

Roger Hainsworth
Mark J. Drinkhill
Maria Rivera-Chira

The autonomic nervous system at high altitude

Received: 2 January 2007
Accepted: 3 January 2007
Published online: 30 January 2007

R. Hainsworth (✉) · M.J. Drinkhill
Institute for Cardiovascular Research
University of Leeds
Leeds LS2 9JT, UK
Tel.: +44-113/3434-821
Fax: +44-113/3434-803
E-Mail: r.hainsworth@leeds.ac.uk

M. Rivera-Chira
Depto. Academico Ciencias
Biologicas y Fisiologicas, UPCH
Lima, Peru

■ **Abstract** The effects of hypobaric hypoxia in visitors depend not only on the actual elevation but also on the rate of ascent. Sympathetic activity increases and there are increases in blood pressure and heart rate. Pulmonary vasoconstriction leads to pulmonary hypertension, particularly during exercise. The sympathetic excitation results from hypoxia, partly through chemoreceptor reflexes and partly through altered baroreceptor function. High pulmonary arterial pressures may also cause reflex systemic vasoconstriction. Most permanent high altitude dwellers show excellent adaptation although there are differences between populations in the extent of the ventilatory drive and the erythropoiesis. Some alti-

tude dwellers, particularly Andeans, may develop chronic mountain sickness, the most prominent characteristic of which being excessive polycythaemia. Excessive hypoxia due to peripheral chemoreceptor dysfunction has been suggested as a cause. The hyperviscous blood leads to pulmonary hypertension, symptoms of cerebral hypoperfusion, and eventually right heart failure and death.

■ **Key words** altitude · mountain sickness · hypoxia · polycythemia · respiration · chemoreceptors · baroreceptors · autonomic nervous system

Introduction

High altitude places are amongst the most inhospitable on earth. According to WHO [70] in 1966 there were approximately 140 million people living at altitudes over 2,500 m and there are several areas of permanent habitation at over 4,000 m. These are in three main regions of the world: the Andes of South America, the highlands of Eastern Africa, and the Himalayas of South-Central Asia. This review is concerned with the effects of the altitude on visitors and the ways by which the permanent high altitude dwellers have adapted to their environment.

The two main challenges to life at high altitude come from hypobaric hypoxia and the low ambient temperatures. Temperature decreases about 1°C for each 150 m elevation, so that at 4,500 m temperature is roughly 30°C lower than at sea level. Barometric pressure falls progressively with increasing altitude. Up to about 2,500 m there are few if any effects of hypoxia. Above 3,000 m some effects of hypoxia are likely to be experienced and above 4,000 m adverse effects would be experienced by most unacclimatized visitors. However, many people live and work at altitude with no apparent adverse effects. One such example is Cerro de Pasco a busy mining town of

72,000 population at 4,300 m in the Peruvian Andes, where much high altitude research has been undertaken. At this altitude barometric pressure is 450 mmHg and without hyperventilation alveolar oxygen tension would be only 34 mmHg.

Autonomic control in visitors

Most adaptive changes occur in the first days and weeks following arrival at altitude, and this is the period when acute mountain sickness with cerebral and/or pulmonary oedema may occur. Recent studies in animals and man have highlighted the role of the autonomic nervous system in adaptation and in particular the importance of sympathetic activation following high altitude exposure.

■ Cardiovascular effects

Acute hypobaric hypoxia results in an increase in resting heart rate and blood pressure and this is seen both during altitude exposure [5] and during simulated exposure using a hypobaric chamber [68]. Vogel et al. [68, 69] demonstrated that the rate of ascent influenced the magnitude of the tachycardia. Gradual increases in altitude over two weeks resulted in larger heart rate changes compared with an abrupt ascent. Later, as subjects acclimatise at altitudes up to about 4,500 m, much of the increase in heart rate is lost and resting heart rates return towards their sea level values.

Acute hypoxia also causes an increase in cardiac output both at rest and for given levels of exercise. This was seen both when breathing hypoxic gas at sea level [34, 68, 69] and on acute exposure to high altitude [21]. As subjects acclimatise to the altitude cardiac output decreases although the heart rate can remain high with a low stroke volume. This may be due to a loss of plasma volume [23, 54].

The effect of hypoxia on the pulmonary circulation is rapid, resulting in an increase in pulmonary vascular resistance and pulmonary hypertension [49]. The maximum response occurs within 5 min [65]. Breathing 11% oxygen for 30 min increases pulmonary artery pressure from 16 to 25 mmHg [72]. The effect of hypoxia on the pulmonary circulation is even more pronounced during exercise, as demonstrated in the Operation Everest II studies [24] where pulmonary artery pressure increased during near-maximal exercise at 8840 m to 54 mmHg.

The mechanism of pulmonary artery vasoconstriction initially involves inhibition of O₂ sensitive K⁺ channels leading to depolarization of pulmonary artery smooth muscle cells and activation of voltage

gated Ca²⁺ channels causing Ca²⁺ influx and vasoconstriction [48]. This process is immediately reversed by breathing oxygen. However, lowlanders exposed to high altitude for 2–3 weeks develop pulmonary hypertension that is not completely reversed by oxygen breathing [24] suggesting remodelling of pulmonary arterioles. Remodelling involves proliferation of smooth muscle cells and thickening of the artery wall [57].

■ Sympathetic activity

Acute hypoxia is a potent activator of sympathetic activity [39, 56]. Studies in several species, including dogs, rats and rabbits, showed that hypoxia stimulated the sympathoadrenal system. Acute hypoxia in spontaneously breathing anaesthetized animals causes increases in sympathetic nerve activity, increased release of catecholamines, increases in heart rate and regional vasoconstriction [28, 60]. However the effects of hypoxia on the human sympathetic nervous system are more difficult to determine and often indirect methods of assessment have been employed.

One method of assessment of sympathetic activity in humans is from blood or urine levels of catecholamines. However, catecholamine levels are the net resultant of secretion, spill-over, reuptake and excretion [59, 18] and results must be interpreted with caution. Mazzeo et al. [40] measured arterial noradrenaline and adrenaline concentrations in subjects at sea level, then after 4 h then 21 days at altitude (4,300 m). They reported an initial decrease in noradrenaline but by day 21 it had increased to 52% above sea level values. Arterial adrenaline values doubled following acute altitude exposure then declined to only 26% above sea-level by day 21. In a later study, however, the same authors [41] measured 24 h urinary noradrenaline and adrenaline excretion and venous plasma catecholamines in women at sea level and during 12 days of exposure to 4,300 m and reported increases in both urinary noradrenaline and adrenaline excretion after only one day at altitude and increases in plasma catecholamines on day 4 at altitude. During the 12 day period noradrenaline continued to increase as assessed both from urinary excretion and in the plasma samples. Adrenaline values however fell back to those recorded at sea level. Rostrup [59] reported initial decreases in both plasma noradrenaline and adrenaline which subsequently recovered. Results from simulated hypoxia are also conflicting with an increase in urinary adrenaline but no change in noradrenaline [29] or no change in either [71]. These results illustrate the difficulty in assessing autonomic activity from blood or urine catecholamines, but they do suggest that in the early

stages of exposure to altitude there is an increase mainly in adrenaline, but that later it is noradrenaline that predominates.

The changes in catecholamines are more consistent during exposure to chronic hypoxia. Calbet [10] measured systemic and skeletal muscle noradrenaline and adrenaline spillover in lowlanders after exposure to 5,260 m. After 9 weeks plasma noradrenaline and adrenaline concentrations were approximately 4 and 2 fold higher than the sea level values. These values were similar to those in patients with compensated chronic heart failure [2].

The heart rate at maximal exercise is reduced at altitude. In Operation Everest II maximal heart rates decreased from 160 at sea level to 118 at 8,848 m [54]. Given the evidence for elevated catecholamines at altitude, at least during chronic exposure, this suggests a down regulation of the cardiac β -adrenergic receptors. Studies in rats following prolonged exposure to hypobaric hypoxia have shown a decreased β -adrenergic receptor density [30, 67]. Short exposures to hypoxia (1–15 days) did not affect β -adrenergic receptor density. However by 21 days there was a 24% reduction. Leon-Velarde et al [35] exposed rats to a simulated altitude of 5,500 m for 21 days and also found a 24% reduction in β -adrenergic receptor density in both left and right ventricles. They also reported an increase in α_1 -adrenergic receptor density in the left ventricle, although Morel et al [48], who exposed rats to 5,500 m for 15 days, found no change in α_1 -adrenergic receptor density in either left or right ventricle. Density of adenosine receptors has also been shown to be decreased by 46% following 30 day exposure to 5,500 m simulated altitude in the rat while muscarinic receptor density increased by 49% [31].

Changes in receptor density have also been estimated indirectly in man by determining the rate of isoprenaline infusion required to increase heart rate by 25 beats/min. The required rate increased with increasing exposure to altitude and this was attributed to a down regulation of the β -adrenergic receptors [56]. Platelet α_2 -adrenergic receptor density decreased after 4 weeks exposure to 5,050 m [19]. Changes in α_2 -adrenergic receptor density on platelets may indicate a similar change in the central nervous system [53]. In the central nervous system α_2 -adrenergic receptors are known to play an important role in cardiovascular regulation [22]. Stimulation of these receptors in the ventrolateral medulla has been shown to reduce sympathetic and increase parasympathetic outflow [55]. If a change in the density of these receptors occurred it may explain many of the effects of altitude on the autonomic system.

The effect on the parasympathetic system has been assessed in humans from the responses to muscarinic

blockade. Following short exposures to hypoxia the changes in heart rate following muscarinic blockade became smaller [11]. However, Boushel et al. [8] exposed subjects to an altitude of 5,260 m for 9 weeks and then studied the effects of muscarinic blockade both at rest and during exercise, and suggested that there was an enhanced parasympathetic activity and that this was responsible for the reduction in heart rate seen during chronic adaptation to altitude.

■ Muscle sympathetic nerve activity

Several studies have examined the effects of acute hypoxia on muscle sympathetic nerve activity and reported increases in discharge [17, 27]. Chronic hypoxia also enhances sympathetic activity and Hanson and Sander [27] reported that, following exposure to an altitude of 5,260 m for 4 weeks, activity remained elevated 3 days following descent.

■ Heart rate variability

Cardiac autonomic nerve activity is often assessed noninvasively from spontaneous changes in heart rate. This is influenced by respiration [9] and this complicates many studies of hypoxia due to the concomitant respiratory stimulation. High frequency R–R interval power is considered to be associated with cardiac parasympathetic activity whereas the low frequency components are associated with both parasympathetic and sympathetic activity. The ratio of low to high frequency power is said to be an index of the “sympathovagal balance”. Power in both high and low frequency bands were found to decrease at altitude although the ratio of low to high frequency power increased [32, 16, 17]. The increase in the ratio is believed to imply that the sympathetic activity is dominant compared to parasympathetic. These findings imply that acute exposure to hypoxia causes decreased parasympathetic and increased sympathetic tone and during acclimatization there is a progressive shift toward still higher sympathetic tone.

■ Arterial baroreflex

Studies in humans of baroreflex control at altitude or simulated altitude have yielded contradictory results. Sagawa et al. [61], using the neck chamber method, reported that acute exposure to simulated altitude of 4,300 m had no effect on carotid baroreflex set point for heart rate control but there was a 50% reduction in the gain of the reflex. Halliwill and Minson [25, 26], on the other hand, using nitroprusside and phenylephrine, found that hypoxic breathing increased set

point but did not change gain. Studies of “spontaneous” baroreflex gain have indicated that it decreases at altitude or simulated altitude [5, 6, 7, 63]. Interpretation of these findings is complicated by the differences in baseline blood pressures and heart rate. Recently, Cooper et al. [15] reported that although acute hypoxia did not change baroreceptor control of heart rate it did decrease the gain of the vascular resistance response without changing “set point”.

■ Mechanisms for sympathetic activation at high altitude

The increase in sympathetic activity at altitude is caused by both the direct and indirect effects of hypoxia. The role of chemoreceptors is reviewed by Marshall [39]. Hypoxia acts directly on vascular smooth muscle in the systemic circulation causing relaxation and therefore hypotension. This, in turn, would lead to baroreceptor-mediated sympathetic excitation. Alterations in baroreflex function: an increase in “set point” and possibly a decrease in gain, are likely to contribute. An additional mechanism for exciting sympathetic activity may also arise through stimulation of pulmonary arterial baroreceptors. Hypoxia induces pulmonary hypertension and we have recently reported that, in the anaesthetized dog, increases in pulmonary artery pressure increase systemic vascular resistance [38, 46].

Autonomic function in high altitude residents

■ Healthy highlanders

Healthy high altitude dwellers show excellent adaptation to their environment. These adaptations are likely to be associated with altered gene expression as the expression of genes associated with vascular control and reactions to hypoxia have been found to be high in altitude dwellers [1]. Different communities, however, seem to adopt different adaptation strategies [4]. For example Andeans hyperventilate to decrease end-tidal and arterial CO₂ levels to as low as 25 mmHg and have haemoglobin levels well above those at sea-level. Ethiopian highlanders, on the other hand, have CO₂ and haemoglobin levels similar to sea-level dwellers [13, 33].

Despite the successful adaptation of permanent residents, some differences do occur. The carotid body shows age-related hyperplasia but blunted responses to hypoxia [62]. High altitude dwellers have been reported to show earlier cardiovascular degenerative changes with aging. Arterial wall stiffness is greater and blood pressures are higher [51, 52]. High

altitude residents, both healthy subjects and patients with chronic mountain sickness (see below) have higher catecholamine levels when measured at altitude than following descent to sea level [20]. Baroreceptors, however, appear to function normally at altitude [5]. We [45] examined cardiac and vascular responses to neck chamber pressures and found that responses were unaffected by descent to sea-level. Moore et al. [47] also studied baroreceptor function in anaesthetized dogs, which allows better control of relevant variables. There was no difference in the gain of the baroreflex control of vascular resistance between lowland animals and animals reared at altitude (4,330 m). Set point, however, was lower in high altitude animals which seems surprising in view of the known hypertensive effect of hypoxia.

Blood volumes are larger in high altitude dwellers. In Andeans this is due to a large packed cell volume whereas in Ethiopians plasma volume was large [12, 13]. Probably as the result of the large blood volumes, tolerance to orthostatic stress was greater than that in sea-level residents [12, 14].

■ Patients with chronic mountain sickness

Chronic mountain sickness (CMS, Monge’s disease; [43]) is a condition frequently found in long-term residents of high altitudes particularly in the Andes where it is a major public health problem. It also occurs in residents on the Tibetan plateau, although not in Ethiopians [13].

Patients with CMS develop excessive polycythemia and various clinical features including dyspnoea, palpitations, insomnia, dizziness, headache, confusion, loss of appetite, lack of mental concentration and memory alterations. Patients may also complain of decreased exercise tolerance, bone pain, acral paraesthesia and occasionally haemoptysis. The impairment of mental function may be reversed by phlebotomy [42]. Physical examination reveals cyanosis, due to the combination of polycythemia and low oxygen saturation, and a marked pigmentation of the skin exposed to the sun. Hyperaemia of conjunctivae is characteristic and the retinal vessels are also dilated and engorged. The second cardiac sound is frequently accentuated and there is an increased cardiac size, mainly due to right ventricular hypertrophy. As the condition progresses, overt congestive heart failure becomes evident, characterized by dyspnoea at rest and during mild effort, peripheral oedema, distension of superficial veins, and progressive cardiac dilation. A clinical score was devised in the attempt to assess the severity of the syndrome and to compare CMS cases within and between different countries in the world [37].

CMS is most likely the result of several influences acting on subjects living at high altitudes. Hypoventilation associated with aging has been proposed as one of the main underlying mechanisms [64]. Many of the clinical features may be attributed to the excessive polycythemia which leads to hyperviscosity of the blood and consequently impaired blood flow and impaired oxygen delivery to several organs including the brain [44].

Sime et al. [64] reported a blunted ventilatory response to hypoxia (VRH) in subjects with CMS and suggested this as the basic underlying cause. However, the same effect may also occur in some subjects without CMS [3, 62]. The function of the peripheral chemoreceptors has been shown to be abnormal [36].

Studies have been carried out to examine the plasticity of chemoreflexes to both long and short term changes in blood gas tensions of chronically hypoxic high-altitude natives with blunted respiratory responses to hypoxia. It was found that natives who had migrated to live at sea level had ventilatory responses to acute hypoxia (few minutes) which had become similar to those of sea-level controls [21]. However, responses to sustained hypoxia (20 min) remained markedly blunted. These results may explain the apparent discrepancy in previous studies.

Recent studies have examined cardiovascular and cerebrovascular control in subjects with CMS. Bernardi et al. [6] assessed baroreflex function and the chemo- and baroreflex interactions in Andean subjects with and without CMS. They found that subjects with CMS showed a reduction in the responses to stimulation of peripheral chemoreflexes. In addition, these subjects also showed a reduction in the baroreflex control of heart rate and blood pressure. The reduction in the arterial baroreflex correlated with an increase in CMS score, and with an increase of haemoglobin levels. They interpreted these findings as suggestive of a functional, reversible central depression rather than of the presence of an organic dysautonomia in CMS. They further suggested that the observed baroreflex alteration might be involved in the causation of some of the symptoms of CMS. In another study on subjects with CMS, performed at

high altitude, the same authors showed that increasing oxygen saturation for an hour by a slow breathing pattern or by oxygen administration was associated with increased arterial baroreflex sensitivity [33].

The major mechanism for the control of blood pressure is through regulation of peripheral vascular resistance, but most studies have examined only the control of heart rate. We have recently studied the responses of forearm vascular resistance to carotid baroreceptor stimulation in high altitude residents with and without CMS, both at their resident altitude and shortly after descent to sea level. Results showed that baroreflex "set point" was higher in CMS, but only at altitude. At sea level, values were similar [45].

Cerebrovascular control Cerebral blood flow is known to be less in CMS patients than in healthy controls and this is attributed to the high viscosity of the blood. Villafuerte et al. [66] estimated that the ideal haemoglobin level for maximal oxygen delivery is 14.7 g/dl, a value similar to that of sea-level dwellers. The cerebral circulation normally shows an efficient autoregulation whereby changes in cerebral perfusion pressure have minimal effect on flow. Claydon et al. [14] assessed autoregulation from the correlation between flow and pressure during orthostatic stress, where a significant correlation with a high coefficient indicates poor autoregulation. Results of this study showed that cerebrovascular autoregulation was impaired in CMS patients. These findings are compatible with those of Roach et al. [58] who reported reduced cerebrovascular sensitivity to carbon dioxide in the presence of hypobaric hypoxia in subjects with CMS.

Norcliffe et al. [50] determined the cerebrovascular responses to hypoxia and hypercapnia, separately and together, in CMS patients and normal high altitude dwellers. CMS patients did not respond differently from the normals, but in both groups at altitude the sensitivity of the cerebral circulation to hypoxia was less than that in sea level residents. Shortly after descent to sea level, however, sensitivity increased. Sensitivity to hypercapnia during hypoxia decreased after descent.

References

1. Appenzeller O, Minko T, Qualls T, et al. (2006) Gene expression, autonomic function and chronic hypoxia: a lesson from the Andes. *Clin Auton Res* 16:217–222
2. Azevedo ER, Newton GE, Floras JS, Parker JD (2000) Reducing cardiac filling pressure lowers norepinephrine spillover in patients with chronic heart failure. *Circulation* 101:2053–2059
3. Bainton CR, Carcelen A, Severinghaus JW (1964) Carotid chemoreceptor insensitivity in Andean natives. *J Physiol* 177:30–31
4. Beall CM (2003) High altitude adaptations. *Lancet* 362:S14–S15

5. Bernadi L, Passino C, Spadacini G, Calciali A, Robers R, Greene R, Martignani E, Anand I, Appenzeller O (1998) Cardiovascular autonomic modulation and activity of carotid baroreceptors at altitude. *Clin Sci* 95:565–573
6. Bernardi L, Roach RC, Keyl C, et al. (2003) Ventilation, autonomic function, sleep and erythropoietin. Chronic mountain sickness of Andean natives. *Adv Exp Med Biol* 543:161–175
7. Blaber AP, Hartley T, Pretorius PJ (2003) Effect of acute exposure to 3,660 m altitude on orthostatic responses and tolerance. *J Appl Physiol* 95:591–601
8. Boushel R, Calbet JA, Radegran G, Sondergaard H, Wagner PD, Saltin B (2001) Parasympathetic neural activity accounts for the lowering of exercise heart rate at high altitude. *Circulation* 104:785–791
9. Brown TE, Beightol LA, Koh J, Eckberg DL (1993) Important influence of respiration on human R-R interval power spectra is largely ignored. *J Appl Physiol* 75:2310–2317
10. Calbet JA (2003) Chronic hypoxia increases blood pressure and noradrenaline spillover in healthy humans. *J Physiol* 551:379–386
11. Clar C, Dorrington KL, Fatemian M, Robbins PA (2001) Effects of 8 h of isocapnic hypoxia with and without muscarinic blockade on ventilation and heart rate in humans. *Exp Physiol* 86:529–538
12. Claydon VE, Norcliffe LJ, Moore JP, et al. (2004) Orthostatic tolerance and blood volumes in Andean high altitude dwellers. *Exp Physiol* 89:565–571
13. Claydon VE, Gulli G, Slessarev M, Huppert TJ, Assefa T, Gebru S, Appenzeller O, Hainsworth R (2005) Blood and plasma volumes in Ethiopian high altitude dwellers. *Clin Auton Res* 15:325
14. Claydon VE, Norcliffe LJ, Moore JP, et al. (2005) Cardiovascular responses to orthostatic stress in healthy altitude dwellers, and altitude residents with chronic mountain sickness. *Exp Physiol* 90:103–110
15. Cooper VL, Pearson SB, Bowker CM, Elliott MW, Hainsworth R (2005) Interaction of chemoreceptor and baroreceptor reflexes by hypoxia and hyperventilation. *J Physiol* 568:677–687
16. Cornolo J, Mollard P, Brugniaux JV, Robach P, Richalet JP (2004) Autonomic control of the cardiovascular system during acclimatization to high altitude: effects of sildenafil. *J Appl Physiol* 97:935–940
17. Duplain H, Vollenweider L, Delabays A, Nicod P, Bartsch P, Scherrer U (1999) Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. *Circulation* 99:1713–1718
18. Esler M (2000) The sympathetic system and hypertension. *Am J Hypert* 13:99S–105S
19. Fischetti F, Fabris B, Zaccaria M, Biagi A, Calci M, Candido R, Bortoletto M, Caretta R (2000) Effects of prolonged high-altitude exposure on peripheral adrenergic receptors in young healthy volunteers. *Eur J Appl Physiol* 82:439–445
20. Gamboa A, Gamboa JL, Holmes C, et al. (2006) Plasma catecholamines and blood volumes in native Andeans during hypoxia and normoxia. *Clin Auton Res* 16:40–45
21. Gamboa A, León-Velarde F, Rivera-Ch M, et al. (2003) Acute and sustained ventilatory responses to hypoxia in high-altitude natives living at sea level. *J Appl Physiol* 94:1255–1262
22. Gavras I, Manolis AJ, Gavras H (2001) The alpha₂-adrenergic receptors in hypertension and heart failure: experimental and clinical studies. *J Hypert* 19:2115–2124
23. Grollman A (1930) Physiological variations of the cardiac output of man. VII. The effect of high altitude on the cardiac output and its related functions: an account of experiments conducted on the summit of Pikes Peak, Colorado. *Am J Physiol* 93:19–40
24. Groves BM, Reeves JT, Sutton JR, Wagner PD, Cymerman A, Malconian MK, Rock PB, Young PM, Houston CS (1987) Operation Everest II: elevated high-altitude pulmonary resistance unresponsive to oxygen. *J Appl Physiol* 63:521–530
25. Halliwill JR, Minson CT (2002) Effect of hypoxia on arterial baroreflex control of heart rate and muscle sympathetic nerve activity in humans. *J Appl Physiol* 93:857–864
26. Halliwill JR, Minson CT (2005) Cardiovascular regulation during combined hypoxic and orthostatic stress: fainters vs. nonfainters. *J Appl Physiol* 98:1050–1056
27. Hansen J, Sander M (2003) Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. *J Physiol* 546:921–929
28. Heistad DD, Abboud FM (1980) Circulatory adjustments to hypoxia. *Circulation* 61:463–470
29. Johnson TS, Rock PB, Young JB, Fulco CS, Trad LA (1988) Hemodynamic and sympathoadrenal responses to altitude in humans: effect of dexmethasone. *Aviation Space Environ Med* 59:208–12
30. Kacimi R, Richalet JP, Corsin A, Abousahl I, Crozatier B (1992) Hypoxia-induced downregulation of beta-adrenergic receptors in rat heart. *J Appl Physiol* 73:1377–1382
31. Kacimi R, Richalet JP, Crozatier B (1993) Hypoxia-induced differential modulation of adenosinergic and muscarinic receptors in rat heart. *J Appl Physiol* 75:1123–1128
32. Kanai M, Nishihara F, Shiga T, Shimada H, Saito S (2001) Alterations in autonomic nervous control of heart rate among tourists at 2700 and 3700 m above sea level. *Wilderness Environ Med* 12:8–12
33. Keyl C, Schneider A, Gamboa A, et al. (2003) Autonomic cardiovascular function in high-altitude Andean natives with chronic mountain sickness. *J Appl Physiol* 94:213–219
34. Kontos HA, Levasseur JE, Richardson DW, Mauck HP Jr, Patterson JL Jr (1967) Comparative circulatory responses to systemic hypoxia in man and in unanesthetized dog. *J Appl Physiol* 23:381–386
35. León-Velarde F, Bourin MC, Germack R, Mohammadi K, Crozatier B, Richalet JP (2001) Differential alterations in cardiac adrenergic signaling in chronic hypoxia or norepinephrine infusion. *Am J Physiol* 280:R274–R281
36. León-Velarde F, Gamboa A, Rivera-Ch M, Palacios JA, Robbins PA (2003) Peripheral chemoreflex function in high-altitude natives and patients with chronic mountain sickness. *J Appl Physiol* 94:1269–1278
37. León-Velarde F, McCullough RG, Reeves JT, et al. (2003) Proposal for scoring severity in chronic mountain sickness (CMS). Background and conclusions of the CMS Working Group. *Adv Med Biol* 543:339–354
38. McMahon NC, Drinkhill MJ, Myers DS, Hainsworth R (2000) Reflex responses from the main pulmonary artery and bifurcation in anaesthetised dogs. *Exp Physiol* 85:411–420
39. Marshall JM (1994) Peripheral chemoreceptors and cardiovascular regulation. *Physiol Rev* 74:543–594
40. Mazzeo RS, Bender PR, Brooks GA, et al. (1991) Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. *Am J Physiol* 261:E419–E424
41. Mazzeo RS, Child A, Butterfield GE, et al. (1998) Catecholamine response during 12 days of high-altitude exposure (4,300 m) in women. *J Appl Physiol* 84:1151–1157

42. Monge MC (1925) *Sobre un caso de enfermedad de Váquez*. Comunicación presentada a la Academia Nacional de Medicina. Lima 1–6
43. Monge CC, León-Velarde F (1991) Physiological adaptation to high altitude: oxygen transport in mammals and birds. *Physiol Rev* 71:135–172
44. Monge CC, Whittombury J (1982) Chronic mountain sickness and the physiopathology of hypoxemic polycythemia. In: Sutton JR, Jones NL, Houston CS (eds) *Hypoxia: man at altitude*. Thieme-Stratton, New York, pp 51–56
45. Moore JP, Claydon VE, Norcliffe LJ, et al. (2006) Carotid baroreflex regulation of vascular resistance in high altitude Andean natives with and without chronic mountain sickness. *Exp Physiol* 91:907–914
46. Moore JP, Hainsworth R, Drinkhill MJ (2004) Phasic negative intrathoracic pressures enhance the vascular responses to stimulation of pulmonary arterial baroreceptors in closed-chest anaesthetized dogs. *J Physiol* 555:815–824
47. Moore JP, Rivera-Chira M, Macarlupu JL, et al. (2004) Carotid baroreflex regulation of vascular resistance in lowland and high altitude anaesthetized dogs. *J Physiol* 560:PC11
48. Morel OE, Buvry A, Le Corvoisier P, et al. (2003) Effects of nifedipine-induced pulmonary vasodilatation on cardiac receptors and protein kinase C isoforms in the chronically hypoxic rat. *Pflugers Archiv* 446:356–364
49. Moudgil R, Michelakis ED, Archer SL (2005) Hypoxic pulmonary vasoconstriction. *J Appl Physiol* 98:390–403
50. Norcliffe LJ, Rivera M, Palacios AJ, et al. (2005) Cerebrovascular Responses to Hypoxia and Hypocapnia in High Altitude Dwellers. *J Physiol (Lond)* 566:287–294
51. Otsuka K, Norboo T, Otsuka Y, et al. (2005) Chronoecological health watch of arterial stiffness and neuro-cardio-pulmonary function in elderly community at high altitude (3524 m) compared with Japanese town. *Biomed Pharmacother* 59(suppl 1):S58–S67
52. Otsuka K, Norboo T, Otsuka Y, et al. (2005) Effect of aging on blood pressure in Leh, Ladakha, a high altitude community by comparison with a Japanese town. *Biomed Pharmacother* 59(suppl 1):S54–S57
53. Piletz JE, Andorn AC, Unnerstall JR, Halaris A (1991) Binding of [3H]-p-aminoclonidine to alpha 2-adrenoceptor states plus a non-adrenergic site on human platelet plasma membranes. *Biochem Pharmacol* 42:569–584
54. Reeves JT, Groves BM, Sutton JT et al. (1987) Operation Everest II: preservation of cardiac function at extreme altitude. *J Appl Physiol* 63:531–539
55. Reis DJ, Golanov EV, Ruggiero DA, Sun MK (1994) Sympatho-excitatory neurons of the rostral ventrolateral medulla are oxygen sensors and essential elements in the tonic and reflex control of the systemic and cerebral circulations. *J Hypertens* 12:S159–S180
56. Richalet JP, Larmignat P, Rathat C, Keromes A, Baud P, Lhoste F (1988) Decreased cardiac response to isoproterenol infusion in acute and chronic hypoxia. *J Appl Physiol* 65:1957–1961
57. Riley DJ (1991) *Vascular remodelling in the lung*. Scientific Foundations (eds Cristal RC, West JB) Raven Press, New York, pp 1189–1198
58. Roach R, Passino C, Bernardi L, Gamboa J, Gamboa A, Appenzeller O (2001) Cerebrovascular reactivity to CO₂ at high altitude and sea level in Andean Natives. *Clin Auton Res* 11:183
59. Rostrup M (1998) Catecholamines, hypoxia and high altitude. *Acta Physiol Scand* 162:389–399
60. Rowell LB, Blackmon JR (1986) Lack of sympathetic vasoconstriction in hypoxemic humans at rest. *Am J Physiol* 251:H562–H570
61. Sagawa S, Torii R, Nagaya K, Wada F, Endo Y, Shiraki K (1997) Carotid baroreflex control of heart rate during acute exposure to simulated altitudes of 3,800 m and 4,300 m. *Am J Physiol* 273:R1219–R1223
62. Severinghaus JW, Bainton CR, Carcelen A (1966) Respiratory insensitivity to hypoxia in chronically hypoxic man. *Resp Physiol* 1:308–334
63. Sevre K, Bendz B, Hanko E, et al. (2001) Reduced autonomic activity during stepwise exposure to high altitude. *Acta Physiol Scand* 173:409–417
64. Sime F, Monge CC, Whittombury J (1975) Age as a cause of chronic mountain sickness. *Int J Biometeorol* 19:93–98
65. Talbot NP, Balanos GM, Dorrington KL, Robbins PA (2005) Two temporal components within the human pulmonary vascular response to 2 h of isocapnic hypoxia. *J Appl Physiol* 98:1125–1139
66. Villafuerte FC, Cardenas R, Monge CC (2004) Optimal haemoglobin concentration and high altitude: a theoretical approach for Andean men at rest. *J Appl Physiol* 96:1579–1580
67. Voelkel NF, Hegstrand L, Reeves JT, McMurty IF, Molinoff PB (1981) Effects of hypoxia on density of beta-adrenergic receptors. *J Appl Physiol* 50:363–366
68. Vogel JA, Harris CW (1967) Cardio-pulmonary responses of resting man during early exposure to high altitude. *J Appl Physiol* 22:1124–1128
69. Vogel JA, Hansen JE, Harris CW (1967) Cardiovascular responses in man during exhaustive work at sea level and high altitude. *J Appl Physiol* 23:531–539
70. WHO (1996) *World Health Statistics Annual 1995*. World Health Organization, Geneva
71. Young PM, Sutton JR, Green HJ, et al. (1992) Operation Everest II: metabolic and hormonal responses to incremental exercise to exhaustion. *J Appl Physiol* 73:2574–2579
72. Zhao L, Mason NA, Morrell NW, et al. (2001) Sildenafil inhibits hypoxia-induced pulmonary hypertension. *Circulation* 104:424–428