Systemic and cerebral hemodynamics in response to cardiovascular challenges : the heart-brain connection

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CHAPTER 2

Physiological principles

REGULATION OF SYSTEMIC BLOOD FLOW

In the Rembrandt project, we performed challenges that influenced the systemic blood flow. To provide context for the discussion, the next sections describe the basic concepts of systemic hemodynamics, cardiac output and cardiovascular control.

SYSTEMIC HEMODYNAMICS

Hemodynamics are defined as the physical factors and physiological mechanisms that govern blood flow. Flow through a vessel follows the laws of mass-equality and inertia, but is simplified in steady-state by using the hemodynamic analog of Ohm's law (generally used to describe electrical current). When applied to the cardiovascular system the blood flow is driven by the pressure difference between two points along the vessel together with the vascular resistance (flow = pressure difference / vascular resistance). Under steady state conditions arterial pressure is considered as the driving force behind flow and organ perfusion and is therefore tightly regulated [28].

The first non-invasive arterial blood pressure device was already invented in 1881 by Von Basch [29]. Notwithstanding that the concept of measuring blood flow was already published in 1870 [30], the measurement of cardiac output, either invasively or non-invasively was not possible before the mid of the 20th century. Determination of blood flow, and in particular the flow leaving the heart, is considered vital when managing critically ill patients (for instance those with severe cardiac or pulmonary disease and/or multi-organ failure). Nowadays, several non-invasive techniques (based on rebreathing Fick, Doppler, impedance and finger plethysmography) are available to provide real-time and continuous estimates of cardiac output and stroke volume [31]. Also MRI quantifies cardiac output in a non-invasive way [32]. In this thesis, we primarily focus on blood flow, as the mechanism responsible for the transport of oxygen and nutrients, with blood pressure as the driving power behind flow.

CARDIAC OUTPUT

The amount of blood leaving the heart in one minute is designated as the cardiac output (CO) and equal to left ventricular stroke volume (the amount of blood ejected with each cardiac cycle) times heart rate. Stroke volume is dependent upon preload, contractility and afterload. Cardiac preload is defined as the amount of blood directly available to the left ventricle and relates to thoracic fluid content rather than to central vascular pressures [33]. Therefore, cardiac preload is often –also in this thesis– being referred to as 'central blood volume'. Contractility refers to the intrinsic muscle strength of the (left) ventricle independent of its loading condition, and afterload refers to the force that opposes ejection of blood out of the ventricle (largely influenced by the

aortic impedance, arterial blood pressure and peripheral vascular resistance). Activities of daily living such as standing-up and physical exercise but also pathophysiological conditions including heart failure and dehydration modify CO by changing one or more of these (extra)cardiac factors [34].

CARDIOVASCULAR CONTROL

To ensure a continuous and appropriate supply of oxygenated blood to the tissues, the cardiovascular system is subject to precise cardiovascular control mechanisms. Although the cardiovascular system is under control of both neural and humoral components of the autonomic nervous system, in this thesis the focus will be on the neuro-cardiovascular system with the arterial baroreflex as its best-known example. The arterial baroreflex is the fastest control mechanism of blood pressure and generally acts within seconds [35]. The reflex arc consist of peripheral (stretch) receptors embedded in the aortic arch and carotid arteries, afferent pathways (toward the central nervous system), pathways within the central nervous system itself, efferent nerves and finally the effector organs (e.g. cardiac conductive tissue, cardiac muscle and vascular wall muscle fibers) [36], see Figure 2.1). Hence, a fall in arterial pressure leads to reflex adjustments by parasympathetic inhibition and sympathetic activation, with an increase in heart rate, in cardiac contractility, and in vascular resistance and venous return [37]. Conversely, an increase in arterial pressure results in opposite reflex changes. This provides a real-time feedback control on the arterial blood pressure, involving the heart as well as the peripheral vasculature.

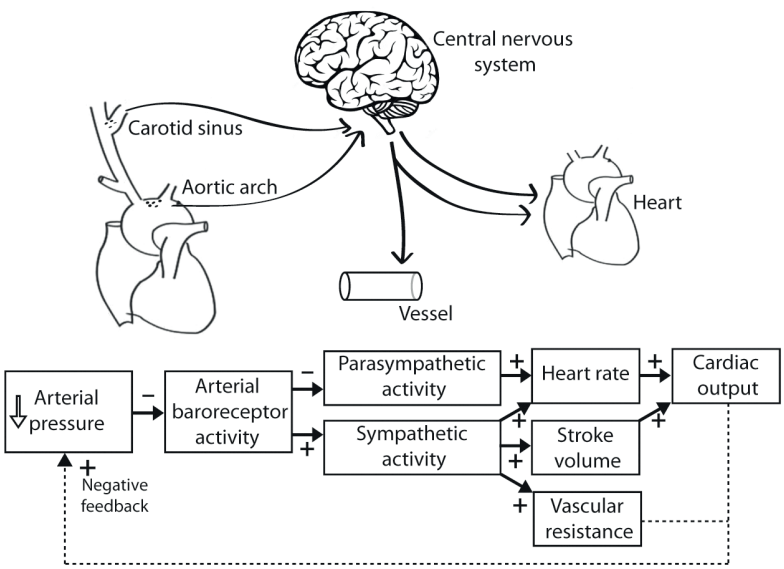

Figure 2.1 | Schematic drawing of the afferent and efferent pathways of the baroreceptor reflex arc (modified from Wehrwein and Joyner 2013) and a block diagram of baroreflex mediated adjustments to a fall in arterial pressure.

REGULATION OF CEREBRAL BLOOD FLOW

The regulation of CBF is considered to be independent of the systemic hemodynamics and the cerebral control mechanisms maintains CBF more or less constant by adjusting the cerebrovascular resistance. Therefore, these regulatory mechanisms provide the "background" to which systemic changes in blood flow effect their influence. The mechanisms involved in CBF regulation, i.e. cerebral autoregulation (i.e. mechanoregulation), chemoregulation, neurogenic regulation, and neurovascular coupling, mechanisms will be discussed in the next few paragraphs.

CEREBRAL AUTOREGULATION

In the late fifties of the last century, Lassen proposed the 'classic' concept of cerebral autoregulation (CA) which relates CBF to the cerebral perfusion pressure (CPP) [2]. The CPP is the difference between mean arterial blood pressure (MAP) at the base of the brain (i.e. the circle of Willis) and intracranial pressure, encompassing cerebral spinal fluid pressure and the central venous pressure [38]. The traditional CA curve suggests a constant CBF for a wide range of perfusion pressures via adaptations in the cerebrovascular resistance (Figure 2.2) [39]. Beyond the so-called pressure limits of regulation (e.g. lower and upper limit), autoregulation is lost and CBF changes proportionally to (the change in) MAP. It has been suggested that the lower limit is not a fixed value and that it may shift towards a higher MAP in hypertensive subjects [38] and vice versa to a lower MAP in patients with orthostatic hypotension related to sympathetic failure [38,40-44]. When the cerebral perfusion pressure falls below the lower limit of autoregulation, CBF decreases and cerebral ischemia ensues.

Within the normal physiological range, CA increases or decreases cerebrovascular tone in response to changes in CPP using a stretch sensing mechanism of the vascular smooth muscle cells ('the Bayliss myogenic response' [46]). Stretching of these cells is considered to induce the signals that provoke vasoconstriction while reduced transmural pressure leads to vasodilation. Although the stretch response is attributed to be a innate property of vascular smooth muscle cells [47], the exact underlying signaling pathways are incompletely defined.

To adapt to the brain's metabolic demand on CBF in daily life, both fast and slower acting components of the CA are required. In the laboratory, static (hours to days) and dynamic (seconds to minutes) components of CA can be distinguished in either the time- or frequency domain. The dynamic component is assumed to reflect mainly the capacity to counteract the alterations in CBF in response to fast changes in blood pressure. This component operates within seconds, and represents the response delay of the cerebral vasoregulatory system [48].

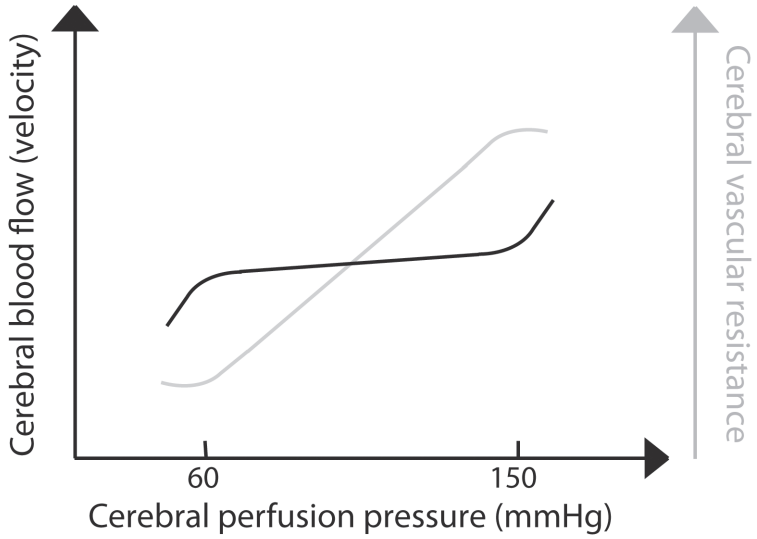

Figure 2.2 | The classical cerebral autoregulation curve describing the pressure-flow relationship for the brain. The CBF(v) is controlled to be more or less constant (the so-called autoregulatory plateau) via changes in the cerebrovascular resistance. Below and above the limits of autoregulation (<60 and >150 mmHg), the brain becomes 'pressure-passive' as represented by the linear portion of the curve. Modified from Lucas et al. 2010 [45].

CHEMOREGULATION

The brain vasculature is extremely sensitive to changes in carbon dioxide partial pressure ($PaCO_2$), designated as the cerebrovascular carbon dioxide responsiveness, and in a similar vein to and oxygen (PaO_2) [49-53]. Lowering vs. elevating the $PaCO_2$ (e.g. hypo- and hypercapnia) causes, respectively, vasoconstriction and vasodilatation of the arteries, leading to alterations in CBF. Conceptually, chemoregulation operates independently from the CA, but they may have common pathways and mechanisms [6,54-58]. The mechanism of chemoregulation is complex has not been fully clarified. For long it has been thought that the $PaCO_2$-driven changes in pH modify CBF by direct relaxation and contraction of the smooth muscle [59-61]. There is, however, also data suggesting that $PaCO_2$ affects CBF both in combination with altered pH and with unaltered pH [56] (see for review [61]).

The sensitivity of CBF to changes in carbon dioxide (CO_2) is generally expressed as the percentage change per mmHg in $PaCO_2$, and is often quantified non-invasively by relating changes in CBF(*v*) to alterations in end-tidal CO_2 [56]. In the normocapnic range, CBF*v* measured in the middle cerebral artery changes approximately 3.5% per mmHg change in end-tidal CO_2 [58,62-64].

NEUROGENIC REGULATION

Sympathetic nerves originating from the cervical ganglion abundantly innervate the cerebral arteries, but the role of the innervations in CBF control is still under debate [42,65,66]. It is assumed that under normal physiological conditions the influence of the central nervous system on CBF and its regulation is minor [66]. Increased sympathethic activation during exercise, however, is likely to enhance cerebral vascular tone thus counteracting imminent cerebral hyperperfusion as a consequence of an excessive increase in BP beyond the cerebral autoregulatory range [67-70]. Both sympathetic and cholinergic mechanisms are considered important for restricting the exercise-induced increase in cerebral perfusion on CBF without affecting the cerebral metabolic rate for oxygen ($CMRO_2$) [71,67].

NEUROVASCULAR COUPLING

Neuronal activation increases cerebral metabolic demand, i.e. the supply of oxygen and nutrients is rapidly adjusted by locally increasing the CBF, as the brain lacks extensive storage for energetic compounds [6,5,72-74]. This interplay of supply and demand implies a connection between neurons and the local vasculature, to which the term neurovascular coupling was coined. This process is probably mediated through the astrocytic end-feet that surround the arterioles [75-78]. In response to neuronal activation, elicited for example by a sensory stimulus, the CBF shows an overshoot with the supply transiently exceeding the demand, resulting in a local increase in oxygenation level. Imaging methods sensitive to either oxygen concentration such as BOLD fMRI or to CBF such as SPECT, PET and ASL, apply this principle in order to identify functional regions in the brain in relation to specific stimuli (e.g. fMRI). Although neurovascular coupling is often portrayed as being independent, interaction with the other regulatory mechanisms is likely, for example the local production of CO_2. The main distinguishing property of neurovascular coupling is the localized nature of this response.