Withstanding the flow

*Human cardiovascular control during postural challenges*

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manipulation is observed among patients. On the other hand, dysfunction of cerebral autoregulation after stroke is associated with an increased risk for development of cerebral edema and hemorrhagic transformation. Hence, the safe upper limit for cerebral perfusion pressure may be easily exceeded with head-of-bed lowering without the interference of functional autoregulation. In Chapter 9, we studied whether the efficacy of cerebral autoregulation after acute ischemic stroke relates to the cerebrovascular response to head-of-bed lowering, of potential importance for individualized positioning and early mobilization of patients in the acute phase of ischemic stroke.

SECTION II

METHODS
Blood flow is essential in maintaining organ function and thus insufficient systemic or regional blood flow commonly implies a medical emergency and requires immediate intervention. Prompt recognition of systemic or local hypoperfusion asks for unremitted monitoring of systemic blood flow as the single cardiovascular parameter represented in the definition of the supply of oxygen to the body tissues:

\[
\text{oxygen delivery (DO}_2\text{)} = \text{cardiac output (CO)} \times \text{arterial oxygen concentration (CaO}_2\text{)}
\]

The primary evaluation of the hemodynamic condition is done indirectly by assessing heart rate (HR) and blood pressure (BP) as a surrogate for tissue perfusion.\textsuperscript{50} When these parameters change rapidly, a single measurement conveys insufficient information, making continuous monitoring desirable. At present, however, only intermittent blood pressure and heart rate are determined to evaluate cardiovascular homeostasis. Although providing vital information, BP and HR due to their regulated nature frequently do not respond to substantial changes in intravascular volume, e.g. fluid administration or blood loss.\textsuperscript{11-15} Therefore these parameters are not ideal for early recognition of compromised blood flow as these values remain regulated for a prolonged period when faced with (patho-)physiological challenges.\textsuperscript{51} In this thesis various methods for non-invasive monitoring of systemic blood circulation were evaluated and applied in several studies. In addition, several non-invasive methods were used to study characteristics of regional blood perfusion in the lower extremities and the brain. The non-invasive nature of these techniques makes them particularly attractive for application in research in both healthy subjects and patients.

The derived continuous data of the blood circulation provide the opportunity to determine and quantify the short-term interaction between the several parameters. Several of these interactions reflect autonomic cardiovascular regulation within the human body and allow evaluation of its role under different conditions. Specifically, the interaction between the fluctuations in BP and HR quantifies baroreflex function, whereas the interaction between BP and cerebral blood flow allows for the quantification of cerebral autoregulation.

**SYSTEMIC CARDIOVASCULAR MONITORING**

As mentioned above continuous monitoring of systemic cardiovascular variables is essential to recognize instant deviations in the blood circulation, while a non-invasive nature of these techniques allows for a widespread application. For that reason non-invasive and continuous monitoring of systemic blood circulation plays a central role in this thesis. A detailed review of methods for non-invasive and continuously systemic cardiovascular monitoring is given in Chapter 2. In this thesis the main techniques applied for monitoring of blood pressure and cardiac output are finger photo-plethysmography\textsuperscript{52, 53} and the pulse contour method,\textsuperscript{7, 9} respectively.

Pulse contour and other methods for non-invasive and continuous determination of cardiac output are generally validated against thermodilution-based intermittent estimates of cardiac output.\textsuperscript{54, 55} Application of the Stewart-Hamilton equation for thermodilution-based assessment of cardiac output assumes constancy of blood flow. On the other hand, fluctuations in finger arterial physiology may affect cardiac output determinations by pulse contour methods from the finger arterial pressure wave. In Chapter 3 we tested whether
variability in hemodynamics and peripheral vascular physiology impact on the comparison between thermodilution and pulse contour determined cardiac output.

**LOCAL CARDIOVASCULAR MONITORING**

Similar to studies on the regulation of systemic blood flow, study of the regulation of local blood flow requires techniques that are able to continuously and non-invasively monitor changes in blood perfusion. Two methods for this purpose used in this thesis are transtemporal Doppler ultrasonography (TCD) and near-infrared spectroscopy (NIRS). Both methods make use of the manipulation of physic waves in the ultrasound or light spectral range, respectively, by the local blood circulation. As the name already suggests TCD is applied to monitor cerebral blood flow changes, while NIRS can be used to evaluate cerebral blood perfusion as well as for circulatory monitoring at any other peripheral site.

*Transcranial Doppler*

The Doppler effect on ultrasound, i.e. the change in the observed frequency of a wave when the source and receiver are moving relatively to each other, is applied in TCD to estimate blood flow velocity in the large cerebral blood vessels. The ultrasound wave emitted by the TCD device is reflected by the blood stream and subsequently observed by the same TCD device. The difference between the emitted and received frequencies is applied to calculate the flow velocity of the blood stream that reflected the ultrasound. When the blood vessel diameter is considered to be constant changes in blood flow velocity equal changes in blood flow. This technique allows for the non-invasive and continuous monitoring of changes in cerebral perfusion, of importance for determining instant changes in perfusion due postural and autonomic influences. A disadvantage of TCD is that it solely detects flow velocity changes in the proximal large cerebral blood vessels, while perfusion changes to the cerebral cortex through collateral blood vessels are missed. Furthermore, the ultrasound beam has to be steadily focussed on the centre of the blood vessel where laminal blood flow is maximal. Even slight deviations from this centre imply changes in blood flow velocity that do not reflect actual perfusion adjustments. To stabilize the TCD probe it is attached to a headband that allows to hold probes at a steady focus over the temporal windows at both sides of the head (Figure 1).
Near-infrared spectroscopy

In contrast to visible light, light in the near-infrared spectral range (700 - 2500 nm) has the ability to relatively easy travel through organic tissues, while photons become absorbed mainly by hemoglobin in the capillary, arteriolar and venular beds. These characteristics of near-infrared light make it applicable for monitoring changes in the microvascular blood circulation.\(^{57, 58}\) Application of a modified Lambert-Beer equation allows for the differentiation of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb), since deoxy-Hb maximally absorbs near-infrared light at a wavelength of approximately 760 nm, whereas the absorption peak for oxy-Hb lies at 900 nm.\(^{59}\) Together deoxy-Hb and oxy-Hb reflect total hemoglobin tissue concentration ([total Hb]) that informs on total blood volume changes. A possible disadvantage of NIRS is that the near-infrared light is also absorbed by myoglobin, which has a comparable absorption profile as hemoglobin making differentiation between the two molecules impossible. However, during relatively short time intervals myoglobin remains relatively constant and variations in the absorbed near-infrared light are mainly caused by fluctuations in the amount of hemoglobin within the path that is travelled by the light (Figure 1).

**Figure 1** A headband provides the opportunity to monitor cerebral perfusion using NIRS and TCD simultaneously on both sides of the head. The 2 glassfiber optodes of NIRS are attached over the forehead, while the TCD probes covers the temporal window.
Application of NIRS is performed by placing two optodes on the skin. One optode transmits the near-infrared light while the other optode receives the photons that have travelled through the tissue. These optodes need to be placed at a predefined distance from each other, where a larger inter-optode distance increases the penetration depth of the light signal while decreasing the signal-to-noise ratio. When the optical path length that is travelled by the light in the studied tissue is known quantitative values of the hemoglobin concentration can be determined. Without knowledge of this path length a differential path length factor, that depends on the tissue of interest, has to be applied to account for the scattering of light.

![Strain gauge plethysmography on forearm and calf.](image)

**Figure 2 Strain gauge plethysmography on forearm and calf.**

**Strain gauge plethysmography**

As mentioned in the General introduction the transfer of the body from the supine to the upright position induces a shift of blood volume to the lower limbs. This blood volume increase in the leg can be determined with the application of strain gauge plethysmography (Figure 2). This method is based on the change in limb circumference that comes with a change in limb volume due to, for instance, a gravitational blood volume shift or venous occlusion. The change in limb circumference is recorded through a mercury-in-silastic strain gauge that is wrapped around the limb. When the silastic tube filled with mercury is stretched the electrical resistance over the mercury core increases from which the level of stretch and hence the relative increase in limb circumference can be quantified.
CARDIOVASCULAR AUTONOMIC REGULATION

Arterial baroreflex

The reduction in venous return and hence cardiac stroke volume in the upright position is partially compensated for by a baroreflex-mediated increase in heart rate. The arterial baroreceptors in the aortic arch and carotid sinuses are stretch sensitive, and the firing rate from the carotid baroreceptors via the glossopharyngeal nerve (cranial nerve IX) and from the aortic baroreceptors via the vagus nerve (cranial nerve X) declines when blood pressure drops. This reduction of firing rate from the afferent part of the baroreflex is received by the nucleus tractus solitarii in the medulla oblongata of the brain stem, which in turn transmits the information to the nucleus ambiguous. From the nucleus ambiguous the firing rate of the efferent signal through the vagus nerve, the parasympathetic pathway to the sinus node, decreases with a resulting increase in heart rate and hence cardiac output. A second efferent signal comes from the rostroventrolateral medulla and activates the sympathetic pathway from the spinal cord to the post-ganglionic neurons, leading to peripheral vasoconstriction and an increment of heart rate and cardiac contractility.

The functionality of the baroreflex can be quantified as baroreflex sensitivity (BRS) both in the frequency domain and in the time domain.\textsuperscript{61-63} BRS in the frequency domain is obtained by Fast Fourier transform. In this methodology beat-to-beat systolic blood pressure (SBP) and inter-beat interval (IBI) power spectral density of SBP variability and IBI variability are computed using discrete Fourier transform. The BRS can then be obtained from the gain of the transfer function between SBP variability and IBI variability in the low frequency band (0.06 – 0.15 Hz) provided that coherence between the signals is above 0.5.\textsuperscript{64} Continuous BRS can be evaluated in the time domain by the sequence method. Here the cross-correlation between 10 sec series of SBP and IBI samples is computed for the delay (τ) between changes in SBP and IBI of 0 – 5 sec. The τ yielding the highest cross-correlation is selected if significant with α set at 0.05. The regression slope is recorded as a single BRS value. Subsequently, this process is repeated for series of SBP and inter-beat interval samples 1 sec later.

Cerebral autoregulation

Besides the mechanisms to control systemic cardiovascular stability, constancy of cerebral blood flow (CBF) is maintained by cerebral autoregulation.\textsuperscript{39} This control mechanism maintains CBF more or less constant despite fluctuations in blood pressure. When blood pressure at brain level decreases, which occurs as the brain is being elevated above heart level, cerebrovascular resistance decreases. In this way CBF is maintained despite the lower perfusion pressure. Vice versa, as arterial pressure at the level of the brain increases constriction of the cerebral resistance vessels averts hyperperfusion of the brain, which in severe cases has been associated with the development of intracranial edema and hemorrhage.\textsuperscript{48,65}

The ability of cerebral autoregulation in dampening the transfer of fluctuations in arterial pressure to CBF can be quantified by the latency between the input (arterial pressure) and output (CBF) signals. To that purpose cerebral autoregulation can be quantified in the frequency domain in order to determine the phase difference (Φ) between mean arterial pressure (MAP) and TCD determined CBF velocity (CBFV), generally measured in the middle cerebral artery (Figure 3).\textsuperscript{40,41,66} Lower Φ implies more passive following of CBF to
fluctuations in arterial pressure and hence reduced function of cerebral autoregulation. The variability of, respectively, MAP and CBFV is quantified by determining their power spectra with discrete Fourier transformation. From the cross spectrum of these signals $\Phi$ is derived by transfer function analysis. According to the high-pass filter properties of cerebral autoregulation, performance of autoregulation is reflected by the $\Phi$ between oscillations of MAP and CBFV at $0.06 - 0.15$ Hz. To examine the strength of the relationship between the MAP and CBFV signals, a coherence >0.5 is considered to imply sufficient covariety between these signals in the transfer function analysis.

**Figure 3** Fictional example of the determination of cerebral autoregulation by transfer function analysis. The red line represents mean cerebral blood flow velocity as measured by transcranial Doppler, whereas the black line represents mean arterial pressure. The latency between the fluctuations in two signals can be expressed as the phase difference ($\Phi$) and reflects the efficacy of cerebral autoregulation. Gain reflects the dampening capability of cerebral autoregulation.