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# Autonomic regulation during orthostatic stress in highlanders: comparison with sea-level residents

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**This report is a comparison of orthostatic tolerance and autonomic function in three groups of high-altitude dwellers: Andeans with and without chronic mountain sickness (CMS) and healthy Ethiopians. Results are compared with those from healthy sea-level residents. The aim was to determine whether different high-altitude populations adapted differently to the prevailing hypobaric hypoxia. Orthostatic tolerance was assessed using a test involving head-up tilt (HUT) and graded lower body suction. This was performed at the subjects' resident altitude. Blood pressure (Portapres) and R–R interval (ECG) were recorded during the test, and spectral and cross-spectral analyses of heart period and systolic blood pressure time series were performed using data obtained both while supine and during HUT. The transfer function gain in the low-frequency range (LF, ∼0.1 Hz) at the point of maximal coherence was used as a measure of cardiac baroreflex sensitivity (BRS). As previously reported, Peruvians displayed an unusually good orthostatic tolerance, while Ethiopians showed an orthostatic tolerance comparable to that of healthy sea-level residents. There were no significant differences between groups in the supine values of the spectral analysis results. Head-up tilt induced the expected changes in Ethiopians (an increase in the LF components and a decrease in the respiratory components) but not in Andeans. Cross-spectral analysis showed abnormal results from all groups of high-altitude dwellers. These results indicate that Ethiopians, but not Peruvians, behave similarly to sea-level residents in terms of orthostatic tolerance and autonomic responses to orthostatic stress, as assessed from spectral analyses, and this indicates good adaptation to their environment. However, in all the high-altitude groups the results of cross-spectral analysis were atypical, suggesting some degree of impairment in baroreflex function.**

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Residents in the Peruvian Andes and the highlands of Ethiopia live permanently at high altitudes. It has been suggested that the Ethiopians are the best adapted for life in hypoxic conditions (Beall *et al.* 2002; Beall, 2003; Appenzeller *et al.* 2006) showing, for instance, no evidence of chronic mountain sickness (CMS), which may be considered a maladaptation to high-altitude living (Monge & Whittembury, 1976).

During the last few years, our group has investigated autonomic function of Andean high-altitude dwellers, both with and without CMS (Claydon *et al.* 2004, 2005; Norcliffe *et al.* 2005; Moore *et al.* 2006; Gamboa *et al.* 2006; Appenzeller *et al.* 2006). We have used an orthostatic stress test involving combined head-up tilt and lower body negative pressure, which has been widely used to assess cardiovascular and cerebrovascular control


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both in normal subjects and in fainting patients (el-Bedawi & Hainsworth, 1994). We have previously reported that healthy Andean high-altitude dwellers, as well as those with CMS, have an extremely good tolerance to orthostatic stress, and we suggested that this might be related to their exceptionally large packed cell and blood volumes (Claydon *et al.* 2004). However, it is known that blood volume is not the only factor influencing an individual's orthostatic tolerance. Other factors include the integrity of the autonomic control of vasoconstriction in the peripheral circulation (Brown & Hainsworth, 2000; Bush *et al.* 2000), the effectiveness of autoregulation in the cerebral circulation (Claydon & Hainsworth, 2003) and the integrity of baroreflex function (Hainsworth, 1999).

The present report extends a recent comparative study of Andean and Ethiopian high-altitude populations, in which we showed that the responsiveness of the cerebral vessels to exogenous NO in Ethiopian and Andean high-altitude populations differed significantly (Appenzeller *et al.* 2006). This would support the hypothesis that Peruvians, even those without CMS, although not Ethiopians, show signs of maladaptation to chronic hypoxia. We now compare orthostatic tolerance and cardiovascular control, estimated by spectral and cross-spectral analysis, during the same orthostatic stress as previously reported.

The aim of this study was to examine whether these two groups of highlanders that are thought to have different genetic profiles also show differences in their autonomic cardiovascular regulation. Our studies were carried out in the high Andes and on the high-altitude Ethiopian plateau. Since all the recordings were obtained in their 'resident' locations, we were also interested to compare these results with those obtained in UK sea-level residents. We considered that similar results to those seen in sea-level residents would imply good adaptation to chronic hypoxia.

## Methods

### Subjects

**Peruvian subjects.** The Andean subjects were those who had taken part in our recently reported studies (Claydon *et al.* 2004, 2005). They were 22 male high-altitude residents from Cerro de Pasco (altitude, 4338 m) in the Peruvian Andes. Of these, 11 were healthy volunteers (PHA; mean age, $39.3 \pm 2$ years) and 11 had been diagnosed with CMS (PCMS; mean age, $43.1 \pm 1.7$ years) on the basis of haematocrit levels consistently in excess of 60% and clinical histories compatible with the disorder. Chronic mountain sickness scores were determined using an internationally recognized scoring system, which assesses the 10 most common symptoms and signs of CMS (Leon-Velarde *et al.* 2003). The CMS score in PHA was $7.0 \pm 4.0$ and in PCMS was $19.0 \pm 5.0$. They were studied in a laboratory at Cerro de Pasco (temperature, approximately 20°C).

**Ethiopian subjects.** These were nine high-altitude-dwelling men (EHA; mean age, $35.6 \pm 1.3$ years), resident in a village in the Simen Mountains at ~3900 m. They had no history of medical disorders, they were examined clinically by local physicians and the Andean CMS scoring system was applied. The CMS score was $0.11 \pm 0.1$. They were studied in a field camp in Chennek at 3622 m (temperature ranging from 18 to 22°C).

**UK subjects.** These were 12 healthy male volunteers (UK residents; mean age, $37 \pm 2.3$ years) with no history of posturally related syncope. Studies were carried out in an air-conditioned laboratory (temperature, approximately 22°C) at sea level.

Written informed consent was obtained from all subjects. The experiments in Peru, in Ethiopia and in the UK were approved by the ethics committee of the local hospital or university and were performed in accordance with the Declaration of Helsinki (2004) of the World Medical Association.

### Procedure

All subjects were asked to eat only a light meal/breakfast at least 3 h before testing, avoiding caffeine. Orthostatic stress testing was performed as described below. During the initial supine phase, we determined end-tidal oxygen and carbon dioxide levels via paired nasal cannulae (Binos-1 $CO_2$ analyser, Leybold-Haraeus Ltd, Köln, Germany).

### Orthostatic tolerance test

A graded orthostatic stress test of combined head-upright tilting (HUT) and lower body suction was used to determine orthostatic tolerance. The protocol was identical to that previously described (el-Bedawi & Hainsworth, 1994; Hainsworth & el-Bedawi, 1994) and included the following consecutive steps: 20 min supine rest; 20 min HUT at 60 deg alone (phase 1); 10 min HUT with –20 mmHg lower body negative pressure (LBNP; phase 2); and 10 min HUT with –40 mmHg LBNP (phase 3). If subjects tolerated this, a further step of 10 min HUT with –60 mmHg LBNP was performed. The test was terminated and the subject returned to supine either when systolic blood pressure fell below 80 mmHg, associated with signs and symptoms of presyncope (such as dizziness, pallor, light-headedness or visual disturbances), or when the protocol was completed. Orthostatic tolerance was taken as the time in minutes from head-up tilt to presyncope or end of test. Orthostatic tolerance (time to termination of the test) for the Andean subjects has previously been reported (Claydon *et al.* 2004, 2005). Throughout the testing procedure, recordings were made of heart rate using a standard three-lead ECG (78352C; Hewlett Packard, Boeblingen, Germany) and beat-to-beat blood pressure using a finger photoplethysmographic device (Portapres model 2, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands), which was calibrated at regular intervals against an auto-inflating sphygmomanometer (78352C; Hewlett Packard) on the opposite arm. The Portapres was positioned on the right arm, which was supported at heart level. In addition, we continuously monitored peripheral oxygen saturation using finger pulse oximetry (78352C; Hewlett Packard). We performed off-line beat-to-beat analysis of the stored signals by extracting the time series of successive values of R–R interval (RR) and systolic arterial pressure (SAP) during the supine and 60 deg HUT periods. When present, we corrected for ectopic beats by substituting their values by linear interpolation of adjacent beats. The time series were stable with no linear trends and they did not require filtering operations to be optimally analysable. An autoregressive monovariate model (Bartoli *et al.* 1985) was fitted to each RR and SAP time series, and the powers associated to each oscillatory component were automatically quantified by computation of the residuals (Johnsen & Andersen, 1978). Two main oscillatory components are generally detected: one at low frequency (LF; ∼0.1Hz) and one at high frequency (HF; related to the respiratory rate). The powers of the LF and HF oscillatory components of the RR period variability are expressed in absolute and in normalized units ($LF_{nu}$; $HF_{nu}$) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Normalized units are used to minimize the effect of the changes in total power. They represent the percentage value of each oscillatory component in proportion to the total power minus the component below 0.04 Hz. We also performed cross-spectral analysis of RR and SAP, using a bivariate autoregressive model. This technique quantifies the frequency-related squared coherence, phase shift, central frequency and transfer function gain between two variables at a given frequency. Since this method provides a smooth estimate of the true cross-spectra, discrete values of phase shift, central frequency and transfer function gain between RR and SAP were taken at the frequency corresponding to the highest coherence value, where the estimate error is minimal (Kay, 1991).

We accepted the cross-spectral data for analysis only when coherence values were above 0.5 (possible range, 0–1) because this is considered to indicate a statistically significant linear correlation between the two signals. A negative phase shift indicates that changes in SAP precede changes in RR. The transfer function gain in the LF frequency region (TFG_LF) was taken as an estimate of baroreflex sensitivity (Cevese *et al.* 2001).

### Statistical analysis

Repeated-measures analysis of variance, with group (PHA/PCMS/EHA/UK residents) as the between-subjects factor, was used to assess statistical changes over body position (supine/HUT). When a significant group–phase interaction was found, between-group *post hoc* comparisons were made by Student's unpaired *t* tests. *Post hoc* within-group comparisons were made by Student's paired *t* tests.

## Results

### Responses to orthostatic stress

**Andeans.** All subjects tolerated the test to the end of the head-up tilt and lower body suction at –40 mmHg phase. Four of the 11 PHA control subjects and five of the PCMS subjects tolerated the whole of a further step of LBNP to –60 mmHg. Assuming the time in the non-syncopal subjects to be 50 min (the time to end of test), the mean time to presyncope in healthy Andeans was 46.2 ± 1.2 min and in CMS patients 47.2 ± 1.2 min.

**Ethiopians.** All the EHA subjects displayed a good orthostatic tolerance but only four tolerated the test to the end of the HUT +40 mmHg phase. Of these four subjects, one of them showed initial signs of presyncope, while the rest showed profound discomfort and uneasiness. For these reasons, the phase at 60 mmHg was not tested in these subjects. The average time to presyncope was 36.6 ± 1.5 min.

**UK residents.** We had selected 12 male age-matched volunteers with normal orthostatic tolerance. The average time to presyncope was 37.2 ± 2.3 min.

### Oxygen saturation, haematocrit and end-tidal $CO_2$

Oxygen saturations in PHA, PCMH and EHA were 86 ± 1.0, 82 ± 1.2 and 88 ± 1.1%, respectively. Respiratory rates in the supine posture were 0.32 ± 0.03, 0.32 ± 0.02 and 0.34 ± 0.02 breaths $min^{-1}$, respectively. Sea-level residents from the UK had a respiratory rate of 0.28 ± 0.01 breaths $min^{-1}$ in the supine posture. End-tidal $CO_2$ values in PHA, PCMS and EHA were 27.3 ± 1.2, 27.8 ± 1.5 and 37.1 ± 0.8 mmHg. Haematocrits were significantly higher in CMS subjects (67.8 ± 2.0%) than in PHA (53.6 ± 1.2%) and EHA subjects (48.5 ± 1.5%). Note that Ethiopian subjects had lower haematocrits than both groups of Peruvian subjects.

**Table 1. Time and frequency domain results whilst supine and during head-up tilt**

| | PHA | PCMS | EHA | UK residents |
|---|---|---|---|---|
| RR (ms) | | | | |
| Supine | 1018 ± 39 | 916 ± 30 | 939 ± 53 | 942 ± 29 |
| HUT | 850 ± 29 | 807 ± 24 | 779 ± 47 | 788 ± 22 |
| SAP (mmHg) | | | | |
| Supine | 113.7 ± 3.0 | 117.2 ± 2.6 | 127.5 ± 3.2 | 123.8 ± 2.2 |
| HUT | 115.7 ± 3.0 | 119.5 ± 2.4 | 122.6 ± 3.9 | 120.8 ± 8.6 |
| LF-RR ($ms^2$) | | | | |
| Supine | 670 ± 387 | 324 ± 87* | 472 ± 141* | 1126 ± 275 |
| HUT | 458 ± 157* | 265 ± 76* | 486 ± 131* | 1316 ± 254 |
| HF-RR ($ms^2$) | | | | |
| Supine | 129 ± 32 | 151 ± 42 | 368 ± 180 | 576 ± 325 |
| HUT | 143 ± 41 | 75 ± 23 | 92 ± 37§ | 156 ± 32§ |
| LE-nu (nu) | | | | |
| Supine | 39.5 ± 11.6 | 38.7 ± 10.9 | 49.9 ± 6.8 | 57.5 ± 5.6 |
| HUT | 52.6 ± 11.3*† | 47.5 ± 13.6*† | 76.7 ± 6.9§ | 82.3 ± 2.5§ |
| HE-nu (nu) | | | | |
| Supine | 10.7 ± 3.5† | 15.3 ± 3.3† | 29.6 ± 4.1 | 19.8 ± 2.4 |
| HUT | 19.0 ± 4.4 | 12.5 ± 3.6 | 11.0 ± 2.8§ | 9.6 ± 1.1§ |
| LF-SAP ($mmHg^2$) | | | | |
| Supine | 7.4 ± 2.9 | 1.5 ± 0.5*†‡ | 4.7 ± 1.2 | 6.4 ± 2.2 |
| HUT | 11.5 ± 4.1 | 14.8 ± 5§ | 8.7 ± 1.5§ | 23 ± 4.4§ |
| LF/HF | | | | |
| Supine | 4.8 ± 1.8 | 3.6 ± 1.7 | 2.2 ± 0.6 | 3.9 ± 0.9 |
| HUT | 6.4 ± 3.9 | 6.0 ± 2.7 | 11.1 ± 2.7§ | 11.2 ± 2.1§ |

Supine and head-up-tilt (HUT) results in Ethiopian high-altitude dwellers (EHA), in Peruvian high-altitude dwellers (PHA), in Peruvians with chronic mountain sickness (PCMS) and in UK residents. Abbreviations: RR, R–R interval; SAP, systolic arterial blood pressure; LF, low-frequency oscillations; HF, high-frequency (respiratory) oscillations; and nu, normalized units of RR variability. Values are means ± S.E.M. *$P < 0.05$, significantly different from UK residents; †$P < 0.05$, significantly different from EHA; ‡$P < 0.05$, significantly different from PHA; §$P < 0.05$, significant changes from supine to HUT.

### Time and frequency domain results

These are reported in Table 1.

Ethiopians and lowland dwellers tended to have higher blood pressures than Peruvians; however, there were no significant differences between groups in terms of steady-state blood pressure or heart rate, either while supine or during HUT.

In the supine posture, the spectral analysis results of all the highlanders showed lower LF-RR powers in comparison with UK residents. Peruvians with CMS also showed lower values in the LF-SAP powers. There were no differences between the groups in the other parameters.

During HUT, the spectral analysis results showed higher LF-RR variability in the UK residents than in any of the altitude dwellers (Fig. 1). When powers were normalized, the two Peruvian groups had lower values in the LFnu. Head-up tilt induced the expected changes in the RR-derived spectral parameters in EHA and UK residents only. These were increases in the LF components, decreases in the HF components and a shift of the LF/HF ratio towards the low frequencies. Head-up tilt induced an increase in the LF-SAP power in EHA and UK residents. There was a very large increase in LF-SAP in PCMS but no changes in PHA.

### Cross-spectral analysis results

Figure 2 reports a representative example of spectral and cross-spectral analysis whilst supine in one UK resident and one Andean with CMS. Results are reported in Table 2.

Both in the supine posture and during HUT, all the highlanders showed large phase shifts, expressed in both time and degrees (particularly the PCMS group) and lower values of coherence in comparison with the UK residents. In the supine posture, in the three highland groups, the LF central frequency is more shifted towards lower values.

The baroreflex sensitivity, estimated by means of the LF transfer function gain between SAP and RR, tended to be lower in the high-altitude groups, particularly in the Peruvians with CMS during 60 deg HUT.

## Discussion

To our knowledge, this is the first study to compare autonomic function in two high-altitude populations thought to have different genetic profiles: Peruvians and Ethiopians. It is an extension of our previous separate reports of responses in the two populations (Appenzeller *et al.* 2006). We have shown previously that, unlike Peruvian altitude dwellers, there was no evidence for chronic mountain sickness in Ethiopians, as assessed by symptoms and signs of the disease. Chronic mountain sickness is thought to represent a form of maladaptation to high altitude (Monge & Whittembury, 1976).

The two populations responded differently to the test of orthostatic tolerance, with the Ethiopians having a much lower tolerance than either group of Peruvians. In fact, the orthostatic tolerance of the Ethiopians was similar to that seen in normal lowland dwellers (el-Bedawi & Hainsworth, 1994). The present report is primarily concerned with the assessment of autonomic function in the two highland populations, using spectral and cross-spectral analysis of blood pressure and heart period variability, and its relation to orthostatic tolerance. Among all the highlanders, only the Ethiopian subjects showed the expected changes in the spectral parameters in response to HUT, namely an increase in the LF components and a decrease in the HF-RR variability. These changes are also seen in the lowland residents and are thought to reflect an increase of the sympathetic drive to heart and vessels and a decrease of the parasympathetic drive to the heart (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In Peruvians, both those with and without CMS, there were no significant changes in the spectral parameters of R–R interval in response to HUT. Based on these results, we conclude that there is an impairment in the autonomic regulation of cardiovascular function in the Andeans. This is in accordance with previous reports on Peruvians with CMS (Keyl *et al.* 2003). In the Peruvians with CMS, HUT induced a considerable increase (∼10-fold) of LF-SAP power. These oscillations are thought to represent the modulation of the sympathetic drive to the resistance

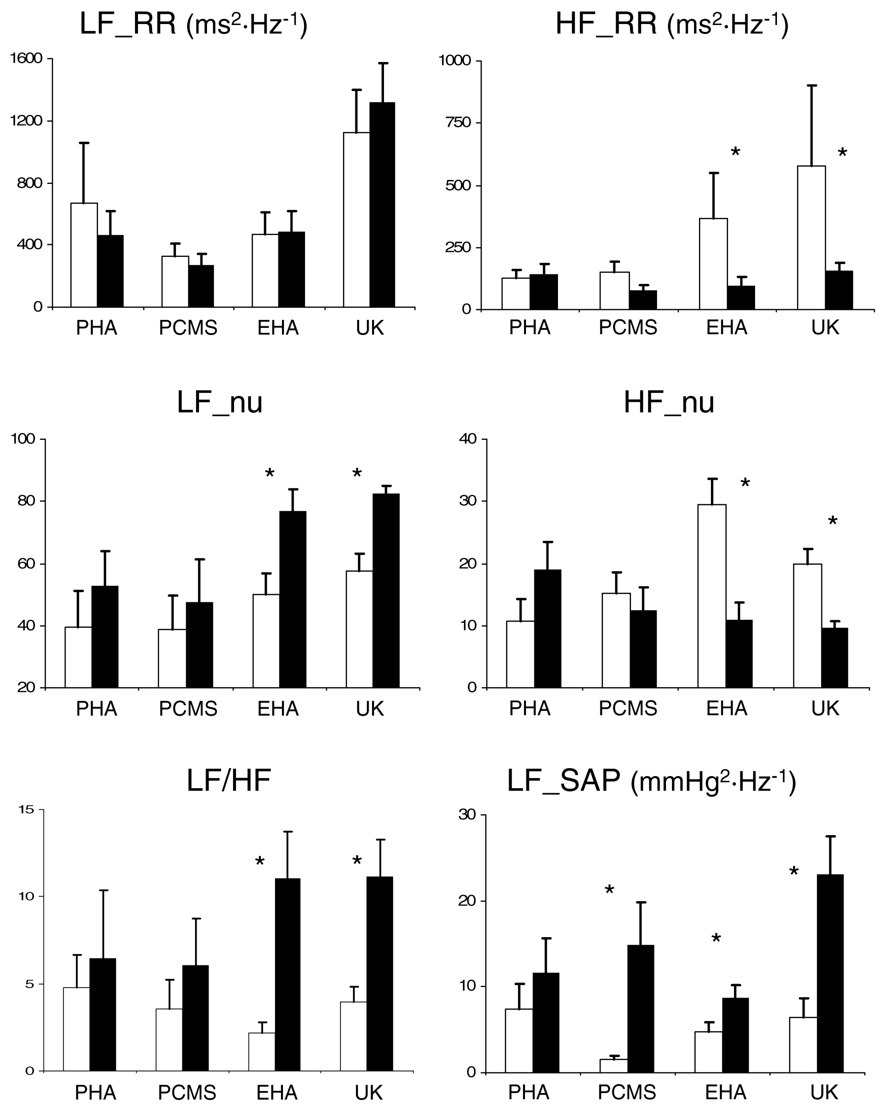


**Figure 1. Spectral analysis results**
Visual representation of the main spectral analysis results during supine (□) and head-up-tilt conditions (■). Groups are: Peruvian high-altitude dwellers with (PCMS) and without (PHA) chronic mountain sickness; Ethiopian high-altitude dwellers (EHA); and UK residents. Note that HUT induced significant changes in the R–R interval spectral analysis results in UK residents and Ethiopians only. RR, R–R interval; SAP, systolic arterial blood pressure; LF, low-frequency oscillations; HF, high-frequency (respiratory) oscillations; nu, normalized units of RR variability; LF/HF, ratio between LF and HF power of RR variability.

vessels (Cevese *et al.* 1995, 2001), and our observation may therefore reflect a possible sympathetic overdrive to the vessels in response to the orthostatic stress. In a recent study, we found that patients with CMS have a higher 'set point' of the vascular resistance baroreflex compared with PHA. We speculated that this may be explained by CMS patients having greater vasoconstrictor activity (Moore *et al.* 2006). Our observation is also compatible with the recent report by Gamboa *et al.* (2006) of sympathetic overactivation in CMS.

The present findings seem to imply that normal modulation of autonomic cardiovascular control is not essential for good orthostatic tolerance, at least in Andeans. Orthostatic tolerance has been shown to be influenced by a number of factors, including the magnitude of reflex vasoconstriction in response to orthostatic stress (Brown & Hainsworth, 2000; Bush *et al.* 2000), plasma and blood volumes (el-Sayed & Hainsworth, 1995, 1996), and the integrity of cerebral autoregulation (Claydon & Hainsworth, 2003). In the Andean subjects, the plasma and blood volumes were large, cerebral autoregulation was not impaired (Claydon *et al.* 2004), and the reflex vascular responses were similar to those seen in lowland dwellers (Moore *et al.* 2006). All these factors would

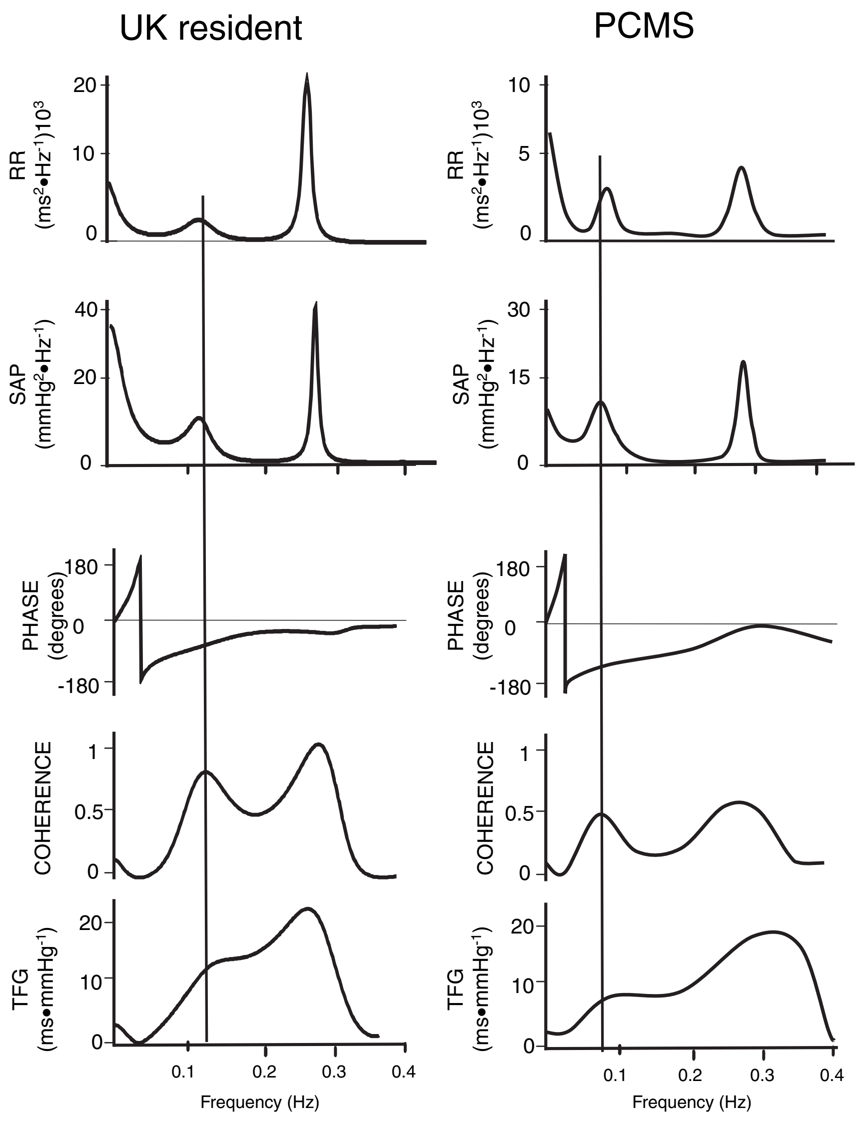


**Figure 2. Example of spectral and cross-spectral analyses**
Representative example of spectral and cross-spectral analysis of R–R period and systolic blood pressure recorded whilst supine in one UK resident and one Andean with CMS. The central frequency in the LF range, phase shift and transfer function gain (TFG) is taken at the point of maximal coherence (vertical line). Note that the Andean subject shows a reduced LF central frequency at around 0.08 Hz, larger phase shift, lower coherence value and lower TFG compared with the UK resident.

**Table 2. Cross-spectral analysis results**

| | PHA | PCMS | EHA | UK residents |
|---|---|---|---|---|
| Phase (deg) | | | | |
| Supine | –72.7 ± 8.9 | –84.0 ± 8.4* | –76.9 ± 13.6 | –58.9 ± 4.1 |
| HUT | –76.7 ± 7.0* | –85.8 ± 5.3*† | –67.0 ± 6.0 | –55.1 ± 2.7 |
| Time lag (s) | | | | |
| Supine | –3.0 ± 0.8* | –3.0 ± 0.5* | –3.1 ± 0.7* | –1.6 ± 0.1 |
| HUT | –2.6 ± 0.4* | –3.3 ± 0.3*† | –2.5 ± 0.3* | –1.7 ± 0.1 |
| Coherence | | | | |
| Supine | 0.69 ± 0.03* | 0.64 ± 0.06* | 0.62 ± 0.06* | 0.77 ± 0.03 |
| HUT | 0.65 ± 0.04* | 0.74 ± 0.04* | 0.67 ± 0.1* | 0.85 ± 0.02 |
| BRS (ms $mmHg^{-1}$) | | | | |
| Supine | 9.8 ± 1.2 | 8.6 ± 1.2 | 8.6 ± 0.9 | 12.3 ± 2.0 |
| HUT | 6.6 ± 0.6§ | 4.7 ± 0.5*§ | 5.5 ± 0.9§ | 6.6 ± 0.7§ |
| Frequency (Hz) | | | | |
| Supine | 0.083 ± 0.011* | 0.086 ± 0.008* | 0.077 ± 0.007* | 0.104 ± 0.002 |
| HUT | 0.089 ± 0.007 | 0.071 ± 0.002*†‡ | 0.080 ± 0.004* | 0.093 ± 0.003 |

Supine and head-up-tilt (HUT) results in Ethiopian high-altitude dwellers (EHA), in Peruvian high-altitude dwellers (PHA), in Peruvians with chronic mountain sickness (PCMS) and in UK residents. Definitions: BRS, baroreflex sensitivity; and frequency, central frequency of the low-frequency oscillations. Values are means ± s.e.m. *$P < 0.05$, significantly different from UK residents; †$P < 0.05$, significantly different from EHA; ‡$P < 0.05$, significantly different from PHA; §$P < 0.05$, significant changes from supine to HUT.

predispose to exceptionally good orthostatic tolerance (Claydon *et al.* 2004). We suggested (Claydon *et al.* 2004) that the main factor determining the very high orthostatic tolerance in these subjects may have been their large packed cell volume because, when they descended to sea level, cerebral autoregulation became impaired and the reflex vascular responses were reduced, but despite this, orthostatic tolerance was unaffected. The pivotal role of the packed cell volume could explain why, despite showing an efficient autonomic modulation of cardiovascular control, Ethiopian highlanders and lowland dwellers had a lower orthostatic tolerance than the Andeans.

As Fig. 2 emphasizes, in both groups of Peruvians and in Ethiopians, we found atypical cross-spectral analysis results in comparison to lowland residents, both those enrolled in this study and those reported in the literature (Cooke *et al.* 1999; Cevese *et al.* 2001; Gulli *et al.* 2003). In the LF range, all altitude dwellers showed reduced coherence and a tendency to have a reduced transfer function gain (BRS) between RR and SAP fluctuations. They also showed a shift of the central frequency of LF variability towards lower levels and a large phase lag between RR and SAP fluctuations. Since the LF oscillation frequency in highlanders is lower, when the phase lag is expressed in time, the difference from the UK residents becomes more evident.

All these findings may indicate some degree of impairment in baroreflex function. Firstly, a reduction in coherence has been found after baroreceptor deafferentation (Mancia *et al.* 1999). A leftward shift of the LF central frequency has also been reported in various abnormal conditions, such as autonomic neuropathies (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Gulli *et al.* 2005*a*), $\alpha$-blockade in humans (Cevese *et al.* 2001), and anaesthesia and haemorrhage in dogs (Polosa, 1984; Cevese *et al.* 1995). Blunted baroreceptor inputs to the cardiovascular medullary centres may be responsible for changes in the pattern of the central sympathetic drive (Lambertz & Langhorst, 1998). Moreover, based on mathematical models (Ringwood & Malpas, 2001), a shift towards lower frequencies of the LF variability can be explained by a prolonged latency in the baroreflex response. This is in agreement with the larger phase shift between SAP and R–R interval fluctuations observed in highlanders. In addition, a delayed baroreflex response to blood pressure changes has been shown to occur in subjects with slower LF central frequency (Gulli *et al.* 2003, 2005*b*,*c*).

These results may be explained as a consequence of living in a chronically hypoxic condition. As we have suggested, a high gain of the cardiac baroreflex does not seem to be essential for a good orthostatic tolerance. This is not entirely surprising, since the baroreflex control of heart rate is much less important than the control of vascular resistance in the maintenance of blood pressure (Hainsworth, 1999). It is also possible that an impaired baroreflex in high-altitude dwellers might be compensated by other factors, such as plasma volume, blood volume and haematocrit.

### Adaptation to high altitude

Except for blunted baroreflex function, Ethiopians showed many similarities to lowland dwellers. This supports the notion that, in contrast to Peruvians, Ethiopians are indeed well adapted to high altitude. Ethiopians showed an orthostatic tolerance similar to that seen in healthy lowland dwellers. They also continued to display modulation of the autonomic function in response to orthostatic stress. A further interesting observation was that the end-tidal carbon dioxide levels in Ethiopian subjects were similar to those normally seen in sea-level dwellers, unlike the Andeans in whom they were very low. This implies that, unlike the Andeans, the Ethiopian pattern of adaptation to high altitude does not include hypocapnia, most probably due to hyperventilation. A further striking difference was that none of the Ethiopians showed any symptoms suggestive of CMS. When we enrolled the Ethiopian subjects, we specifically asked the local communities for subjects with signs and symptoms suggestive of CMS but did not find any. This contrasts with even the healthy Andeans, who had significantly higher CMS scores (a clinical assessment of CMS based on signs and symptoms of the disease; Leon-Velarde *et al.* 2003). To support the notion that Ethiopians are better adapted, we have recently reported that they had a greater cerebral vascular response to exogenous nitric oxide than Andeans, which is suggested to be an index of fitness for life at high altitude (Appenzeller *et al.* 2006).

These observations support the hypothesis that there are genetic differences that influence the pattern of altitude adaptation in the different populations. This may be due to the different evolutionary ages of the two populations. In line with this theory, many examples of genetic adaptation have been suggested. However, actual genetic data are few because these adaptations are complicated and quantitative traits are affected by many different gene loci, as well as being highly variable depending on age, sex and other environmental factors (Beall *et al.* 2002, 2003).

For the same reason, a possible explanation for our findings may be ascribed to other genetic contributors, rather than to adaptation to altitude alone. Only a few studies have investigated the hypothesis that orthostatic tolerance, spectral analysis parameters and baroreflex sensitivity may be affected by ethnicity. In these studies, Afro-Caribbean and Caucasian subjects were compared. No data are available on Peruvians. Franke *et al.* (2004) found that Afro-Caribbeans and Caucasians did not differ in their orthostatic tolerance or in the spectral parameters in response to orthostatic stress. Afro-Caribbean subjects showed bigger LF/HF ratio in comparison with Caucasian subjects, but only in the presyncopal phase. In two other studies (Liao *et al.* 1995; Wang *et al.* 2005), the authors showed differences in the baseline values of spectral parameters, with Afro-Caribbeans showing higher values of HF and lower values of LF variability. These observations are directionally opposite to our results, suggesting that our findings are more likely to result from adaptation to high altitude rather than to interethnic differences. However, to have a definitive answer on this issue, one should compare parameters obtained from Peruvian and Ethiopian highlanders with those obtained in Peruvian and Ethiopian lowlanders that are genetically similar.

To conclude, our observations indicate that Ethiopians have characteristics which are similar in many ways to those of lowland dwellers, in terms of orthostatic tolerance, respiratory drive and autonomic modulation, and this suggests good adaptation to chronic hypoxia. Normal modulation of autonomic function to orthostatic stress and intact baroreflex function seem not to be essential for good orthostatic tolerance, at least in high-altitude dwellers. In these subjects, other factors, including haematocrit, plasma volume and blood volume, appear to play a more important role.

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