Cardiac Performance with Chronic Hypoxia: Mechanisms regulating stroke volume

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This work investigated the changes in cardiac function seen with high altitude exposure in health lowlanders and Highlanders, as well as those suffering from chronic mountain sickness.


This study mapped the temporal changes in cardiac function over the first week of exposure and the normalisation following return to sea level.


This elegant non-invasive study provides evidence that right heart function is maintained at rest and in response to exercise at high altitude, even in those suffering from chronic mountain sickness and exhibiting an exaggerated pulmonary pressure response to exercise.


The authors employed a double-blind, randomised placebo-controlled trial to independently manipulate two of the mechanisms responsible for the decrease in stroke volume at high altitude. The decrease in blood volume had the largest effect on stroke volume, but increased pulmonary artery pressure also plays a role in reducing stroke volume in chronic hypoxia.
This study was the first to apply speckle-tracking imaging techniques to the assessment of cardiac function in chronic hypoxia, and showed an increase in the mechanical function of the heart that underpins the decrease in end-systolic volume previously reported.
Abstract

When humans are exposed to high altitude hypoxia for a sustained period, the cardiac stroke volume is reduced. The changes in cardiac performance seen at high altitude are a result of complex and concomitant changes in preload, afterload and contractility, although the precise mechanisms underpinning the decrease in stroke volume are not known despite being of scientific interest for over fifty years. In this review, we briefly revisit the seminal work performed in the area before focusing on recent developments that have applied mechanistic experimental models and novel imaging technologies to further understand why stroke volume is decreased in chronic hypoxia. First, the review focuses on systolic contractile function before considering the role of diastolic function and ventricular filling.
Introduction

Afterload, preload and contractility (the latter mediated in the chronic state primarily by autonomic control) are the three fundamental influences on stroke volume, all of which change with acclimatisation to chronic hypoxia. For example, (i) the afterload on the left and right ventricles is mildly (Parati et al., 2012) and moderately-severely (Penaloza & Arias-Stella, 2007) increased compared to sea level, respectively; (ii) sympathetic activation (Hansen & Sander, 2003; Lundby et al., 2017) and parasympathetic withdrawal (Siebenmann et al., 2015) together increase inotropy and chronotropy and (iii) right atrial pressure and left ventricular filling are both reduced (Alexander & Grover, 1983; Reeves et al., 1990). The consequence is a cardiac output that is the same as it is at sea level, but achieved via a higher heart rate and a lower stroke volume; a pattern that remains evident during exercise for a given oxygen uptake or absolute workload (Sutton et al., 1992). The physiological mechanisms underpinning the decrease in stroke volume have been of scientific interest for over 50 years, but no unifying theory has been established. The concomitant decrease in ejection and filling has stimulated the investigation of both systolic and diastolic function as potential underlying causes. This review will focus on the recent developments that have attempted to shed light on this phenomenon by first focusing on the changes in contractile function that occur in chronic hypoxia, followed by a discussion of the factors that influence ventricular filling and how these may translate to a decrease in stroke volume.

Ventricular Contractile Function

The reduction in stroke volume was first definitively described by Alexander et al. (1967) who used the direct Fick method to determine cardiac output at rest and during exercise at sea level and following 10 days at 3100 m. The authors proposed six potential mechanisms to explain the reduction in stroke volume, including the possible impairment of myocardial contraction due to the lower arterial oxygen tension. However this hypothesis was simply refuted by observations that acute restoration of arterial oxygen tension via 30 minutes of oxygen breathing did not increase stroke volume (Saltin et al., 1968). These findings suggest any impairment was either not related to oxygen tension, or was not reversible in the relatively short time-frame.

Subsequent work by this same group of researchers utilised an elegant animal model to assess stroke volume (aortic electromagnetic flow transducer) and left ventricular pressure development (ventricular pressure transducer) in six goats before and after 14 days in hypobaric hypoxia equivalent to an altitude of 4300 m (Tucker et al., 1976) under conditions of pacing (to keep heart rate constant) and beta blockade. The authors reported a decrease in stoke volume and contractile function in hypoxia, that was normalised after at least 48 hrs following return to sea level, but not with acute hypoxic reversal while exposed to hypobaric hypoxia.

This question of rest and exercise stroke volume was examined invasively in autonomically intact humans in the seminal series of studies entitled Operation Everest II. Here, Reeves et al. (1987) demonstrated that stroke volume was well preserved for any given right atrial or wedge pressure, even at a simulated barometric pressure near the limits of human
tolerance (barometric pressure = 240 Torr). To date, this study provides the best evidence of preserved cardiac contractile function in hypobaric hypoxia using gold-standard techniques. These invasive measurements were also complimented by the use of two-dimensional echocardiography during maximal exercise. Specifically, Suarez et al. (1987) reported a progressive decrease in end-diastolic volume and stroke volume with increasing altitude, but importantly also a decrease in end-systolic volume which emphasized that end-systolic elastance and contractility (estimated from end-systolic pressure/volume) was well preserved even at maximal exercise in extreme hypoxia in healthy humans. Furthermore, Fowles and Hultgren (1983) normalised markers of systolic function to the decrease in LV end-diastolic diameter during altitude acclimatization and concluded that contractile function was actually enhanced. Collectively, these findings indicate that despite a decrease in preload, and presumably Frank-Starling mediated contractility, systolic function is maintained or enhanced in chronic hypoxia in healthy individuals.

The seminal work performed in the latter half of the 20th century has stood the test of time, as modern imaging techniques have since confirmed and extended these findings through the interrogation of myocardial mechanics. ‘Left ventricular mechanics’ is an umbrella term for the assessment of systolic and diastolic function through the determination of the deformation (strain) and movement (rotation) of the heart. By assessing the counter-directional rotation that occurs during systolic contraction at the base and apex of the left ventricle, ‘LV twist’ can be measured and applied as a metric of systolic function (for a comprehensive review on this technique, please see Sengupta et al. (2008). The rate of relaxation or ‘untwisting’ can also be assessed (Notomi et al., 2008), and this will be discussed in the subsequent section in the context of diastolic function. The rotational movement and multi-plane deformation are a consequence of the unique fibre alignment within the heart, and together allow a detailed and sensitive interrogation of myocardial movement throughout different phases of the cardiac cycle (Marwick, 2006). The first assessments of left ventricular mechanics at high altitude have revealed that the decreased end-systolic volume and maintained ejection fraction were supported by a progressive increase in LV twist both at rest (Stembridge et al., 2014; Osculati et al., 2015; Maufrais et al., 2016) and during exercise in most (Stembridge et al., 2015), but not all studies. (Dedobbeleer et al. (2015) summarised in Figure 1).

The increase in LV twist observed with chronic altitude exposure has multiple possible interpretations. The most straightforward and widely accepted (Stembridge et al., 2014; Stembridge et al., 2015; Maufrais et al., 2016) is that the increase in twist is simply compensatory in nature, to support the maintenance of ejection fraction as the heart starts from a smaller end-diastolic volume. However, (Osculati et al., 2015) raised the possibility that the increase in twist is reflective of a combination of geometric changes to the LV and subendocardial dysfunction. The latter speculation is based on the theory that the inner subendocardial layer acts as the braking force on the twisting motion, and is the layer most affected by decreased oxygen tension due to regional disparity in oxygen distribution across the myocardial wall (Decking & Schrader, 1998). However, the analysis technique used by the investigators to justify this conclusion (multiple linear regression) is indirect, and it is the opinion of the authors that this hypothesis is unlikely to be true for two reasons. Firstly, whilst oxygen availability may be lower in the subendocardial layer, a decrease in myocardial oxygen supply has been shown to actually decrease twist (Zhou et al., 2013).
Moreover, after the initial few days of exposure, arterial oxygen content is normalised via haemoconcentration meaning myocardial oxygen delivery could be achieved with the same coronary blood flow. Recent studies of LV mechanics at high altitude have also been performed at rest in young healthy individuals who will possess a substantial ability to vasodilate so that delivery can easily meet demand (Duncker & Bache, 2008). Secondly, it is unlikely that changes in LV geometry secondary to decreased LV filling result in such marked changes in LV twist, as even during extraction of 25% blood volume, twist remains unchanged (Lord et al., 2018). Moreover, when plasma volume is restored to sea level values at high altitude via saline infusion, LV twist remains elevated from sea level (Stembridge et al., 2018). Given LV twist is known to be highly dependent on inotropic state (Hansen et al., 1991; Dong et al., 1999), and sympathetic nervous system activity is elevated at high altitude (Hansen & Sander, 2003; Lundby et al., 2017), a more plausible explanation is that a sympathetically-mediated increase in contractility results in a smaller end-systolic volume and thus increasing twist. This hypothesis has recently been tested, where the effects of increased adrenergic stimulation were blunted with a beta-adrenergic receptor (β1-AR) antagonist and oxygen content was normalised with supplementary oxygen. LV twist was reduced at high altitude following β1-AR antagonist and further attenuated with combined β1-AR antagonist and oxygen supplementation (Williams et al., 2017). These findings suggest that the increase in LV twist in chronic hypoxia is primarily regulated by β1-AR activation.

Much of the work in high altitude physiology has focused on the LV, partially due to the relative ease of measurement with non-invasive techniques compared to the right side. However, it is the right ventricle that experiences the most substantial change in afterload during chronic hypoxia, with anywhere between a 50-300% increase in pulmonary pressure from sea level, from hypoxic pulmonary vasoconstriction (HPV) (Swenson, 2013). Despite the pulmonary hypertension and the particular afterload sensitivity of the right ventricle, the majority of the literature describes preserved right ventricular function assessed via traditional echocardiographic indices (Huez et al., 2009; Maufrais et al., 2016), although RV longitudinal strain derived via speckle-tracking echocardiography was mildly reduced in one study of lowlanders at 5050 m (Stembridge et al., 2014). Decreased RV function has also been shown at rest in high altitude natives diagnosed with chronic mountain sickness; however, upon exercise, the RV contractile reserve (estimated from end-systolic pressure-area relationship) was the same as in healthy participants (Pratali et al., 2013).
**Left and Right Ventricular Filling**

Within the first few days of exposure to high altitude, LV end-diastolic volume is decreased relative to sea level both at rest (Alexander & Grover, 1983; Boussuges et al., 2000; Stembridge et al., 2014) and during exercise (Stembridge et al., 2015). The decrease in volume is accompanied by a reduction in the ratio of early to late transmitral filling (E/A ratio), indicative of reduced atrial-ventricular pressure gradients at the onset of mitral valve opening (Boussuges et al., 2000). The two-dimensional echocardiographic techniques previously employed on high altitude expeditions are not well suited to the geometric assessment of the right ventricle, and as such no accurate volume data exist. Surrogates for volume show that right ventricular area is maintained (Stembridge et al., 2014) and diameter mildly increased (Boussuges et al., 2000) when assessed in the supine position. Right atrial pressure is decreased from sea level to 6100 m at rest and during exercise (Reeves et al., 1990) when measured in a seated position.

Plasma volume contraction occurs upon exposure to high altitude (Singh et al., 1990) and remains lower than at sea level even after 4-6 months above 4000 m (Pugh, 1964). Given that there is no meaningful change in red cell volume within the initial time period (Ryan et al., 2014), absolute blood volume is decreased. Alexander et al. (1967) were among the first to postulate that the decrease in blood volume could be the cause of the lower stroke volume, and tested their hypothesis via intravenous dextran infusion in two subjects at high altitude. To the authors’ surprise, restoration of plasma volume only restored stroke volume in one subject, despite normalisation of right atrial pressure in both. Over the years this theory has been tested numerous times with varying results. For example, Grover et al. (1976) kept five participants normovolemic by preventing hypocapnia-related alkalosis with supplementary CO$_2$ (3.77%) in the atmosphere. After five days, stroke volume was maintained in the experimental group (with supplementary CO$_2$) and decreased in the control group. In contrast, Calbet et al. (2004) observed an increase in heart rate and no change in stroke volume following plasma volume expansion after 9 weeks at 5260 m. Siebenmann et al. (2013) reported that plasma volume expansion restored stroke volume after 25 days at altitude to sea level values, regardless of body posture (head down vs head up tilt). Most recently, Stembridge et al. (2018) also restored plasma volume following acclimatisation to 3800 m. Plasma volume expansion restored left ventricular end-diastolic volume, transmitral filling velocity and stroke volume in 10 participants. Although some degree of ambiguity still exists, it seems highly likely that the decrease in plasma volume with acclimatisation to high altitude plays a considerable but not exclusive role in the decrease in left ventricular filling.

Given that the heart works as two pumps in series which share a ventricular wall and are linked by horizontal ventricular interaction (Glantz et al., 1978; Beyar et al., 1993), any impairment to right ventricular ejection will impair left ventricular filling. This process of ventricular interaction was first discussed over a century ago (Henderson & Prince, 1914) and occurs with pulmonary hypertension where both restriction of right ventricular output and a leftward shift of the interventricular septum have been shown to independently decrease left ventricular filling (Lumens et al., 2010). Septal deviation towards the left ventricle has previously (Stembridge et al., 2014) but not always been observed at high altitude (Huez et al., 2009), and may only occur at more extreme altitudes due to the
progressive rise in RV pressure with ascent (Boussuges et al., 2000). Recently, the influence of RV pressure on LV filling has been investigated experimentally through the reversal of the HPV response at 3800 m with administration of the phosphodiesterase-5 inhibitor, Sildenafil. Compared to placebo, Sildenafil reduced pulmonary pressure and increased LV filling to some extent (Stembridge et al., 2018), suggesting that increased RV afterload may reduce RV stroke volume and, in turn, contribute at least in part to left ventricular filling. The same study also combined the sildenafil administration with a saline infusion (300-500 ml) but observed no further increase in LV end-diastolic volume. It is possible that, due to the increase in RV pressure, right ventricular volume is increased. If this is the case, then LV volume would be reduced via pericardial constraint with total cardiac volume remaining constant (Atherton et al., 1997).

Similar to systolic function in chronic hypoxia, it has also been suggested that diastolic relaxation may be impaired when oxygen availability is limited. However, this notion is often based on the fact that traditional markers of LV diastolic function are reduced at high altitude, such as E/A ratio (Holloway et al., 2011), and the somewhat distant link to animal models of chronic disease reporting increased LV stiffness (Gomez & Mink, 1986) or in vitro myocyte preparations demonstrating altered calcium reuptake (Silverman et al., 1997). The reduction in E/A ratio observed at high altitude could purely reflect the lower filling pressure, and therefore does not directly indicate an impairment of myocardial relaxation. Moreover, if LV relaxation were to impair filling, then one would expect an increase in left atrial pressure; however, pulmonary capillary wedge pressure (as a surrogate of left atrial pressure) is not elevated at high altitude (Reeves et al., 1987).

The rate of ventricular recoil (i.e. untwisting) during early diastole plays a pivotal role in the generation of atrioventricular pressure gradients that facilitate fast and efficient LV filling (Rademakers et al., 1992). Recently, a number of groups have tried to quantify how chronic hypoxemia influences the rate of diastolic relaxation using LV untwisting velocity derived from speckle tracking echocardiography. Whilst untwist velocity is load-dependent, and will be markedly influenced by gravitational forces (Negishi et al., 2017), it does correlate with invasive measurements of LV stiffness and pressure decay (Zhou et al., 2013) and remains unchanged following a marked reduction in end-diastolic volume (Lord et al., 2018). Virtually all investigators report an increase in LV untwist velocity despite the decrease in LV filling (Dedobbeleer et al., 2015; Osculati et al., 2015; Stembridge et al., 2015). This increase suggests a maintained or enhanced LV relaxation that is likely a consequence of increased sympathetic activation (Rademakers et al., 1992).

Conclusions

Collectively, recent and historical data consistently report a decrease in stroke volume at high altitude that is a consequence of the integrative changes in afterload, preload and contractility, modulated by autonomic control (Figure 2). The reduction in left ventricular filling is most likely due to decreased blood volume, although other factors such as the increase in right ventricular afterload also play a role. In response to the decrease in LV filling, contractility is increased and end-systolic volume subsequently reduced to maximise ejection. On balance, it is unlikely that the degree of chronic hypoxia tolerated by healthy
humans at high altitudes has a negative effect on cardiac systolic or diastolic performance directly.
Figure 1- Summary of the changes in stoke volume and left ventricular twist during the first 22 days of acclimatisation to altitudes between 3400 m and 5400 m above sea level. The decrease in stroke volume has been consistently described in the literature over the last fifty years, but recent evidence shows an increase in LV twist mechanics that is compensatory in nature, helping to maintain stroke volume via a decrease in end-systolic volume when ventricular filling is decreased.
Figure 2 - The integrative cardiac response to chronic hypoxia. Changes in afterload, preload and autonomic control all act to both increase (blue) and decrease (red) stroke volume at high altitude, with the net result being a decrease in stroke volume compared to sea level. Supporting literature is denoted by numbers.
References


