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PERSPECTIVES

Perfusion of the human brain: a matter of interactions

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A characteristic feature of the cerebral circulation is that the cerebral blood flow is dynamically adjusted to protect brain blood flow from changes in perfusion pressure (Roy & Sherrington 1890). Cerebral blood flow tends to remain constant over a range of systemic blood pressures. This is termed cerebral autoregulation. Both local mechanisms and autonomic neural control participate in cerebral autoregulation. Increases and decreases of the arterial CO_2 tension (P_{a,CO_2}) will increase and decrease cerebral blood flow by cerebral vasodilatation and vasoconstriction, respectively, independent of cerebral autoregulation (Lennox & Gibbs 1932). This phenomenon is known as the CO_2 reactivity of the brain. The limits of the blood pressure range within which cerebral autoregulation operates are modified by P_{a,CO_2} and the CO_2 reactivity of the brain can interfere with cerebral autoregulation.

In this issue of *The Journal of Physiology*, LeMarbre *et al.* (2003) add valuable new data by their study of the effects of sympathetic activation on the CO_2 reactivity of the brain. With ventilation kept constant, they documented that an increase in sympathetic vasomotor outflow by baroreceptor unloading using 40 mmHg lower body negative pressure (LBNP) does not alter CO_2 reactivity of the brain. The issue has been addressed earlier by Tominaga *et al.* (1976) in a different setting when they demonstrated that the rise in cerebral blood flow during CO_2 inhalation was not influenced by ganglionic blockade with trimethaphan that blocked the concomitant rise in systemic blood pressure. The physiological significance of the findings of the present study is that sympathetic tone and end-tidal CO_2 level (P_{ET,CO_2}) as a reflection of P_{a,CO_2} are two determinants of cerebral perfusion in humans that seem to operate independently. In order to account for the effects of CO_2 on respiration, LeMarbre *et al.* had to maintain ventilation at a level almost fourfold higher than the control situation. That the circumstances of this elegantly designed study therefore do not directly reflect the normal situation does not detract from the conclusions. They illustrate the complexity of neural, local and mechanical interactions of the cerebral circulation when studied in intact humans.

When we stand still for some minutes, cerebral blood flow volume (CBFV) and cerebral cortical oxygenation decrease, although the drop in blood pressure at the level of the cerebral arteries may well be within the autoregulatory range (Harms *et al.* 2000). CO_2 may play a role since orthostatic stress itself is associated with a reduction in P_{ET,CO_2}. This is attributed to an increase in tidal volume and/or functional residual capacity and a slight gravity-induced ventilation-perfusion mismatch upon standing (Bjurstedt *et al.* 1962). Until recently the sympathetic nervous system was held to exert only an insignificant tonic influence on human cerebral vessels under physiological conditions. There is, however, accumulating evidence that cerebral perfusion may be affected by sympathetically mediated cerebral vasoconstriction in response to a large reduction in cardiac output (van Lieshout *et al.* 2003). This may be the case in subjects with postural tachycardia syndrome who exhibit a reduction in CBFV with presyncopal symptoms despite well maintained mean arterial pressure and presumably cerebral perfusion pressure (Jacob *et al.* 1999). This is different from what happens during an actual faint where the low systemic blood pressure and the hyperventilation associated hypocapnia decrease cerebral blood flow below levels sufficient to maintain consciousness.

LeMarbre *et al.* found that during LBNP with P_{ET,CO_2} held constant CBFV was maintained. However, during isocapnic passive head-up tilt CBFV declines ~15 % (Blaber *et al.* 2001). Then why do the brain vessels appear to constrict more during normal orthostatic stress than during orthostatic stress simulated by LBNP? The degree of baroreflex unloading by 40 mmHg LBNP was assumed by LeMarbre *et al.* to be equivalent to that produced by the upright posture. A possible explanation is that the upright position with the carotid baroreceptors placed above heart level elicits additional baroreceptor unloading. The idea that autonomic sympathetic control of the cerebral circulation is tonically active is still speculative (Zhang *et al.* 2002) and new studies that define the circumstances are needed. The issue of why brain blood flow falls during orthostatic stress in the apparent presence of adequate perfusion pressure is an important issue for those who seek to understand how humans remain upright.

Bjurstedt H, Hesser CM, Liljestrand G & Matell G (1962). *Acta Physiol Scand* **54**, 65–82.

Blaber AP, Bondar RL, Moradshahi P, Serrador JM & Hughson RL (2001). *Aviat Space Environ Med* **72**, 985–991.

Harms MPM, Colier WNJM, Wieling W, Lenders JW, Secher NH & van Lieshout JJ (2000). *Stroke* **31**, 1608–1614.

Jacob G, Atkinson D, Jordan J, Shannon JR, Furlan R, Black BK & Robertson D (1999). *Am J Med* **106**, 59–64.

LeMarbre G, Stauber S, Khayat RN, Puleo DS, Skatrud JB & Morgan BJ. *et al.* (2003). *J Physiol* **551**, 609–616.

Lennox WG & Gibbs EL (1932). *J Clin Invest* **11**, 1155–1177.

Roy CS & Sherrington CS (1890). *J Physiol* **11**, 85–108.

Tominaga S, Strandgaard S, Uemura K, Ito K & Kutsuzawa T (1976). *Stroke* **7**, 507–510.

van Lieshout JJ, Wieling W, Karemaker JM & Secher NH (2003). *J Appl Physiol* **94**, 833–848.

Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG & Levine BD (2002). *Circulation* **106**, 1814–1820.