

Hypoxia-induced endothelial dysfunction: Could targeting oxidative stress provide protection?

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Title: Hypoxia-induced endothelial dysfunction: Could targeting oxidative stress provide protection?

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Hypoxia can cause disturbances to vascular homeostasis and endothelial dysfunction, and is believed to contribute to pathophysiology of atherosclerosis. Over the past 10 years, a growing body of evidence implicates oxidative stress and diminished nitric oxide (NO) bioavailability as a key mechanistic pathway to explain the deleterious effects of acute and chronic hypoxia on endothelial function. In this connections article, we highlight three key papers which combine to characterize the effect of hypoxia on endothelial function, support the mechanistic role of oxidative stress and NO bioavailability, and set the scene for targeted interventions to prevent endothelial dysfunction in the presence of hypoxia.

The endothelium is a heterogeneous tissue for structure and function; therefore, a comprehensive assessment of endothelial function is crucial to understand the significance of hypoxia-induced endothelial dysfunction. In the first (and to date, only) article to examine the effect of hypoxia on microvascular and large-vessel endothelial function in the same study, we observed hypoxia-induced reduction in endothelium-dependent microvascular function (43% reduction in perfusion response to acetylcholine) and endothelium-dependent large vessel vasodilatation (18% reduction in flow-mediated dilatation of the brachial artery [FMD]) (Jones *et al.*, 2021). Notably, the extent of the decrease was approximately two-fold higher in the microcirculation compared with the large vessels. This finding is interesting in the context of an oxidative stress model of hypoxia-induced endothelial dysfunction since the microvasculature is generally more sensitive to oxidative stress than large blood vessels. This is due to a greater surface-area-to-volume ratio, making it more exposed to reactive oxygen species (ROS), which can cause oxidative stress. Further, a greater prevalence of adhesion molecules in microvascular endothelial cells (compared to endothelial cells in large blood vessels) increases susceptibility to infiltration of inflammatory molecules, which can activate endothelial cells and diminish NO bioavailability.

37

38 In addition to intra-individual comparisons across vascular beds (microvasculature versus
39 large blood vessels), we demonstrated that individuals with greater cardiorespiratory fitness
40 better preserve microvascular endothelial function during hypoxic exposure. One of the well-
41 known benefits of cardiorespiratory fitness is an improved redox status (the balance between
42 ROS production and antioxidant defence). Regular exercise and physical activity have been
43 shown to increase antioxidant levels and reduce the production of ROS. In our study, we
44 observed that those with superior cardiorespiratory fitness had the smallest hypoxia-induced
45 reduction in microvascular function, which may be due to a beneficial redox status and
46 greater NO bioavailability in these individuals.

47

48 Early evidence for the role of oxidative stress and NO bioavailability in hypoxia-induced
49 endothelial dysfunction came from Bailey *et al.*, (2013). Bailey and colleagues investigated
50 blood oxygen saturation, redox status, NO bioavailability, and endothelial function in
51 lowlanders under three experimental conditions of increasing oxidative stress (normoxia,
52 acute hypoxia, and exhaustive exercise) and compared to well-adapted (healthy) and
53 maladapted (chronic mountain sickness) high altitude residents. They identified that
54 oxidative stress measured by the presence of free radicals was mildly elevated in adapted
55 highlanders, but substantially increased in maladapted highlanders. Further, maladapted
56 highlanders exhibited worse hypoxaemia (lower oxygen saturations), which was
57 accompanied by greater concentrations of free radicals, lower concentrations of
58 antioxidants, lower nitrite bioavailability, and worse vascular reactivity, with significant
59 correlations between each of these variables. Our own work (Jones *et al.*, 2021) is
60 consistent with the original mechanism proposed by Bailey *et al.*, but rather than comparing
61 lowlanders and genetically distinct high-altitude natives, we identified intra-individual
62 differences between vascular beds, and inter-individual differences within lowlanders. Our
63 finding that superior cardiorespiratory fitness is associated with protection from hypoxia-
64 induced endothelial dysfunction begins to move the field on from the necessary work of
65 characterizing the nature of hypoxic effects, to identifying protective countermeasures and
66 possible preventative interventions. However, we reported only a cross-sectional correlation,
67 and did not conduct an experimental intervention.

68

69 Though the application in hypoxia is novel, the idea that exercise training status can protect
70 against endothelial dysfunction in physiological states of elevated oxidative stress is not
71 new. Oxidative stress is generally increased with older age, and has been implicated in the
72 aging process, and the development of age-related diseases. Indeed, more than 20 years

ago, Taddei *et al.*, (2000) used strain-gauge venous occlusion plethysmography to investigate the combined effects of older age and exercise training status on forearm blood flow response to acetylcholine with and without intravenous vitamin C. The age-associated decline in response to acetylcholine was ameliorated by exercise training status in older adults. In addition, older sedentary participants showed age-associated increased inhibition with L-NMMA (NO inhibitor) that was ameliorated in older athletes. The administration of vitamin C, which donates electrons to neutralize ROS and other free radicals, corrected the L-NMMA-induced inhibition in older sedentary individuals but not in older athletes. Since administering vitamin C does not improve endothelial function in populations with a 'healthy' redox status (young adults and older athletes), the observed vitamin C improvement in endothelial function, supports the potential for targeted interventions to reverse endothelial function impairment specifically in the context of oxidative stress (e.g., in hypoxia).

In a recent study, Stone *et al.*, (2022) utilized the same methodology as Taddei and colleagues (strain-gauge plethysmography) to investigate the effects of intravenous vitamin C administration on hypoxia-induced endothelial dysfunction. Forearm blood flow response to acetylcholine decreased by ~30% at high altitude (4300m) compared to sea level but was largely restored with the addition of vitamin C infusion. Further, consistent with the original work of Bailey *et al.*, (2013), the magnitude of both the reduction in endothelial function and the response to vitamin C, were positively associated with the severity of hypoxaemia. In other words, those with the lowest oxygen saturations appeared to experience the greatest reduction in endothelial function that was explained by greater oxidative stress. Taken together these papers support the notion that endothelial function impairment in hypoxia is at least in part due to oxidative stress, and that oxidative stress may be a modifiable target for protection.

While Bailey and colleagues (2013) highlighted those at exacerbated risk due to this pathway, our own work (Jones *et al.*, 2021) identified individuals protected from vascular decline, possibly due to this pathway, and subsequently Stone *et al.*, (2022) have built on this to demonstrate targeted experimental manipulation of the pathway overcomes the impairment. Interventions to target each point of the pathway (hypoxaemia, oxidative stress, NO bioavailability), may protect against hypoxia-induced impairment in vascular dysfunction in both lowlanders sojourning to high altitude, and in high-altitude natives. However, there is currently no evidence that supplemental antioxidants provide effective protection for vascular function. To date, studies using oral supplementation of antioxidant cocktails (e.g., 1 g of ascorbic acid; 400 IU of alpha-tocopherol acetate, and 600 mg of alpha-lipoic acid) haven't

109 been consistently successful at improving oxygen saturations, and importantly, have not
110 assessed endothelial function. Equivocal results in the efficacy of oral antioxidant
111 supplementation to improve oxygen saturations may be due to different ascent profiles,
112 dosages and intervention durations, or due to the method of administration (oral versus
113 intravenous). Oral administration may not reach the endothelium, and intravenous injection
114 is used as an acute experimental manipulation to investigate mechanisms; it is not proposed
115 as a feasible prophylactic treatment. Indeed, Stone is careful to not overstate whether
116 vitamin C is a viable intervention (particularly if it requires intravenous injection). The
117 evidence is not yet clear enough to provide practical recommendations and future studies
118 are needed to determine the feasibility and efficacy of specific antioxidant interventions.
119 Though our own study implies that easily practicable interventions to improve sea-level
120 cardiorespiratory fitness may provide protection (Jones *et al.*, 2021), we used a cross-
121 sectional approach. Experimental research is needed to confirm the efficacy of any practical
122 recommendations relating to exercise training.

123
124 A consistent finding across all these papers is that hypoxia, and other conditions associated
125 with oxidative stress (ageing and a sedentary lifestyle), reduce endothelial-dependent
126 vascular reactivity (measured by FMD and response to acetylcholine), but do not affect
127 endothelial independent vascular reactivity (measured by NO donors GTN or SNP). This is
128 regardless of the method of assessment, or the vascular bed being assessed
129 (microvasculature or large vessels). Combined, this provides compelling evidence that it is
130 NO-dependent endothelial function that is impaired by hypoxia, and not the capacity of
131 smooth muscle to respond to NO. These papers provide diverse evidence but consistently
132 support the interpretation that the hypoxia-induced impairment in endothelial function is, at
133 least in part, caused by elevated oxidative stress and impaired NO bioavailability. Further,
134 individual differences appear to influence susceptibility to this effect; individuals experiencing
135 worse hypoxaemia, worse oxidative stress, and/or lower bioavailability of NO, will experience
136 greater impairments in vascular function. Methods to reduce oxidative stress and improve
137 endogenous NO bioavailability (e.g. exercise training and antioxidants) may protect against
138 hypoxia-induced impairments in vascular reactivity. These findings have implications not
139 only for those travelling or residing at high altitude. Since hypoxia is characteristic of several
140 diseases at sea level (e.g., COPD), and implicated in the progression of cardiovascular
141 disease, which itself exacerbates vascular hypoxia, resulting in a positive feedback loop. The
142 research progression outlined in this article sets the scene for targeted interventions to
143 protect against hypoxia-induced endothelial dysfunction at high altitude, and in pathological
144 states.

References

- Bailey DM, Rimoldi SF, Rexhaj E, Pratali L, Salmòn CS, Villena M, McEneny J, Young IS, Nicod P, Allemann Y, Scherrer U & Sartori C (2013). Oxidative-nitrosative stress and systemic vascular function in highlanders with and without exaggerated hypoxemia. *CHEST* **143**, 444–451.
- Jones DT, Macdonald JH, Sandoo A, Oliver SJ & Rossetti GMK (2021). The deleterious effects of acute hypoxia on microvascular and large vessel endothelial function. *Experimental Physiology* **106**, 1699–1709.
- Stone RM, Ainslie PN, Tremblay JC, Akins JD, MacLeod DB, Tymko MM, DeSouza CA & Bain AR (2022). GLOBAL REACH 2018: intra-arterial vitamin C improves endothelial-dependent vasodilatory function in humans at high altitude. *The Journal of Physiology* **600**, 1373–1383.
- Taddei S, Galetta F, Viridis A, Ghiadoni L, Salvetti G, Franzoni F, Giusti C & Salvetti A (2000). Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation* **101**, 2896–2901.

Conflict of interest

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