy, no history of severe mountain sickness, no recent exposure to altitudes ≥2000 m, and no contraindications to acetazolamide were included in the study, provided that a stress test immediately before the inclusion did not show evidence of reduced coronary reserve. After recruitment, subjects were randomly assigned to receive placebo or acetazolamide, 250 mg twice daily, for 3 days at sea level and again during the entire duration of the permanence at high altitude starting from departure day.

Ascent from Milan (122 m above sea level) to the high-altitude laboratory (Capanna Regina Margherita, CRM, Monte Rosa, 4559 m) was completed in <28 hours. CRM was reached from Alagna Valsesia (altitude 1130 m) with subjects being first transported by cable-car up to Punta Indren (3200 m) and then hiking to Gnifetti hut (altitude 3647 m). After an overnight stay at this altitude, subjects continued their hike up to CRM.

All measurements were obtained in 4 conditions: (1) at sea level, off-treatment; (2) at sea level, on the third day of the double-blind treatment with acetazolamide or placebo; (3) early at high altitude (on the first day after arrival to CRM), on treatment with acetazolamide or placebo; and (4) after 3 full days of permanence at high altitude, while on the same treatments.

To avoid interference by the physical activity involved in the ascent to the high-altitude laboratory, data collection was started at least 4 hours after reaching CRM. Data were always collected in rooms kept at the stable ambient air temperatures of 19°C to 20°C.

The study protocol was approved by the ethical committee of the Istituto Auxologico Italiano, Milan, Italy. All participants gave their written informed consent to the study procedures.

Subendocardial Viability Ratio

The myocardial perfusion relative to left ventricle workload has been indirectly estimated by SEVR12 (Figure 1), calculated using the following formula: SEVR = DPTI/SPTI.

DPTI represents the area between the aortic and left-ventricular pressure curves in diastole: DPTI = ([mean diastolic aortic pressure−mean diastolic left ventricular pressure]/diastolic time). Left-ventricular mean diastolic pressure was estimated from the left-ventricular end-diastolic pressure value provided by echocardiography,14 as detailed in the online-only Data Supplement.

SPTI represents the area under the aortic pressure curve in systole: SPTI = mean systolic aortic pressure (corresponding to left-ventricular mean systolic pressure)/left-ventricular ejection time. The 2 areas, thus, reflect blood flow supply (DPTI) and demand (SPTI) and their ratio (ie, SEVR) indirectly gives information on the adequacy of subendocardial blood flow.

A critical value for SEVR of 0.5 has been suggested,7,8,13-16 below which insufficient subendocardial perfusion may occur, as indicated by a corresponding reduction of the ratio of subendocardial/subepicardial flow per gram of left-ventricular myocardium.

Oxygen Supply/Demand Ratio (SEVR × CaO2)

Taking into account that high altitude is characterized by low-oxygen arterial saturation, which might make subendocardial oxygen supply worse, the traditional formula defining SEVR was modified, converting the measure of myocardial blood flow supply (DPTI) into a measure of myocardial oxygen delivery. This was done by multiplying SEVR by the arterial oxygen content (CaO2)8 to evaluate the oxygen supply/demand ratio as follows:

\[
SEVR \times CaO_2 = \frac{CaO_2 \times DPTI}{SPTI}
\]

Figure 1. Parameters used in the definition of subendocardial viability ratio (SEVR). The figure shows the pressure curves recorded in the left ventricle (dotted line) and in ascending aorta (continuous line). DPTI indicates diastolic pressure–time index (dark gray area); DT, diastolic time; LVET, left-ventricular ejection time; LVEDP, left-ventricular end-diastolic pressure; MDBP, mean diastolic blood pressure; MSBP, mean systolic blood pressure; and SPTI, systolic pressure–time index (light gray area).

The blood oxygen content was determined using the following formula: CaO2 = 1.34x blood hemoglobin concentration (g/dL) × arterial oxygen saturation (%) +0.003x arterial pressure of oxygen (mm Hg). A possible critical value for oxygen supply/demand ratio was suggested to be ≤10, where endocardial/epicardial tissue blood flow ratio and the related oxygen supply may begin to fall significantly.64

Central Pulse Wave Analysis

Central blood pressure values and aortic pressure waveforms were obtained directly from the common carotid artery using a PulsePen device (DiaTecne srl, Milan, Italy). This is a validated, easy-to-use, and high-fidelity applanation tonometer, described in detail in previous articles17,18 and in the online-only Data Supplement. Pulse pressure waveforms were recorded with patients resting supine and in temperature-controlled environment in accordance with consensus recommendations.79

Other Measurements

In each measuring condition, blood pressure and heart rate were measured 3 times, in the supine position with a validated oscillometric device (UA-767PC, AND Company Ltd, Tokyo).

In all subjects, arterial blood oxygen saturation was checked daily through a finger pulse oximeter (Ohmeda TuFT Sat with sensor OxyTip Finger 6051-0000-160, GE Healthcare-Finland). Arterial gas analysis and hemoglobin concentration assessment were performed through radial artery puncture, 1 day after arrival to the high-altitude laboratory and after 3 full days of permanence at high altitude. A standardized questionnaire for the clinical assessment of acute mountain sickness (Lake Louise Acute Mountain Sickness Score)20 was completed daily.

Statistical Analysis

All data analyses were performed by means of SAS version 9.1. Continuous variables are reported as mean±SD. The effects of the study condition and treatment were subjected to repeated measure ANOVA. Post hoc t test was performed using Bonferroni correction. An α level of 0.05 was used for all hypothesis tests.

Results

A total of 22 subjects were randomized to acetazolamide and 22 subjects to placebo. Three subjects were not included in the analysis because of their need to be treated with dexamethasone for acute mountain sickness symptoms (2 subjects on placebo and 1 subject on acetazolamide). One
subject in the acetazolamide group did not ascend to high altitude for personal reasons, and another subject from the same group was not compliant with the prescribed treatment. Thus, analysis was performed on data from 19 and 20 subjects on acetazolamide and placebo, respectively. At baseline, there was no significant difference between the demographic, metabolic, and hemodynamic characteristics of the 2 groups (Table in the online-only Data Supplement).

**Arterial Oxygen Saturation Changes With Altitude**

Table 1 shows the changes of oxygen saturation and arterial oxygen content with altitude. The oxygen saturation was always significantly lower in the placebo than in the acetazolamide-treated patients.

**Subendocardial Viability Changes With Altitude**

In subjects under placebo, at arrival at high altitude, SEVR values were significantly reduced as compared with sea level, from 1.63±0.15 to 1.18±0.17; P<0.001 (Figure 2, top). After 3 days at high altitude, SEVR values showed an increase, although they remained significantly lower than at sea level (1.42±0.22; P<0.005 versus sea level values).

To allow for the effect of hypoxia, in our subjects, SEVR was multiplied by CaO2, thus offering a global index of oxygen brought to the subendocardial muscle per minute (Figure 2, bottom). In the placebo group also, oxygen supply/demand ratio (SEVR×CaO2) fell at high altitude from 29.6±4.0 to 17.3±3.0; P<0.001. A clinical case report on SEVR×CaO2 changes at altitude in one of the study subjects is available in the online-only Data Supplement.

Taking into account the lowest values of hemoglobin oxygen saturation recorded during polysomnography on the first night at high altitude, the corresponding lowest night SEVR×CaO2 values were 14.1±2.6. After 3 days at high altitude, SEVR×CaO2 values remained significantly lower than at baseline (22.4±4.7; P<0.001).

**Effect of Acetazolamide**

On arrival at high altitude, SEVR significantly fell (from 1.68±0.25 to 1.35±0.18; P<0.001), also in subjects under acetazolamide. However, its values were significantly (P<0.005) higher than in the placebo group (Figure 2, top), with a return to sea level values after 3 days of high-altitude exposure (1.65±0.24) and a persisting significant difference with the placebo group (P<0.005).

On arrival at high altitude, SEVR×CaO2 fell in subjects under acetazolamide from 32.1±7.0 to 22.3±4.6; P<0.001 (Figure 2, bottom), with values that were significantly higher than under placebo with acute exposure to altitude (P<0.001). Under acetazolamide, SEVR×CaO2 returned toward sea level values after 3 days at high altitude (28.8±5.7, ns versus baseline). Also, in this case, the difference between acetazolamide and placebo groups remained significant (P<0.001).

**Change With Altitude of Parameters Determining SEVR**

The changes induced by high altitude in the parameters determining SEVR values are shown in Table 2. In the placebo group, heart rate increased markedly after acute high-altitude exposure with a return toward sea level values after 36 hours. The trend was similar in the acetazolamide-treated group in which, however, the acute increase was significantly less pronounced, and the values obtained after prolonged exposure to high altitude were only few beats/min higher than the sea level ones.

In relation to the increase in heart rate at high altitude, the diastolic time was reduced more than the systolic time, both reductions being less pronounced after a few days at altitude, with no significant difference between placebo and acetazolamide. With acute high-altitude exposure, there was a significant reduction in diastolic time/systolic time ratio: −29% in placebo-treated (P<0.001) and −23% in acetazolamide-treated (P<0.005) subjects. No significant altitude-induced change in mean diastolic/mean systolic blood pressure ratio was found in either group on arrival at high altitude.

**Acute Mountain Sickness**

Twenty subjects had a Lake Louise Acute Mountain Sickness Score >3 with acute exposure to high altitude (47.6% of all participants); 14 of these were in the placebo group (63.6%), and 6 in the acetazolamide group (30.0%). The difference

| Table 1. Behavior of Arterial Oxygen Saturation and of Arterial Oxygen Content in Placebo Group (n=20) and Acetazolamide Group (n=19) in the Different Study Conditions |
|------------------------------------------|------------------|------------------|------------------|
| Parameter                                | Treatment        | Sea Level        | First Day        | Third Day       |
| O2 Sat, %                                | Placebo          | 98.2±0.7         | 79.3±3.6†        | 82.0±4.6†       |
|                                         | Acetazolamide    | 98.4±0.8         | 84.7±4.2†        | 87.5±3.9†       |
|                                         | n.s.             | P<0.001          | P<0.001          |                 |
| CaO2, mL/dL                              | Placebo          | 18.1±1.8         | 14.6±1.6†        | 15.7±1.9†       |
|                                         | Acetazolamide    | 19.0±1.8         | 16.4±1.6†        | 17.4±1.8*       |

Data are mean±SD. CaO2 indicates arterial oxygen content; O2 Sat, arterial oxygen saturation; and n.s., not significant.

*P<0.005; †P<0.001 vs sea level.
Figure 2. Changes of subendocardial viability ratio (SEVR; top) and of SEVR multiplied by arterial oxygen content (SEVR×CaO₂) (bottom) in placebo group (white) and acetazolamide group (dark gray) in the different study conditions. DPTI indicates diastolic pressure–time index; HA1, values under treatment, after arrival at high altitude; HA2, values under treatment, after 3 full days of permanence at high altitude; SL-post, values obtained at sea level under treatment; SL-pre, baseline values at sea level; and SPTI, systolic pressure–time index. In the figure, data are expressed as means±SD. *P<0.005, **P<0.001 vs sea level basal values of the same group; †P<0.005, ††P<0.001 acetazolamide vs placebo group at same step.

was statistically significant (Pearson χ² test; P=0.019). No differences in blood pressure and heart rate values were observed in subjects with or without symptoms of acute mountain sickness, as quantified by the Lake Louise score. On the contrary, oxygen saturation was slightly lower in the group with as compared with the group without acute mountain sickness symptoms (80.1±5.1% versus 83.3±5.0%; P=0.046).

Discussion

Our study provides 2 new findings. One, in healthy subjects, acute exposure to high altitude causes a significant reduction in subendocardial oxygen supply/demand ratio. Two, reductions in subendocardial viability with acute high-altitude exposure are markedly attenuated by acetazolamide administration. This is relevant to high-altitude physiology and pathophysiology and may have clinical implications.

Subendocardial Viability Ratio

Our results are based on SEVR (ie, a noninvasive estimate of myocardial perfusion in relation to left ventricle workload), which consists in a pressure/time integral ratio (DPTI/SPTI) derived from pressures approaching those measured in the aorta and left ventricle. SPTI is reported to reliably reflect the level of left-ventricular afterload and has been shown to directly correlate with myocardial consumption of oxygen.6,21-23 As well known from physiological and pathophysiological studies, blood supply to subendocardial layers is made difficult in systole because of development of 2 extravascular compressive forces. The first is left-ventricular intracavitary pressure, which is fully transmitted to subendocardial layers, but which falls off to almost zero at the epicardium level. The second one is the vascular occluding force caused by ventricular contraction. Thus, in systole, subendocardial coronary arteries are compressed in the ventricular wall, whereas subepicardial layers are normally perfused. During diastole, conversely, the whole myocardium is regularly perfused. Assessment of DPTI takes into account the following 3 main factors affecting subendocardial flow: (1) coronary artery diastolic pressure,24,25 which, with undamaged coronary arteries, is equal to aortic diastolic pressure; (2) the gradient in diastole between coronary arteries pressure and left-ventricular pressure; and (3) the time duration of diastole.26,27

Therefore, SEVR (ie, DPTI/SPTI ratio) estimates the balance between cardiac blood flow supply and demand4,24 and is, thus, a predictor of coronary flow reserve.28 Indeed, a decrease of this ratio below a critical level has been shown to be related to the occurrence of myocardial ischemia in coronary patients.7,29 Even in some of our subjects, who were selected after carefully excluding subclinical coronary artery disease, the marked reduction in SEVR at very high altitude observed at night was accompanied by the appearance of asymptomatic ventricular arrhythmias.

Several studies showed that diastolic time/left ventricular ejection time ratio affects SEVR more than heart rate.14,30,31 The importance of diastolic perfusion time as a determinant of subendocardial perfusion has been well demonstrated in experimental studies.26,32 Ferro et al27 showed a close relation between ischemic threshold and degree of coronary stenosis during diastolic perfusion time, but no correlation was found when explored throughout the whole cardiac cycle. In a recent invasive study, Chemla et al30 confirmed these observations and showed that diastolic time/left ventricular ejection time ratio is the main factor affecting SEVR and is responsible for 81% of the variability of SEVR in resting humans.14 Moreover, these authors provided evidence that diastolic time/left ventricular ejection time ratio and heart rate are not interchangeable as determinants of SEVR, and that SEVR was only weakly related to heart rate and diastolic time in resting subjects.

In our study, we observed a relative increase in left-ventricular ejection time and a decrease in diastolic time normalized by heart interval under high-altitude exposure, with a resulting reduction in diastolic time/left-ventricular ejection time ratio.

Among the possible factors responsible for these changes, previous studies performed at high altitude indicate the contribution of an increased activity of the sympathetic system.
combined with vagal withdrawal.\textsuperscript{34} This is relevant to the previous demonstration that not only heart rate but also changes in myocardial inotropism\textsuperscript{35} and increase of catecholamines release\textsuperscript{33} can produce changes in diastolic time/left-ventricular ejection time ratio. All these factors tend to occur at high altitude; an activation of the sympathetic system leads to increased myocardial inotropism, and this is associated with prolongation of the left-ventricular systolic period and with the corresponding relative reduction in duration of diastole\textsuperscript{9} associated with changes in central pulse waveform.\textsuperscript{36} All these hemodynamic changes may become more relevant from a pathophysiologic perspective when considering the severe hypoxemia caused by acute exposure to high altitude, which can further worsen subendocardial oxygenation, given the dependence of subendocardial viability not only on coronary blood flow but also on arterial oxygen content.

**Acetazolamide**

Evidence is available that administration of acetazolamide to subjects acutely exposed to hypobaric hypoxia at altitude may partly counteract the increase in blood pressure and heart rate induced in these conditions by the activation of peripheral chemoreceptors with the subsequent increase in sympathetic nervous system activity.\textsuperscript{37,38} The attenuation of high-altitude–induced increase in heart rate as well as in peripheral and central blood pressure in subjects receiving acetazolamide\textsuperscript{36} may be secondary to a direct inhibitory effect of this drug on oxygen sensing at the carotid body level\textsuperscript{39} or may be mediated by acid–base balance changes within the carotid body.\textsuperscript{40,41} Whatever the responsible mechanism might be, the results of our study indicate that the inhibitory effect of acetazolamide on peripheral chemoreceptor activity is unable to completely abolish the effects of high-altitude hypoxia on sympathetic activation, as shown by the heart rate increase we observed on the first day at high altitude also in actively treated subjects, although less pronounced than in the placebo group. Indeed, in our study, oxygen supply/demand ratio fell significantly with acute exposure to high altitude in all study participants, although in subjects treated with acetazolamide SEVR values were always significantly higher than in placebo group.

### Table 2. Changes Induced by High Altitude in Parameters Determining Subendocardial Viability Ratio

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Sea Level</th>
<th>High Altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Basal</td>
<td>Post-Treatment</td>
</tr>
<tr>
<td>MDBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>81.8 ± 7.5</td>
<td>80.0 ± 7.4</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>80.6 ± 8.9</td>
<td>77.5 ± 7.2</td>
</tr>
<tr>
<td>MSBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>97.5 ± 9.1</td>
<td>97.0 ± 9.6</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>97.3 ± 11.3</td>
<td>93.8 ± 10.0</td>
</tr>
<tr>
<td>MDPB/MSBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>0.84 ± 0.03</td>
<td>0.83 ± 0.04</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>0.83 ± 0.03</td>
<td>0.83 ± 0.03</td>
</tr>
<tr>
<td>DT, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>722 ± 106</td>
<td>737 ± 86</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>655 ± 123</td>
<td>729 ± 156</td>
</tr>
<tr>
<td>LVET, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>304 ± 14</td>
<td>311 ± 20</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>302 ± 19</td>
<td>300 ± 19</td>
</tr>
<tr>
<td>DT/LVET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>2.37 ± 0.29</td>
<td>2.36 ± 0.20</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>2.16 ± 0.37</td>
<td>2.42 ± 0.42*</td>
</tr>
<tr>
<td>HP, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>1026 ± 116</td>
<td>1049 ± 100</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>957 ± 133</td>
<td>1028 ± 169</td>
</tr>
</tbody>
</table>

Data are separately shown for subjects under treatment with placebo or acetazolamide. Data are mean±SD. DT indicates diastolic time; HP, heart period (R-R interval); LVET, left ventricular ejection time; MDPB, mean diastolic blood pressure; MSBP, mean systolic blood pressure; and n.s., not significant. *P<0.05; †P<0.001 vs sea level basal value.
Differences between the effects of placebo and acetazolamide on subendocardial viability were more evident when we considered the degree of subendocardial oxygen supply (SEVR×CaO₂) rather than just SEVR. This protective effect of acetazolamide against high altitude–induced reduction in the subendocardial oxygen supply/demand ratio may depend on several mechanisms besides a reduced sympathetic activation. Actually, acetazolamide leads to increased urine bicarbonate excretion and the resulting tendency toward metabolic acidosis stimulates ventilation.

Moreover, acetazolamide is able to reduce periodic breathing and the associated worsening in blood oxygenation during sleep, commonly occurring in subjects acutely exposed to high altitude. All these factors ameliorate respiratory adaptation, as clearly confirmed in this study by higher values of arterial oxygen saturation and blood oxygen content in acetazolamide group as compared with placebo group.

Latshang et al recently showed that combined therapy with acetazolamide and auto-continuous positive airway pressure ventilation, as compared with positive air pressure ventilation alone, provides an improvement in nocturnal oxygen saturation, and an almost complete control of sleep apnea at altitude in patients with obstructive sleep apnea syndrome. Our results contribute to strengthen Latshang’s suggestion that alleviating hypoxemia at altitude by acetazolamide may potentially contribute to reducing the risk of adverse effects of altitude exposure, in particular in patients with cardiovascular comorbidities.

Relevant Methodological Issues
A few additional issues, related to the methods used in our study, would deserve to be discussed. First, the participants in our scientific expedition were relatively young adults (mean age, 36 years; age range, 24–59 years) with presumed normal or only mildly altered viscoelastic properties of aorta. We may speculate that ascent to high altitude of subjects with stiffer arteries, as in the case of associated arterial hypertension, metabolic alterations, subclinical coronary artery disease or just advanced age, might expose them to a more pronounced reduction in myocardial oxygen supply/demand ratio and, thus, might lead to more critical levels of myocardial perfusion reduction as compared with our healthy young individuals. Second, our study was characterized by a relatively small sample size, which could be seen as a limitation of our work. The number of subjects we could include was imposed by the challenging conditions in which our study was performed at an altitude of 4559 m. In spite of this, however, because of the highly consistent hemodynamic changes we could observe in all investigated subjects, we have been able to demonstrate that the reduction in SEVR induced by acute exposure to high altitude can be partly but significantly counteracted by treatment with acetazolamide.

Perspectives
The demonstration provided in our study of the impact of high-altitude exposure on subendocardial oxygen supply/demand ratio in healthy subjects, and of the favorable effect of acetazolamide on myocardial viability in these conditions, may be particularly interesting on the background of the increasing number of people ascending to moderate or high altitude for work or leisure. Every day cable cars, cable railways, and chair lifts allow several thousand of subjects, including elderly individuals, and subjects with known or subclinical coronary artery disease, to easily access high-altitude locations. In these subjects, acute exposure to high altitude might lead to relative cardiac ischemia, with possible clinical manifestations. Further studies are needed to confirm our findings also in these populations and to support our suggestion that preventive administration of acetazolamide might improve subendocardial oxygen supply also in these subjects, providing protection on myocardial viability at the time of their ascent to high altitude.

Acknowledgments
We express our gratitude toward Club Alpino Italiano, Division of Varallo Sesia, the staff of the high altitude laboratory Cappanna Regina Margherita, and the Alpine Guides of Varallo Sesia for their valuable organizational support; Dr Luca Grappiolo for the careful administrative management of the project; and Dr Licia Pietrobon for the effective secretarial support.

Sources of Funding
The primary financial support of this study has come from a Research Grant of Italian Ministry of Health. Supplementary financial support was provided by the IRCCS Istituto Auxologico Italiano, Milan, Italy. There is no financial relationship with any drug company to be disclosed in relation to this work.

Disclosures
Paolo Salvi is consultant for DiaTecne srl, Milan, Italy, and Michael R. O’Rourke is a founding director of AtCor Medical Pty Ltd, West Ryde, Australia, both manufacturers of systems for analyzing the arterial pulse. The other authors have no conflicts to report.

References
Novelty and Significance

What Is New?

- Acute exposure to very high altitude is responsible for a reduction in subendocardial oxygen supply/demand ratio in healthy subjects.
- Changes in subendocardial viability with acute altitude exposure are markedly attenuated by acetazolamide administration.

What Is Relevant?

- The reduction in subendocardial oxygen supply/demand ratio under exposure to high-altitude hypoxic hypoxia may have clinical implications for subjects with known or subclinical coronary artery disease and with advancing age.
- The preventive administration of acetazolamide might have a protective action on myocardial viability in subjects with known or subclinical coronary artery disease at the time of their ascent to high altitude.

Summary

The acute exposure to high-altitude hypobaric hypoxia causes a significant reduction in the supply/demand ratio for myocardial blood flow. These altitude-induced changes in myocardial viability are significantly attenuated in subjects treated with acetazolamide.
Changes in Subendocardial Viability Ratio With Acute High Altitude Exposure and Protective Role of Acetazolamide

Paolo Salvi, Miriam Revera, Andrea Faini, Andrea Giuliano, Francesca Gregorini, Piergiuseppe Agostoni, Carlos G. Ramos Becerra, Grzegorz Bilo, Carolina Lombardi, Michael F. O’Rourke, Giuseppe Mancia, Gianfranco Parati.

From the Department of Cardiology (P.S., M.R., A.F., A.G., F.G., C.G.R.B., G.B., C.L., G.M., G.P.), S. Luca Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy; Chair of Cardiology (GP) and Department of Health Sciences (A.G., G.M., G.P.), University of Milano-Bicocca, Milan, Italy; IRCCS Centro Cardiologico Monzino and Department of Cardiovascular Sciences (P.A.), University of Milano, Milan, Italy; The Graduate School of Biomedical Engineering (M.O’R’), University of New South Wales, Sydney, Australia.

Correspondence to Gianfranco Parati, Department of Cardiology, S. Luca Hospital, IRCCS Istituto Auxologico Italiano and Chair of Cardiology, University of Milano-Bicocca. P.zza Brescia 20, Milano 20149. Telephone: +39 02 61911 2949. Fax number: +30 02 61911 2956. E-mail gianfranco.parati@unimib.it
METHODS

Left ventricular end-diastolic pressure

In this study left ventricular end-diastolic pressure (LVEDP) was determined non-invasively with ultrasound scanner by a recently proposed method, regarded as a reliable approach when applied in patients with preserved left ventricular ejection fraction\(^1\). The echocardiogram was performed using a portable Vivid i cardiovascular ultrasound system with a 3S-RS probe (General Electric Company, GE Healthcare, Milwaukee, WI, USA). Left ventricular ejection fraction was assessed with the biplane Simpson’s method.

Central pulse wave analysis

Arterial pressure waves recorded non-invasively by the PulsePen tonometer are virtually the same as the pressure waveforms obtained invasively by means of an intra-arterial catheter\(^2\). Moreover, several studies have demonstrated that carotid arterial tonometry may be an acceptable surrogate for central aortic waveform analysis\(^2,5\). Central blood pressure values were obtained by the carotid blood pressure curve integral after calibration with brachial mean and diastolic blood pressure measured noninvasively by a validated oscillometric sphygmomanometer at the brachial artery\(^6,7\).

Pulse wave analysis was then performed with dedicated software (PulsePen version 2.0, DiaTecne, Milan, Italy). The following parameters were provided by the automated software of the device: carotid systolic blood pressure, carotid pulse pressure, mean blood pressure value during the systolic phase of heart cycle (mean systolic blood pressure), mean blood pressure value during the diastolic phase of heart cycle (mean diastolic blood pressure), left ventricle ejection time, diastolic time and heart period.

Methodological issues

The results of our study may even underestimate the true high altitude induced reduction of myocardial oxygen supply-demand ratio. Indeed, use of non-invasive calibration of tonometry assessed pulse waves through arm cuff blood pressure values usually leads to lower estimates of systolic, and to higher estimates of diastolic blood pressure values as compared to invasive methods. Thus, it is likely that in our study we recorded higher values of DPTI and lower values of SPTI than those invasively measured by Buckberg et al.\(^8,9\). Therefore we may hypothesize, in the conditions where our data were collected, that SEVR critical threshold for a reduction in subendocardial-subepicardial blood flow ratio at high altitude could be at a higher level than that suggested through invasive studies\(^10-14\).
References


RESULTS

Table S1. Basal sea level values of clinical, hemodynamic, and anthropometric parameters of all subjects included in the study and randomized to placebo or acetazolamide

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>10 / 10</td>
<td>9 / 10</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>37.0 ± 9.5</td>
<td>35.6 ± 7.1</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>66.5 ± 13.2</td>
<td>63.3 ± 12.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.1 ± 9.8</td>
<td>171.8 ± 8.8</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.3 ± 2.7</td>
<td>21.3 ± 2.7</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.78 ± 0.22</td>
<td>1.74 ± 0.20</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>115.1 ± 11.8</td>
<td>115.9 ± 13.2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.1 ± 6.5</td>
<td>70.9 ± 8.6</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>86.4 ± 7.7</td>
<td>85.9 ± 9.4</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>13.4 ± 2.2</td>
<td>12.6 ± 2.2</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>59.2 ± 6.7</td>
<td>63.9 ± 9.1</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>66.8 ± 2.5</td>
<td>68.1 ± 2.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.6 ± 1.4</td>
<td>14.2 ± 1.4</td>
</tr>
<tr>
<td>CaO₂ (ml/dl)</td>
<td>18.1 ± 1.8</td>
<td>19.0 ± 1.8</td>
</tr>
</tbody>
</table>

Data are means ± standard deviation. BMI, body mass index; BP, blood pressure; BSA, body surface area; CaO₂, arterial oxygen content; LVEDP, left ventricular end-diastolic pressure. No between-group difference was statistically significant.

Clinical Case Report

Figure S1 shows an example of change in pressure waveform at high altitude and its effects on DPTI-SPTI ratio in one of our subjects. This graph refers to a healthy 59 years-old man, without any history of cardiovascular disease, randomized to placebo. Under acute exposure to high altitude, frequent ventricular ectopic beats with some couples and triplets particularly at night, were recorded, in association with low oxygen saturation values (minimum 59% on
the first night). In this subject, who never experienced arrhythmias at sea level, SEVR x CaO2 was markedly reduced after acute exposure to 4559 meters altitude, shifting from 32.9 (sea level) to 14.5 (with a night-time value of 12.6), with SEVR being reduced from 1.77 to 1.18. These data indicate a significant fall in myocardial oxygen supply-demand ratio which might have been responsible for the observed appearance of arrhythmias.

Figure S1. Example of changes in blood pressure waveform at high altitude in a 59 yrs old man and of their effects on DPTI-SPTI ratio.
Left panel: pressure waveform at sea level. Right panel: pressure waveform recorded after arrival at an altitude of 4559 m above sea level. DPTI, diastolic pressure-time index (yellow area); DT, diastolic time; LEFT, left ventricular ejection time; LVEDP, left ventricular end-diastolic pressure; MDBP, mean diastolic blood pressure; MSBP, mean systolic blood pressure; SPTI, systolic pressure-time index (green area).
Changes in Subendocardial Viability Ratio With Acute High-Altitude Exposure and Protective Role of Acetazolamide
Paolo Salvi, Miriam Revera, Andrea Faini, Andrea Giuliani, Francesca Gregorini, Piergiuseppe Agostoni, Carlos G. Ramos Becerra, Grzegorz Bilo, Carolina Lombardi, Michael F. O’Rourke, Giuseppe Mancia and Gianfranco Parati

Hypertension. 2013;61:793-799; originally published online February 25, 2013; doi: 10.1161/HYPERTENSIONAHA.111.00707

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/4/793

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2013/02/25/HYPERTENSIONAHA.111.00707.DC1.html

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/