

Cardiovascular Physiology at High Altitude

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Abstract

The role of the cardiovascular system is to deliver oxygenated blood to the tissues and remove metabolic effluent. It is clear that this complex system will have to adapt to maintain oxygen delivery in the profound hypoxia of high altitude. The literature on the adaptation of both the systemic and pulmonary circulations to high altitude is reviewed.

Introduction

The role of the cardiovascular system is simple; to drive the delivery of oxygen to the tissues that need it and carry away the metabolic effluent. It needs to respond to the changing metabolic needs of the tissues in such a way that oxygen delivery meets demand. How it does this is complex, even more so at altitude, where the reduced barometric pressure, and therefore partial pressure of oxygen, cause further stress on the body.

During the late 19th and early 20th century interest grew in travelling to the mountains in search of the sublime; the quality of greatness or vast magnitude with which nothing else can be compared. As such there are many references in the literature about cardiovascular symptoms as people travelled to altitude, often with a fast ascent profile, and many intriguing explanations and hypotheses for the symptoms they felt. Today, many of these accounts seem grossly over exaggerated such as blood pouring from the eyes and nose due to an imbalance of pressure on the blood vessels or violent palpitations. Much research has been carried out, both in hypobaric chambers and field studies, into the cardiovascular changes associated with altitude and the part it plays in acclimatisation and adaptation.

In this article the literature is reviewed to summarise our current understanding of cardiovascular changes of both the systemic and pulmonary circulation with altitude. It is worthy of note that there are many areas that have yet to be studied. This is often due to the difficulties of carrying out invasive and complex monitoring on subjects at altitude, such as accurately assessing pulmonary vasculature pressures using flotation catheters.

Cardiac Function

A few basic equations are useful when considering the cardiovascular system and its response to hypobaric hypoxia. These can be found in Table 1.

Cardiac Output

On acute exposure to a hypoxic environment it is generally accepted that cardiac output increases. This makes good physiological sense; as the partial pressure of oxygen falls in the atmosphere then so does the SaO₂ (Figure 1) and therefore the oxygen content of blood decreases (Table 1-Equation 1). In order

Equation 1.

Oxygen Content = (Hb x SaO₂ x Constant) + (small amount of dissolved O₂)

Equation 2.

Oxygen Delivery = Oxygen Content of Blood x Cardiac Output

Equation 3.

Cardiac Output = Heart Rate x Stroke Volume

Equation 4.

Blood Pressure = Cardiac Output x Vascular Resistance

Table 1: Equations of the Cardiovascular System

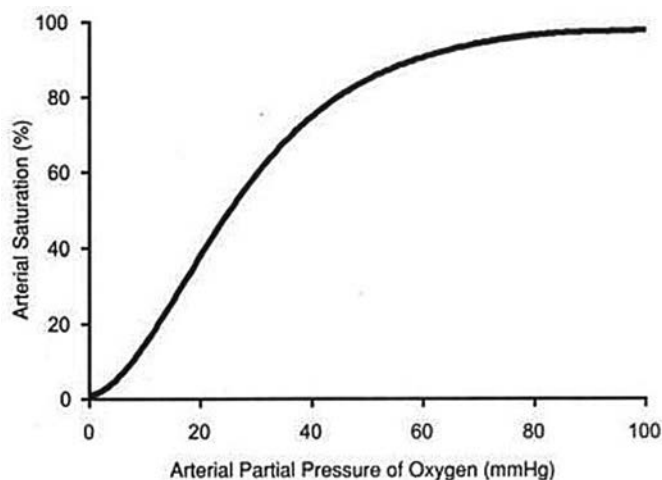


Figure 1: Oxygen dissociation curve

to maintain oxygen delivery to the tissues (Table 1-Equation 2) cardiac output must increase.

Once acclimatised cardiac output returns towards sea level values both at rest and for any given work rate, except at a maximal level where cardiac output and maximum work rate is reduced [1,2]. This seems paradoxical but is probably due in part to the fact that VO₂ max (maximum oxygen consumption) is reduced at extreme altitude because oxygen transfer from the lung and to the tissue is diffusion, rather than perfusion, limited. This means that the uptake of oxygen at the alveolar/capillary membrane and offload at the capillary/cell membrane is limited by the properties of the membrane rather than the flow of blood to those areas. An alternative explanation is that the rise in haemoglobin levels reduces the effect of the hypoxia on the oxygen content of the blood (Table 1-Equation 1).

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Heart Rate

Acute hypoxia causes an increase in both resting and exercising heart rate, due to increased sympathetic drive. The higher the altitude, then the greater the increase in heart rate. As a subject acclimatises the resting heart rate generally returns to that of sea level values up to an altitude of approximately 4500m. On exercise however, even in acclimatised subjects, heart rate for a given work load is greater than at sea level except at maximal exercise where maximal heart rate is reduced compared to sea level values.

There are a number of different theories as to why maximal heart rate should be lower at altitude compared to sea level. Pugh et al noted in 1964 that oxygen consumption at maximal heart rate at altitude was reduced compared to sea level values, suggesting for the given work rate much was achieved using anaerobic respiration [3]. Later Richalet and colleagues suggested the reduction is a physiological adaptation that reduces cardiac work in environments with limited oxygen availability - it has been shown that hypoxia down regulates β -adrenergic receptors in animal models [4]. This adaptation of limited maximum heart rate seems likely to be beneficial given the diffusion limitation of oxygen uptake in the lungs.

Interestingly breathing oxygen at high altitude may reduce the heart rate for a given work load to below sea level values [3]. This may be due to the higher haemoglobin levels (see later) and therefore increased oxygen content (Table 1 - Equation 1) in comparison to sea level.

Stroke Volume

Both cardiac output and heart rate rise acutely with exposure to hypoxia and there is no consistent change to stroke volume (Table 1- Equation 3). Once acclimatised a subject's cardiac output during exercise returns towards sea level values whereas heart rate continues to be elevated. Thus stroke volume must be reduced and this has been confirmed in several studies [1]. This is not due to a loss of myocardial contractility (see below) but perhaps due to a reduction in plasma volume and therefore preload or a reduction in cardiac filling time secondary to the increased heart rate.

Myocardial Contractility and Coronary Circulation

Measuring cardiac contractility is difficult in the field but has been studied in several chamber studies using measurements from pulmonary artery flotation catheters as surrogate markers and 2D echocardiography [5] as well as Doppler echocardiography [2]. The findings suggest that in spite of the severe hypoxaemia, pulmonary hypertension and reduction in preload, cardiac contractility is maintained even at a simulated altitude of 8000m.

The myocardium has one of the highest extraction ratios for oxygen in the body. As such, in acute hypoxic conditions it has been shown that coronary blood flow proportionally increases to compensate for this. Permanent residents at high altitude have a reduced coronary blood flow compared to sea level residents and yet there appears to be no increase in incidence of myocardial ischaemia. One explanation is that there is a greater density of coronary artery terminal branches in these residents compared to sea level controls [6].

Blood Pressure

Blood pressure changes little with acute exposure to altitude; however there is usually an increase for the first few weeks

when lowlanders travel to altitude. This is probably due to an increase in the sympathetic drive and vascular tone. Conversely lowlanders resident at altitude for some years show a decrease in both systolic and diastolic pressures and subjects with known systemic hypertension often show an improvement in blood pressure [7]. On the Defence Medical Services (DMS) expedition to Aconcagua in 2007 resting mean systolic blood pressure (SBP) increased from 116 +/- 15 mmHg at sea level to 136 +/-13 mmHg at 4250m [8]. The Birmingham Medical Research Expeditionary Society similarly report changes in mean SBP of 131 +/-23 mmHg at sea level increasing to 145 +/- 23 mmHg at 3450m [9].

During exercise at altitude acclimatised lowlanders show an increase in blood pressure similar to that seen in unacclimatised sea level residents while high altitude natives show a consistently higher rise [10].

Abnormal Rhythms

Sinus arrhythmia associated with the periodic breathing seen at altitude is very common. Despite the severe hypoxaemia other arrhythmias are uncommon but when present are usually atrial or ventricular premature contractions. These are more frequently seen during the most profound times of tissue hypoxia i.e. during the apnoea phase of the periodic breathing cycle.

The changes in cardiac function at altitude are summarised in Box 1

- Cardiac output increases following acute exposure to altitude
- In acclimatised subjects and natives of high altitude cardiac output tends towards sea level values both at rest and for a given work load
- Heart rate is increased, while stroke volume is reduced for a given work rate
- Myocardial contractility is preserved even at very high altitudes in normal subjects
- Symptoms of myocardial ischaemia are no more prominent in subjects living at altitude
- Studies looking at changes in blood pressure with altitude have shown varying results with some showing an elevation while others a reduction
- Sinus arrhythmia, secondary to periodic breathing, is very common. However pathological heart rhythms are uncommon despite the severe hypoxaemia

Box 1: Summary of Cardiac Function at Altitude

Pulmonary Circulation

Pulmonary Hypertension

Increases in pulmonary vasculature resistance secondary to hypoxic pulmonary vasoconstriction (HPV) leads to pulmonary hypertension at altitude. This is seen in subjects exposed to acute hypoxia, acclimatised lowlanders and high altitude natives alike. With acute exposure to hypoxia pulmonary hypertension is reversed with oxygen although there is variation between subjects in reversibility, leading to Read and Fowler referring to responders and non-responders [11].

The response seen in adults is probably a residual mechanism from when the foetal circulation changes to the newborn circulation at birth; there is a very high pulmonary vasculature resistance in the foetal circulation meaning that oxygen rich right

atrial blood from the placenta passes through the foramen ovale into the systemic circulation. At birth, the pulmonary vasculature resistance rapidly falls with the onset of breathing, causing the foramen ovale to close and blood to pass through the pulmonary vessels. In certain disease states such as asthma and chronic obstructive pulmonary disease, HPV is of value in that it limits ventilation/perfusion mismatch i.e. in areas of the lung that are not being ventilated HPV occurs diverting blood away from these regions. However at altitude, HPV serves no purpose and is thought to be one of the causes of high altitude pulmonary oedema (HAPE).

During Operation Everest II pulmonary vascular pressures were measured using flotation catheters. The pulmonary vascular pressure gradient (mean pulmonary arterial – pulmonary wedge) was measured at different cardiac outputs at various altitudes. At rest the gradient increased with increasing altitude but most striking was the increase in slope of pressure gradient against cardiac output at the higher altitudes [12]. This indicates the marked increase in resistance at high altitude.

The pulmonary hypertension associated with altitude leads to right ventricular and atrial hypertrophy. Changes associated with this hypertrophy are often seen on the ECG with right axis deviation of the QRS axis and increase in amplitude of the P wave in lead II.

Hypoxic Pulmonary Vasoconstriction

The mechanism for hypoxic pulmonary vasoconstriction (HPV) is not fully understood. It is still seen in isolated lung and when the lung is perfused with oxygen rich blood while ventilating it with a hypoxic mixture [13]. This suggests it is a local action of hypoxia on the artery itself, predominately the pulmonary arterioles.

Calcium and potassium channels in the smooth muscle and nitric oxide may all play a role in HPV. As is common with all muscle cells, an increase in intracellular calcium leads to

muscle contraction. Hypoxia causes a decrease in potassium channel activity leading to membrane depolarisation (it is the efflux of potassium ions from the cell that maintains the potential across the cell membrane and prevents depolarisation), influx of calcium ions and contraction of smooth muscle cells. Nitric Oxide, a relaxing factor, is produced from L-arginine in endothelial cells of blood vessels by nitric oxide synthase (NOS). In smooth muscle cells it activates guanylate cyclase (GC) that converts guanylate triphosphate (GTP) to cyclic guanylate monophosphate (cGMP). This in turn causes smooth muscle relaxation via cGMP dependant protein kinase (PK). Figure 2 summarises these intracellular mechanisms.

NOS inhibitors have been shown to augment HPV, while inhaled nitric oxide is used in neonates with pulmonary hypertension and has been shown to reduce pulmonary vascular resistance in subjects with HAPE [14]. Calcium channel blockers such as nifedipine are used in the treatment and prevention of HAPE (by causing pulmonary vasodilatation) and more recently 5-phosphodiesterase inhibitors (5-PDEi) such as sildenafil have been shown to reduce pulmonary hypertension and may also be useful in the treatment of HAPE [15,16].

Remodelling

The structural changes that occur in the pulmonary vasculature as a result of exposure to raised vascular pressures are known as remodelling. Pulmonary arterioles usually have a wall made only of elastic fibres, however the arterioles of long term high altitude residents develop smooth muscle in the walls between the elastic fibres. This explains why pulmonary hypertension in high altitude natives is not reversed with 100% oxygen and suggests that a degree of remodelling occurs after only a few weeks at altitude since the pulmonary hypertension of these lowlanders is also not reversed with 100% oxygen [12].

A summary of the pulmonary changes at altitude are given in Box 2

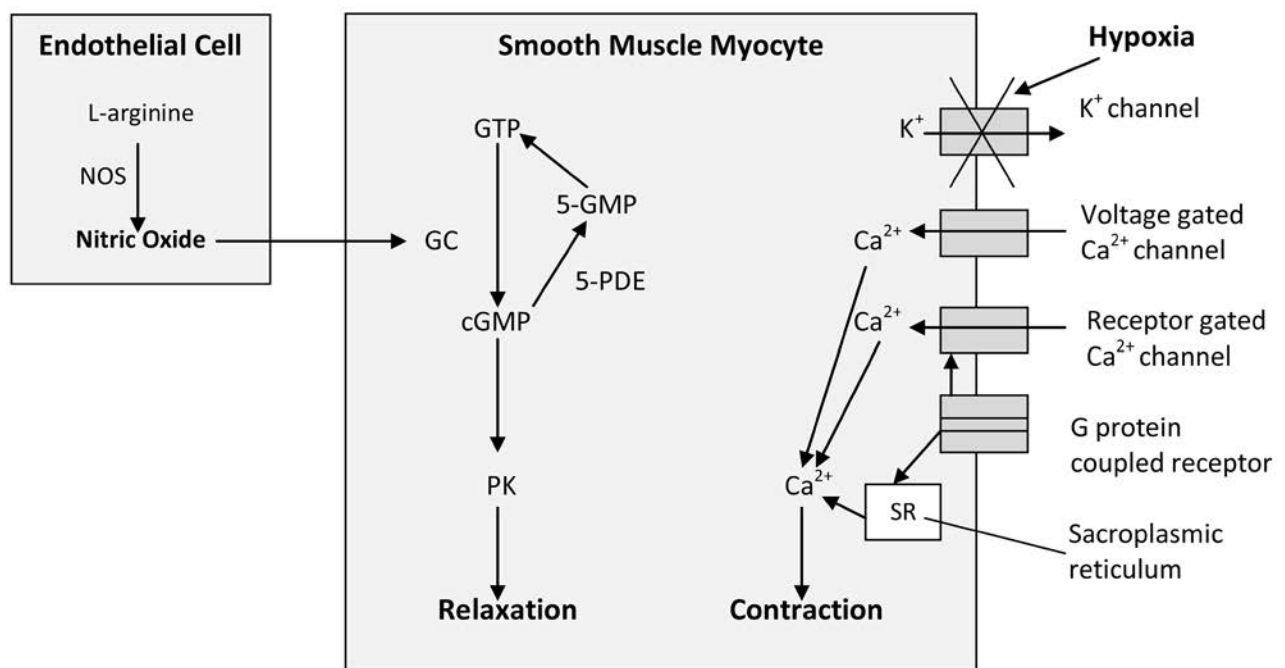


Figure 2: Intracellular Mechanisms of Smooth Muscle Relaxation and Contraction

- Pulmonary hypertension is seen in subjects regardless of whether it is acute or chronic exposure
- Pulmonary hypertension is caused by an increase in pulmonary vascular resistance secondary to hypoxic pulmonary vasoconstriction (HPV)
- HPV in an adult may be a residual response from birth when the foetal circulation transforms into the newborn circulation
- HPV is due to the local action of alveolar hypoxia (and not arterial hypoxia) on the small pulmonary artery itself
- Pulmonary hypertension leads to right ventricular hypertrophy with a resultant right axis deviation often seen on ECG
- With prolonged exposure to hypoxia the pulmonary vasculature undergoes structural changes known as remodelling

Box 2: Summary of Pulmonary Function at Altitude

Plasma Volume

Regulation of plasma volume

Plasma volume is normally controlled by a number of different feedback loops working to maintain homeostasis of the circulating volume. These include atrial natriuretic peptide (ANP), the renin/aldosterone system, and secretion of antidiuretic hormone (ADH).

At altitude there is generally a reduction in plasma volume as a result of diuresis. This is likely to be caused by changes in the feedback loops as a result of hypoxia. Hypoxic stimulation of the carotid bodies reduces sodium reabsorption in the kidneys via neural pathways leading to both a natriuresis and diuresis [17,18]. ANP (and BNP) is produced in the right atrium and is normally released as a result of atrial stretch but more recently has also been shown to be released in the presence of hypoxia [19] although this has been contradicted in human studies [20].

Multiple other factors also affect plasma volume. Dehydration from evaporative losses from high respiratory rates and reduced oral intake will reduce plasma volume as will the standing position as a result of venous pooling and increased loss into the extravascular space. Hypothermia leads to vasoconstriction and an apparent increase in plasma volume. The reduction in plasma volume, although increasing packed red cell volume (PCV), causes a reduction in blood volume (until red cell production increases) and maybe one of the causes for the reduction in stroke volume seen at altitude.

Regulation of haemoglobin concentration

Erythropoietin (EPO) is a glycoprotein hormone secreted by the kidney (and to a lesser extent the liver) in response to hypoxia (and hypovolaemia) causing erythropoiesis in the bone marrow and an increase in PCV. The EPO gene is induced by hypoxia inducible factor-1 α (HIF-1 α). Interestingly this nuclear factor, which is rapidly broken down in normoxia, but accumulates in hypoxia, is responsible for inducing multiple other genes that may well play a part in acclimatisation and adaptation to altitude; products include lactate dehydrogenase, nitric oxide synthase and vascular endothelial growth factor.

There is an elevation in EPO production within the first 2 hours of hypoxia, peaking at 24-48 hours and declining to normal

levels within 3 weeks. However the increase in PCV continues even after the EPO levels have fallen to near normal values. The reason for this remains elusive.

As the life span of the red cell remains unchanged (approximately 120 days) there is a net gain in red cells over time and therefore an increase in red cell mass (RCM). Pugh found that, when corrected for loss of body weight, there was a mean increase of 67.5% in RCM with a resultant increase in blood volume of 22.8% [21]. This increase results in a rise in haemoglobin concentration thus the oxygen carrying capacity of blood is maintained despite hypoxia up to altitudes of 5300m (Table 1-Equation 1).

However, the benefit of an increase in haemoglobin on the oxygen content of the blood is offset by the fact that it increases viscosity; there is an exponential increase when levels rise above 18g/dl. Blood flow is inversely proportional to viscosity and at high levels the increase in resistance of flow through the pulmonary and systemic circulation is sufficient to reduce cardiac output (Table 1-Equation 4). Hence although oxygen content may be increased, oxygen delivery to the tissues may be reduced (Table 1-Equation 2).

In a study looking at lowlanders acclimatised to 5260m Calbet concluded that the increase in haemoglobin levels associated with acclimatisation does not improve maximal exercise capacity and performance and local factors may be more important in preserving $\dot{V}O_{2\max}$ [22]. Plasma volume changes are summarised in Box 3.

- Packed red cell volume and haemoglobin concentration increase with acclimatisation – initially by a reduction of plasma volume, later by an increase in red cell erythropoiesis
- The reduction in plasma volume is likely to be due to hypoxic stimulation of the carotid bodies and subsequent natriuresis and diuresis
- Hypoxia stimulates bone marrow erythropoiesis by an increase in erythropoietin
- Hypoxia induces the erythropoietin gene through a nuclear factor (HIF-1 α)
- By increasing haemoglobin concentration the oxygen carrying capacity of blood is maintained despite the hypoxia to altitudes of 5300m

Box 3: Summary of Plasma Volume at Altitude

Cardiovascular Response to Exercise at Altitude and Limiting Factors of Extreme Altitude

Exercising at Altitude

Cardiac output for a given workload returns towards sea level values in acclimatised subjects (except at maximal work rates), the heart rate remains increased and stroke volume is reduced..

Uniquely at extreme altitude both oxygen loading at the alveolus and offloading at the muscles becomes diffusion limited [23,24]. The diffusion limitation at the muscle level is a relatively new concept, previously it was thought that the work able to be done by muscles at altitude was determined by the oxygen delivery to that muscle (Table 1-Equation 1). This is evident even though the average distance over which oxygen has to diffuse from the capillary to the mitochondria is reduced due to muscle fibres becoming smaller at altitude [25].

Maximal Oxygen Consumption

Maximal oxygen consumption (VO_2max) in acclimatised subjects at altitude is reduced. The reason is unclear but may be caused by a reduction in muscle mass or the increased blood viscosity at altitude leading to interference in capillary blood flow and oxygen exchange at the tissue level. Other reasons suggested include the diffusion limitation in exercising muscle and that blood flow to the muscles of locomotion is reduced as a consequence of the increased demand of the respiratory muscles. Cibella et al looked at the increased oxygen needs of the respiratory muscles at altitude due to the increased workload. They found that at altitude breathing accounted for 26% of VO_2max compared to only 5.5% at sea level [26]. The responses to exercise at altitude are summarised in Box 4.

- The linear relationship between oxygen uptake and work load is independent of altitude
- Maximal oxygen consumption is reduced at altitude
- Oxygen transfer at the tissue level is likely to be diffusion limited even though there is a reduced distance from capillary to mitochondria

Box 4: Summary of Exercise Response and Limiting Factors at Altitude

Pre-existing Cardiovascular Disorders at Altitude

In general, travelling to altitude increases the stress placed on the body and may therefore increase the symptoms of cardiovascular disease. However with sensible ascent profiles, in well controlled patients, there seems little reason why the mountains can't be enjoyed. Inevitably the patient must consider the risks and benefits and make a sensible informed decision. It must also be remembered however that rash decisions, while placing the subject in danger, may also place many other people at risk including other team members and potential rescuers.

Coronary Artery Disease

Angina is likely to be worsened by ascent to altitude secondary to the insult of hypoxia and the increased exercise. It seems prudent that subjects with unstable or exercise induced angina should not undertake an expedition at altitude. However observational studies [27,28] have reported that the incidence of cardiac ischaemic symptoms in subjects with known coronary artery disease at moderate altitude does not increase.

Strenuous exercise after a recent myocardial infarction is obviously ill advised and not travelling to altitude, until totally rehabilitated and symptom free, seems sensible. The same can be said for subjects with signs and symptoms of heart failure. Altitude increases the viscosity of blood and the cold may cause platelet aggregation and coronary artery spasm.

Hypertension

In general acute hypoxia (both in chambers and initial ascent to altitude) causes a rise in both resting and exercise blood pressure in hypertensive patients. However with prolonged exposure the response is variable with some subjects showing a decrease in both systolic and diastolic pressures while others have little or no change [29]. Recommendations have been made for adjusting blood pressure medication [30]. In this review the authors suggest that blood pressure should be monitored and treatment only changed if blood pressure rises to a systolic blood pressure greater than 180

mmHg or diastolic blood pressure greater than 120 mmHg with symptoms possibly related to elevated blood pressure (including vision changes, shortness of breath, chest pain, or altered mental status) or if systolic blood pressure is greater than 220 mmHg or diastolic pressure is greater than 140 mmHg in the absence of symptoms. There is no published data on which antihypertensive medication is most beneficial but there are good physiological reasons to use a calcium channel or alpha blocker. The changes are summarized in Box 5.

- The initial phases of acclimatisation involve an increase in sympathetic tone with resultant increases in cardiac output and blood pressure. As a result of this symptoms of cardiovascular disease may be expected to increase

Box 5: Summary of Cardiovascular Disorders at Altitude

Conclusions

There is a broad spectrum of cardiovascular adaptation to prolonged exposure to hypobaric hypoxia. Many of these changes are beneficial in part but may also play a part in high altitude pathology, for example a rise in haemoglobin results in greater oxygen carriage but may actually reduce oxygen delivery to the tissues by increasing viscosity and reducing blood flow, whilst hypoxic pulmonary vasoconstriction is a beneficial adaptation to regional hypoxia in the lung but may be part of the pathogenesis of high altitude pulmonary oedema.

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