Chronic intermittent hypoxia and renovascular hypertension: a case of one plus one equals one-half!

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On the means of a heightened blood pressure—

A conundrum providing much pleasure:

Arithmetic sum

To make one feel dumb…

O! Those secrets of her that we treasure.

--- Under Pressure

The homeostatic regulation of blood pressure depends on an exquisite interplay between multimodal sensors, several brain regions and long-range control systems that serve to maintain and defend cardiovascular constancy. Neurogenic hypertension is characterised by heightened sympathetic nervous outflow to various effector target tissues. This insidious signature has been recognised for many years, with contemporary studies placing much emphasis on the causal role of aberrant afferent signalling as a major instigator of high blood pressure in several disease states, including obesity, diabetes, sleep apnoea, and essential hypertension.

Exposure to chronic intermittent hypoxia, modelling the arterial oxygen swings characteristic of human sleep apnoea, elaborates a hypertensive phenotype that is dependent upon sensitization of the principal peripheral oxygen sensing organs, the carotid bodies. Persistent hyperactivity in afferent nerves from the carotid bodies to the brainstem is critical to the development of sympathetic over-activity and resultant hypertension. The phenomenon extends to the kidneys, pivotal players in neurohumoral control of blood pressure. Renovascular hypertension, which arises

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from reductions in renal perfusion, also produces a pernicious portrait of sympathetic over-activity, responsible for persistent elevation of blood pressure. Moreover, enhanced afferent signalling from injured kidneys contributes to the development and maintenance of hypertension. A recent robust argument in support of cooperative oxygen sensing by the kidneys and carotid bodies with implications for blood pressure regulation is elegant and convincing (Patinha et al. 2017). Reno-renal reflexes accompanied by elevated chemosensory reflexes with consequential autonomic imbalance, conspire in synergistic fashion, a catastrophic collaboration evoking blood pressure dysregulation. Of interest, there is a recognised association between sleep apnoea and chronic kidney disease, both of which are independently linked to hypertension. One wonders then what the outcome is for blood pressure regulation of a combination of exposure to chronic intermittent hypoxia and reduced renal artery flow. One variant of this question is addressed by Perim et al. (2018) in this issue of *Experimental Physiology*.

Perim et al. (2018) explored the effects of chronic intermittent hypoxia pre-conditioning on baroreflex sensitivity and blood pressure in the one-kidney one-clip model of hypertension. Fifteen days following exposure to chronic intermittent hypoxia or normoxia, rats underwent left renal artery clipping and removal of the contralateral kidney, or sham surgery. One might reasonably have expected that exposure to sequential independently pro-hypertensive experimental interventions would yield an additive or synergistic outcome for blood pressure, or perhaps given the potential for recovery between successive interventions that antecedent exposure to chronic intermittent hypoxia might be without measureable effect on the magnitude of renovascular hypertension. Of note, previous work has shown no cumulative effect on the magnitude of hypertension of repeated exposures to chronic intermittent hypoxia separated by an equivalent recovery period of 15 days (Perim et al. 2015). Contrary to expectation, prior exposure to chronic intermittent hypoxia attenuated renovascular hypertension assessed in conscious rats following renal clipping (Perim et al. 2018). Moreover, the apparent 'protective' effect of pre-conditioning was absent in animals with selective carotid body ablation, preserving baroreflex function, which surprisingly was unaffected by the experimental stressors. As such, the study by Perim et al. (2018) reveals occlusive effects of sequential pro-hypertensive stimuli revealing the capacity for persistent hypoxia-dependent plasticity within the carotid body chemoreflex pathway that *limits* subsequent sympatho-excitation in response to renal hypoperfusion. The precise mechanisms accounting for the arithmetic quandary producing an apparent hypo-additive outcome remain unclear.

One might reasonably have considered that chronic intermittent hypoxia pre-conditioning establishes renal hypoxic tolerance, for example, through HIF-1α activation or other mechanisms,

such that renal afferent responses to renal artery clipping are blunted. Although this would be consistent with decreased sympatho-excitation, it is incongruent with the observation by Perim et al. (2018) that pre-conditioning has no discernible effect on renovascular hypertension following prior carotid body denervation, highlighting an obligatory role for carotid body afferent inputs to the central network. Moreover, because renovascular hypertension develops in carotid body-denervated normoxic animals to a level equivalent to that of carotid body-intact normoxic animals (Perim et al. 2018), it appears that one-kidney one-clip hypertension in this setting does not depend upon potentiated chemoreflexes, as has been described in other models of renal hypertension (Pijacka et al. 2016). Yet, the suppression of renovascular hypertension by prior exposure to chronic intermittent hypoxia is carotid body-dependent! Chronic intermittent hypoxia does not affect the intrinsic firing properties of brainstem pre-sympathetic neurons. Perhaps the buffering effect of hypoxic pre-conditioning on renovascular hypertension, relates to plasticity within the nucleus tractus solitarius, a nodal point for the integration of multi-afferent inputs. On the face of it, the finding of Perim et al. (2018) is bewildering in the light of observations that chronic intermittent hypoxia causes epigenetic modifications affecting redox status within the nucleus tractus solitarius and efferent arm of the chemoreflex pathway, an effect requiring carotid body neural activity that underpins chronic intermittent hypoxia induced hypertension (Nanduri et al. 2017). The data of Perim et al. (2018) reveal a penchant for divergent forms of plasticity within the chemoreflex pathway in response to chronic intermittent hypoxia (or recovery from it), which probably relates to differential temporal redox changes within key brainstem sites. Whatever the mechanism, it is evident from the work of Perim et al. (2018) that the chemoreflex pathway can be habituated by prior experience, a form of meta-plasticity that buffers responsiveness to a subsequent stressor. Of course, the findings do not preclude the capacity for summation of afferent inputs under different circumstances. One wonders what the outcome would be of exposure to chronic intermittent hypoxia coincident with renal clipping and the elaboration of a pro-hypertensive state arising from contemporaneous hyperactivity in afferent inputs from the carotid bodies and kidneys. Would one plus one equal three!

The study of Perim et al. (2018) offers one interesting chapter in a complex story. The many experimental paradigms one can ponder provides a rich landscape for further fruitful exploration. Beyond those interests, we are reminded of the remarkable and at times surprising complexity at play in physiological control systems.

Competing interests

None.

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