Arterial baroreflex regulation of cerebral blood flow in humans

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Received: October 12, 2012 / Accepted: November 19, 2012

Abstract The arterial baroreflex plays an essential role in the short-term regulation of arterial blood pressure, and thus helps ensure that the vital organs are adequately perfused. For standing humans, appropriate arterial baroreflex control of cardiac output and vasomotor tone are particularly important for cerebral blood flow regulation. However, the numerous mechanisms implicated in the regulation of the cerebral vasculature (e.g. cerebral autoregulation, carbon dioxide reactivity) mean that the precise nature of the direct and indirect effects of the arterial baroreflex on cerebral blood flow regulation are highly complex and remain incompletely understood. This review paper provides an update on recent insights into the influence of the arterial baroreflex on cerebral circulation.

Keywords : arterial blood pressure, cardiac output, cerebral autoregulation, cerebral CO₂ reactivity, autonomic nervous system

Introduction

Adequate oxygen delivery is essential for the maintenance of cerebral function, and a loss of consciousness rapidly results from inadequate cerebral perfusion and oxygen delivery. The importance of adequate perfusion pressure for the delivery of oxygen to the tissues of the body is well established. Thus, the regulation of arterial blood pressure (ABP) by arterial baroreflex modulation of sympathetic outflow to the heart and vasculature, and parasympathetic nerve activity to the heart¹⁾, would intuitively seem to be an important mechanism for cerebral blood flow (CBF) regulation. However, regulation of CBF is highly complex, and neurogenic, hemodynamic, autoregulatory and metabolic factors can all contribute. This means that the precise direct and indirect contribution of the arterial baroreflex to the maintenance of cerebral perfusion remains challenging to distinguish. This review paper will provide an update on recent insights into the influence of cerebral autoregulation, arterial blood gases and the arterial baroreflex, on cerebral circulation.

Cerebral autoregulation

The classic work of Lassen²⁾ established the concept that human CBF is maintained within a narrow range despite changes in mean arterial pressure (MAP) between 60 to 150 mmHg (Fig. 1). This relationship is termed cerebral autoregulation (CA). CA is a homeostatic mechanism that buffers fluctuations in CBF when cerebral perfusion pressure changes and acts through vasomotor effectors that

control cerebral vascular resistance³⁾.

The concept that CA is a powerful mechanism of blood flow regulation in the brain has become well established. However, in the early studies of Lassen (1959), the CA curve relating CBF to MAP was derived from eleven steady-state data points, obtained under several different conditions and presented in previous publications. For example, the lower limit of CA was determined from MAP and CBF data in young normotensive human subjects who had a decreased CBF during acute hypotension (35 mmHg)⁵⁾ and in volunteers who had no change in CBF during pharmacologically induced mild hypotension (57 mmHg)⁶⁾. However, this approach is problematic as steady-state CBF is regulated by other physiological factors (e.g. cardiac output) as well as CA⁷⁻⁹⁾. Recently, Lu-

Fig. 1 Human Cerebral Autoregulation Curve presented by Lassen²⁾ and Lucas et al.⁴⁾

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cas et al.⁴⁾ re-evaluated the CA curve in healthy humans, by monitoring cerebral perfusion while pharmacologically manipulating ABP over a wide range (Fig. 1). In contrast to Lassen²⁾, it was observed that cerebral perfusion closely followed the pharmacologically-induced change in blood pressure. This indicates that CA is imperfect and that a finite slope of the plateau region does not necessarily imply a defective CA⁴⁾. However, it should be acknowledged that the vasoactive substances used by Lucas et al.⁴⁾ may have had a direct effect on the cerebral vasculature^{10,11)}.

Partial pressure of arterial carbon dioxide (PaCO₂)

PaCO₂ is a powerful mediator of CBF (Fig. 2). Hypocapnia causes cerebral vasoconstriction and reduces CBF. The resulting reduction in cerebral 'washout' attenuates the fall of brain tissue PCO₂. In contrast, hypercapnia increases CBF by vasodilating the cerebral vasculature, thus limiting elevations in brain tissue PCO₂. As sleep decreases cerebral CO₂ reactivity, the level of cerebral neural activation may also influence cerebrovascular reactivity to CO₂¹²⁾. Dynamic CA, the rapid change in CBF that buffers a transient change in ABP, is also influenced by CO₂ reactivity¹³⁾; because when perfusion pressure is low, CO₂ accumulates (hypercapnia), and at a high perfusion pressure, CO₂ washout (hypocapnia) occurs. The early work of Aaslid et al.³⁾ provided experimental evidence that hypocapnia improves dynamic CA while hypercapnia impairs it.

An increase in PaCO₂ exponentially elevates CBF, but this hypercapnic cerebral CO₂ reactivity is greater than hypocapnic reactivity^{14,15)}. Animal studies indicate that this may be related to a greater influence of vasodilator mediators on intracranial vascular tone compared to vasoconstrictive mediators¹⁶⁾. In humans, Peebles et al.¹⁷⁾ reported that during hypercapnia there is a large release of nitric oxide from the brain, whereas this response is absent during hypocapnia.

The blood-brain barrier is permeable to CO₂, and rela-

tively impermeable to [H⁺] and [HCO₃⁻] ions. Therefore, CO₂ also acts as a powerful respiratory stimulant at the level of the central chemoreceptors in the brain¹⁴⁾. The periodic nature of inspiration and expiration is finely controlled by changes in PaCO₂, via the respiratory chemoreflex, such that pH remains relatively constant. Therefore, changes in CBF have an important role in stabilizing the breathing pattern during fluctuating levels of chemical stimuli, especially PCO₂ at the level of the central chemoreceptors¹⁸⁾. Indeed, Peebles et al.¹⁷⁾ reported that hypercapnic cerebral CO₂ reactivity was inversely related to the increase in minute ventilation (V_E). In goats, severe brain ischemia blunts the ventilatory responses to CO₂¹⁹⁾. Our research group also demonstrated that under conditions of hypercapnia and exercise, the total respiratory loop gain (i.e., the sensitivity of the total respiratory system, including the central chemoreflex and lung system, to changes in CO₂) was markedly reduced, while cerebrovascular CO₂ reactivity increased¹⁴⁾. These findings suggest that cerebrovascular CO₂ reactivity is tightly linked to the ventilatory response to CO₂, meaning that central chemoreflex control of minute ventilation (V_E) affects CBF regulation. Of note, abnormal chemoreflex control of breathing is evident in a range of pathological conditions (e.g. chronic lung disease, heart failure, and sleep apnea) and may alter dynamic CBF regulation²⁰⁻²²⁾.

Partial pressure of arterial oxygen (PaO₂)

PaO₂ is another important regulator of CBF under specific conditions, such as high altitude, hypoxic exercise, chronic lung disease, and sleep apnea. However, while hypoxia *per se* is a cerebral vasodilator and CBF rises in proportion to the severity of isocapnic hypoxia, under normal conditions the hypoxia-induced activation of peripheral respiratory chemoreceptor activity leads to a hyperventilation-induced lowering of PaCO₂ and subsequent cerebral vasoconstriction^{23,24)}. Therefore, the cerebrovascular bed receives conflicting signals during exposure to acute hypoxia at rest, with the net result often being a transient decrease in CBF coinciding with the peak hypoxic ventilatory response and the greatest degree of hypocapnia²³⁾. Conversely, CBF is well maintained with acute hypoxia during sub-maximal exercise, despite a greater degree of hypocapnia²³⁾. This indicates that exercise modifies the interaction between PaO₂ and PaCO₂ in the regulation of CBF. This is potentially due to hypoxia-induced changes in CA, sympathetic nerve activity and/or changes in the sensitivity of the cerebrovascular bed to hypoxia and hypocapnia²³⁾. Recently, we examined the interaction between PO₂ and PCO₂ in CBF regulation (Ogoh et al. unpublished) and observed that during hypoxia (12%), CO₂ reactivity was attenuated, indicating that hypoxia may affect the CBF response to CO₂ (Fig. 2).

Fig. 2 CBF responses to CO₂ during normoxia¹⁴⁾ and hypoxia condition (Ogoh unpublished data).

Sympathetic nerve activity: interactions with cerebral CO₂ reactivity and autoregulation

Traditional thought dictates that increases in sympathetic activity appear to have a limited effect on the cerebral vasculature of humans, particularly at rest. However, the effect of sympathetic nerve activity on CBF regulation remains controversial. Some studies suggest that an increase in sympathetic nerve activity appears to prevent forced dilatation of the arterioles, therefore, limiting any regional over-perfusion, and protect against the breakdown of the blood-brain barrier^{10,25-27}. In addition, sympathetic deactivation through ganglionic blockade enhances the reactivity of CBF to PaCO₂²⁸ and attenuates cerebral autoregulation^{10,11}.

The arterial baroreflex

Arterial baroreceptors, located in the carotid sinus bifurcation and aortic arch, play a pivotal role in the short-term regulation of ABP. The carotid and aortic baroreflexes are comprised of unencapsulated free nerve endings located at the medial-adventitial border of blood vessels in the carotid sinus bifurcation and aortic arch. Alterations in ABP cause a conformational change in the baroreceptors themselves, leading to changes in afferent neuronal firing. A branch of the glossopharyngeal nerve, “Hering’s nerve”, carries impulses from the carotid baroreceptors, while small vagal branches carry impulses from the aortic baroreceptors. These afferent signals converge centrally within the nucleus tractus solitarius (NTS) of the medulla oblongata. Previously it has been estimated that the contribution of the carotid baroreflex to overall baroreflex control in humans ranges from 30% to 50%²⁹. However, bilateral carotid sinus denervation in patients produces chronic impairment in overall baroreflex function³⁰. Thus, the carotid baroreflex may play a greater role in controlling arterial blood pressure than has been estimated.

These mechanoreceptors function as the sensors in a negative feedback control system³¹. When ABP is elevated, the baroreceptors are stretched and this deformation causes an increase in afferent neuronal firing, which results in a reflex-mediated increase in parasympathetic nerve activity and decrease in sympathetic nerve activity. Conversely, when ABP is lowered, afferent firing is reduced, resulting in a decrease in parasympathetic nerve activity and an increase in sympathetic nerve activity. In both cases, the neural adjustments will affect both the heart and the blood vessels in the appropriate fashion to return ABP to its original pressure. Thus, arterial baroreflex responds to beat-to-beat changes in ABP by reflexively altering autonomic neural outflow to adjust heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR) in accordance with the following equation: $ABP = (HR \times SV) \times TPR$

In our previous study, carotid baroreceptor stimula-

tion in humans did not elicit significant changes in SV, in either the seated or supine positions^{32,33}. These results confirm the data of Geerdes et al.³⁴ in animals. This suggests that at rest, SV changes have minimal influence in regulating ABP via the carotid baroreflex. Therefore, carotid baroreflex-mediated changes in HR are the principal factor controlling changes in cardiac output. However, it is important to note that the carotid baroreflex has been reported to influence changes in SV under different stimulus conditions; changes in myocardial contractility³⁵ or venous capacitance³⁶. Alterations in vascular resistance (vasomotor) appear to be the primary means by which the carotid baroreflex responds to acute changes in carotid sinus pressure^{32,33}. In the other words, carotid baroreflex-mediated changes in Q or HR only make a small (~20%), albeit rapid, contribution to ABP regulation (Fig. 3).

Arterial baroreflex and CBF regulation: direct effect of the autonomic nervous system

A direct link between the arterial baroreflex and cerebral circulation, via the autonomic nervous system, is well established in animal models³⁷⁻⁴¹. For example, unilateral electrical stimulation of the NTS increases CBF in rats with cervical cordotomy and vagotomy⁴⁰, while lesions within the NTS impair cerebral autoregulation³⁸. In addition, it has been indicated that stimulation of baroreceptors influences cerebral vasomotion⁴²⁻⁴⁴. Sinoaortic denervation eliminates cerebral vasodilatation during marked acute hypertension⁴⁴, and during baroreflex deactivation efferent sympathetic activity to the cervical sympathetic trunk is elevated⁴³.

Despite these previous animal studies, and the cerebral vasculature being innervated with sympathetic nerve fibers in humans, it is not likely that the arterial baroreflex directly affects these vessels. Indeed, the response of cerebral vasculature to acute changes in ABP is the opposite of that which occurs in the peripheral vasculature due to the arterial baroreflex. For example, an acute increase in ABP induces peripheral vasodilatation via the barore-

Fig. 3 The contribution of carotid baroreflex-mediated changes in Q or HR to ABP response during hypotensive stimulation^{32,33}.

flex in order to maintain a 'normal' ABP, while it causes cerebral vasoconstriction, via dynamic CA, to preserve CBF. Thus cerebral vasomotion via the baroreflex, may be viewed as a paradoxical reaction with little physiological benefit⁴⁵). Furthermore, during orthostatic stress, the arterial and cardiopulmonary baroreflexes appear to be the major mechanisms for maintaining perfusion pressure homeostasis to the brain. Thus, the teleological relevance of cerebral vasoconstriction during orthostatic stress⁴⁵⁻⁴⁷) is unclear. Therefore, the major influence of the arterial baroreflex in CBF regulation seems to be the indirect result of its hemodynamic effects.

Arterial baroreflex and CBF regulation: indirect hemodynamic effect

Cardiac output can directly influence CBF. The normal increase in CBF during dynamic exercise is reduced when cardiac output is attenuated by β_1 -blockade⁴⁸), or in patients with heart failure⁴⁹) or atrial fibrillation⁵⁰). In a recent investigation, we examined the influences of changes in cardiac output induced by manipulation of central blood volume, on CBF at rest and during exercise⁷). We observed that cardiac output was linearly related to CBF at rest and during exercise, and its regulation is independent of cerebral autoregulation. Furthermore, the slope of the regression relationship between cardiac output and CBF was greater at rest ($P=0.035$) than during exercise (Fig. 4)⁷). These findings indicate that cardiac output is an important factor in the establishment of the CBF, and any regulation of cardiac output via the arterial baroreflex could directly influence CBF regulation⁵¹).

The contribution of changes in cardiac output to the carotid baroreflex control of ABP during exercise was found to be minimal^{32,33,52}). Moreover, a carotid baroreflex-mediated change in total vascular conductance was observed to be the major contributor to change in ABP^{32,33,52}). However, carotid baroreflex control of the heart may provide under-appreciated regulation of CBF.

Fig. 4 The effect of cardiac output on CBF at rest and during exercise⁷).

Thigh cuff release has been applied for the evaluation of dynamic CA, because it is non-invasive and non-pharmacological^{8,53}). However, thigh cuff release elicits an integrated physiological response that involves not only cerebrovascular changes but also arterial baroreflex-mediated changes in peripheral vascular tone and HR⁵⁴). As the drop in arterial pressure, associated with thigh cuff release, does not alter central venous pressure (and hence SV)⁵⁵), the reflex tachycardia transiently augments cardiac output in proportion to the degree of tachycardia. Recently, we identified dynamic CA during acute hypotension with and without the arterial baroreflex-mediated tachycardia and the consequent changes in cardiac output⁵⁶). Hypotension was induced before and after full cardiac autonomic blockade (sympathetic-cholinergic blockade). Thigh cuff release elicited a transient drop in ABP and a resultant tachycardia, while this tachycardic response was diminished with full cardiac autonomic blockade. Dynamic CA was also attenuated in the full blockade condition compared to both control and β_1 -adrenergic blockade conditions, and was related to the attenuated tachycardia response. These data also highlight the important role of the cardiac baroreflex in CBF regulation.

This relationship has important implications for the interpretation of a range of previous studies because the baroreflex and CA are, typically, held as separate entities, and data has historically been viewed from this perspective. For example, it has been demonstrated that chronic cardiovascular disease impairs dynamic CA^{57,58}). Moreover, this impairment of CBF regulation may be due to baroreflex dysfunction⁵⁹⁻⁶¹) rather than specific dysfunction of cerebrovascular regulation.

Summary

The arterial baroreflex plays an important role in the regulation of CBF. However, the complexity of the relationship between the arterial baroreflex and many of the other mechanisms intricately involved in the regulation of CBF (e.g. CA, PaCO_2 , PaO_2 , respiratory chemoreflex, and autonomic nervous system) has meant that the role of the arterial baroreflex in CBF control has been challenging to identify and, thus, under appreciated.

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