

No heartbreak at high altitude; preserved cardiac function in chronic hypoxia

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High altitude hypoxia presents a series of challenges to the human heart due to concomitant changes in preload, afterload and contractility. This challenge is characterised by a decrease in blood volume due to plasma volume constriction, an increase in right ventricular afterload via hypoxic pulmonary vasoconstriction, and an increase in sympathetic nerve activity. As such, understanding how the heart adapts to this multifaceted challenge has been a topic of interest to physiologists and clinicians for decades. In the current issue of *Experimental Physiology*, Maufrais *et al.* (2019) use modern speckle tracking technology to investigate region-specific cardiac performance in chronic hypoxia.

On a global level, the heart copes admirably with the challenge presented by high altitude hypoxia, best evidenced by the maintenance of stroke volume for a given wedge pressure as described by the seminal work performed during Operation Everest II. Recently, novel imaging techniques have been applied to further quantify the cardiac response to hypoxia. Some, but not all, of these studies have shown an increase in left ventricular twist at high altitude (recently reviewed in Stembridge & Levine, 2019). Whilst some authors concluded this response is compensatory in nature to maximise stroke volume when left ventricular filling is decreased (Stembridge *et al.*, 2018), an alternative hypothesis has been advanced by Osculati *et al.* (2015). The authors proposed that the increase in left ventricular twist is a consequence of subendocardial dysfunction, as the inner layer of the myocardium acts as a breaking force on the rotational movement observed during systole. The authors also cited an increase in the twist-shortening ratio (TSR) as evidence of impaired contractile function in the subendocardial layer. Maufrais *et al.* (2019) therefore set out to comprehensively characterise regional and global myocardial function, using region-specific speckle-tracking imaging before and after a 10-day ascent to Manaslu Basecamp at 5085 m.

Consistent with previous assessments of cardiac function at high altitude, the investigators report an increase in pulmonary artery systolic pressure, a decrease in left ventricular filling and an increase in left ventricular untwisting velocity. In contrast to the work of Osculati *et al.* (2015), the authors report no change in left ventricular twist or twist-shortening ratio. This difference in twist response may be explained by the shorter exposure in the study by Maufrais *et al.* (2019). Despite the absence of a change in twist, the authors did observe an *increase* in circumferential strain and strain rate that was driven by *increased* deformation in the subendocardial layer. These findings are in direct contrast to the hypothesis proposed by Osculati *et al.* (2015) that chronic hypoxia results in subendocardial dysfunction, and suggest that region-specific cardiac function is well preserved in healthy individuals at high altitude.

If subendocardial dysfunction does not occur, then the question remains *why* left ventricular twist is elevated at high altitude? To address this question, the authors also highlight the increase in strain rate as a key finding from their work, and interpret this change as an increase in contractility due to the relatively load-independent nature of strain rate. Left ventricular twist is known to be sensitive to changes in contractility, and thus we agree with the authors that an elevation in sympathetic nerve activity is the most likely explanation for the rise in twist seen with chronic hypoxia, given subendocardial function is maintained. Indeed, Williams *et al.* (2019) have recently demonstrated that the rise in left ventricular twist in chronic hypoxia can be attenuated by the administration of cardiac specific β_1 -adrenergic antagonist, and that subendocardial strain was preserved in both hypoxic conditions. Together, these recent findings suggest that the increase in left ventricular twist is an appropriate response to sympathetic activation, rather than an adverse consequence of dysfunction or myocardial ischemia.

Of further note is the increase in right ventricular volume observed by Maufrais *et al.* (2019), presumably due to the increase in right ventricular afterload via hypoxic pulmonary vasoconstriction. Lowering pulmonary artery pressure at altitude has previously been shown to increase left ventricular filling (Stembridge *et al.*, 2018), and direct ventricular interaction through pericardial constraint may play a significant role in the reduction of left ventricular filling observed in the current study and others. This hypothesis however, remains to be experimentally investigated at high altitude, and the two-dimensional echocardiographic techniques currently employed for the volumetric assessment of the right heart lack the required accuracy due to the unique anatomy of the right ventricle. In future, a combination of direct right heart catheterisation and indirect three-dimensional echocardiography may help to elucidate whether left heart function is indeed impaired secondary to hypoxic pulmonary vasoconstriction.

In summary, the authors are to be commended on a logistically difficult study and their use of novel analysis techniques for myocardial function. Their data support the notion that cardiac performance is preserved in chronic hypoxia.

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