Maintaining cerebral blood flow
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Physiological principles
2.1 REGULATION OF SYSTEMIC BLOOD FLOW

The following sections describe the basic concepts of systemic hemodynamics, cardiac output and cardiovascular control as these concepts are part of the research that we performed in Chapters 4-6.

2.1.1 Systemic hemodynamics

Hemodynamics is defined as the dynamics of 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.36

Quantification of blood flow in living humans continues to be difficult whereas the measurement of blood pressure is much easier. The first non-invasive arterial blood pressure device was already invented in 1881 by Von Basch.37 Notwithstanding that the concept of measuring blood flow was already published in 1870,38 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 and provide real-time and continuous estimates of cardiac output and stroke volume.39 Also MRI can provide non-invasive quantifications of cardiac output.40 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.

2.1.2 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.41 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 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.  

2.1.3 Cardiovascular control
To ensure a continuous and appropriate supply of oxygenated blood to the tissues, the systemic circulation 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. 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), see Figure 2.1.1. 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. Conversely, an increase in arterial pressure results in opposite reflex changes. This provides a real-time feedback control loop on the arterial blood pressure, involving the heart but also the peripheral vasculature.

2.1.4 Central hypovolemia
Severe central hypovolemia challenges cardiovascular control. An example of a critical reduction in central blood volume is uncontrolled hemorrhage or severe dehydration, e.g. by burn wounds or cholera. The central blood volume will also decrease in response to orthostatic stress (e.g. standing or passive head-up tilt) due to a gravitational shift of blood from the central circulation into the lower extremities leading to a decline in venous return. These (patho)physiological conditions are characterized by insufficient availability of intravascular volume, resulting in a progressive reduction in preload, stroke volume and finally CO. When reflex adjustments in heart rate and vascular resistance can no longer compensate for the progressive reduction in central blood volume, re-establishment of normovolemia by fluid administration is considered the cornerstone of treatment in hemodynamically unstable patients. The rationale behind volume expansion is to restore appropriate tissue perfusion and oxygenation by increasing the central blood volume.
Diagnosing a clinically relevant volume deficit is difficult because traditional clinical signs considered specific for hypovolemia including diminished skin turgor and high urine osmolarity, do regularly not accurately reflect a reduction in central blood volume. A meta-analysis of 12 clinical studies showed that with current clinical practice, between 40 and 70% of critically ill patients are so-called 'fluid responders'. The substantial number of patients not responding to fluid administration by increasing stroke volume or CO, calls for physiological markers capable to detect fluid responsiveness. To this end, variations in arterial pressure, like systolic (SVP) and pulse pressure variation (PPV) have been proposed as potentially useful biomarkers to guide fluid administration. These dynamic indices are based on respiratory-induced changes in venous return and associated variations in left ventricular preload transferred to arterial pressure (Figure 2.1.2).

Although in previous research these indices have been proven of clinical value, their application remains limited to patients who are mechanically ventilated with high tidal volumes. Chapters 4.4 and 6.1 focuses on arterial pressure variations as biomarkers for fluid responsiveness in spontaneously breathing subjects and their relation with brain perfusion as actual therapeutic endpoint.
2.2 REGULATION OF CEREBRAL BLOOD FLOW

CBF is defined as the blood supply to (a given part of) the brain in a given time, which in rest equals to approximately 50-55 mL per 100 g brain tissue per minute in normotensive adults. The regulation of CBF is considered to act directly on the cerebrovascular resistance independently of systemic hemodynamics. The mechanisms involved in CBF control, i.e. cerebral autoregulation (also known as mechanoregulation), chemoregulation, neurogenic regulation and neurovascular coupling will be discussed in the following paragraphs.

2.2.1 Cerebral autoregulation

In the late fifties of the last century, Lassen proposed the ‘classic’ cerebral autoregulation (CA) curve relating CBF to cerebral perfusion pressure (CPP). The CPP is the difference between mean arterial blood pressure (MAP) at the level of the circle of Willis and intracranial pressure, encompassing central venous pressure and the cerebral spinal fluid pressure. The traditional CA curve suggests more or less constant CBF for a wide range of perfusion pressures via adaptations in the cerebrovascular resistance (Figure 2.2.1). Recent data showed that the human brain is more effective at compensating for transient hypertension than hypotension, providing evidence for hysteresis in the cerebral pressure-flow relationship. 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 CPP. It has been
suggested that the lower limit is not a fixed value and that it may shift towards a higher CPP in hypertensive subjects and vice versa to a lower CPP in patients with orthostatic hypotension related to sympathetic failure.\textsuperscript{12,13,58-61} When the CPP falls below the lower limit of autoregulation, CBF decreases and cerebral ischemia ensues.

\textbf{Figure 2.2.1.} The classical cerebral autoregulation curve describing the pressure-flow relationship for the brain. The CBF (velocity) is maintained 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.\textsuperscript{65}

Under physiological conditions, CA adapts cerebrovascular tone in response to changes in CPP using a stretch sensing mechanism of the vascular smooth muscle cells (‘the Bayliss myogenic response’).\textsuperscript{62} Stretching of these cells is considered to induce the signals that provoke vasoconstriction while a reduction in transmural pressure leads to vasodilation. Although this phenomenon is assumed to be an inherent property of vascular smooth muscle cells,\textsuperscript{63} 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 the capacity to counteract alterations in CBF in response to fast changes in blood pressure. This component operates within seconds and represents the latency of the cerebral vasoregulatory system.\textsuperscript{64} The static component reflects the capacity to adapt the CBF in response to long term changes in blood pressure and rather represents the efficiency of the system.

\textbf{2.2.2 Chemoregulation}

The cerebral chemoregulation involves the strong cerebrovascular responsiveness to changes in arterial partial pressures of carbon dioxide (PaCO\textsubscript{2}) and oxygen (PaO\textsubscript{2}).\textsuperscript{66-70}
Lowering versus elevating the PaCO₂ (e.g. hypo- and hypercapnia) causes, respectively, vasoconstriction and vasodilatation of the capillaries, arterioles, and large extracranial vessels, leading to alterations in CBF. Conceptually, chemoregulation operates independently from the CA, but they may have common pathways and mechanisms. The exact mechanism of action has not been fully clarified. For long it has been thought that the PaCO₂-driven changes in pH modify CBF by direct relaxation and contraction of the smooth muscle cells. There is, however, also data suggesting that PaCO₂ regulates CBF both independently and/or in conjunction with altered pH.

The sensitivity of CBF to changes in carbon dioxide is generally expressed as its percentage change per mmHg in PaCO₂ (the CO₂ reactivity of the brain), and is often quantified non-invasively by relating changes in CBF (velocity) to those in end-tidal CO₂. In the normocapnic range, transcranial Doppler determined CBF velocity in the middle cerebral artery changes approximately 3.5% per mmHg change in end-tidal CO₂.

2.2.3 Neurogenic regulation

Cerebral arteries are abundantly innervated by sympathetic nerves originating from the cervical ganglion but their role in CBF control is still under debate. It is assumed that under normal physiological conditions there is probably little influence of the central nervous system on CBF and its regulation. However, increased sympathetic activation during, for instance, exercise likely enhances cerebral vascular tone thus counteracting imminent cerebral hyperperfusion as a consequence of an excessive increase in BP beyond the cerebral autoregulatory range. 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.

2.2.4 Neurovascular coupling

Neuronal activation increases cerebral metabolic demand. Since the brain lacks extensive storage of energetic compounds, the required supply of oxygen and nutrients is rapidly adjusted by locally increasing the CBF. This interplay of supply and demand implies a connection between neurons and the local cerebral vasculature, to which the term neurovascular coupling was coined. This process is probably mediated through the astrocytes that surround the arterioles. 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 locally increased oxygenation level. Imaging methods sensitive to either CBF or oxygen concentration, apply this principle in order to identify functional regions in the brain in relation to neuronal activation. The localized nature of the response is the main distinguishing property of neurovascular coupling compared to other regulatory mechanisms.