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

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CHAPTER 3

Methods

PARAMETERS

Investigation of the cardio- and cerebrovascular response to physiological stress requires (simultaneous) monitoring of systemic, cerebral and respiratory parameters. This chapter provides an overview of the parameters that were measured in the studies described in this thesis.

SYSTEMIC

Blood pressure

Continuous arterial blood pressure (BP) can be measured non-invasively by finger plethysmography (Nexfin, Edwards Lifesciences BMEYE, Amsterdam, the Netherlands) using a volume-clamp technique [79]. The cuff is placed around the midphalanx of the non-dominant hand and held at heart level. An optical plethysmograph in the finger cuff measured arterial volume continuously. The pressure in the cuff around the finger is adjusted in near real-time (~100 Hz) to keep the arterial volume clamped, allowing continuous tracking of the blood pressure. A height reference system is placed around a finger next to the cuff and at heart level to account for the hydrostatic pressure difference. To estimate changes in BP accurately over time, an automatic built-in calibration system (Physiocal) tracks the unloaded diameter of the finger artery to keep the arterial unloaded volume constant [80]. The arterial pressure measured at the finger is fundamentally different from brachial pressure both in absolute terms (hydrostatic difference) and wave shape, such that necessary corrections are applied in the Nexfin system to transform finger pressure into brachial pressure [81].

In case finger plethysmography is not available (for instance in the MR-environment), BP measurements were taken every 2–4 min using an inflatable arm-cuff (Magnitude, In-Vivo, Orlando, FL) while HR is continuously monitored by means of an MR-compatible finger pulse-oximetry unit.

Heart rate, stroke volume and cardiac output

A pulse contour method (Nexfin CO-trek, Edwards Lifesciences BMEYE, Amsterdam, the Netherlands) – adapted for age, sex, height and weight [82] – can provide left ventricular stroke volume (SV) and cardiac output (CO; SV multiplied by instantaneous HR). This method has been thoroughly validated against invasive thermodilution measurements [82,83]. In our work , Nexfin derived CO was validated by means of inert gas rebreathing (Innocor, Innovision A/S, Odense, Denmark) [84,85]. The rebreathing method relies on two inert gasses that are inhaled in tracer quantities through a bag. The blood-soluble N_20 diffuses into the lung capplilaries and the blood insoluble NF_6 remains in the alveoli and airl. The rate at which the soluble gas disappears from the bag is assumed to be equal to the CO of the left ventricle [86].

BRAIN

In this thesis, we assessed using two non-invasive modalities the CBF response to a variety of physiological challenges. The first modality, transcranial Doppler ultrasonography (TCD), provides high temporal resolution assessments of CBF velocity (CBF*v*) in large brain-feeding arteries. This method is a relatively simple and low-cost bedside technique and is assumed to provide accurate quantification of the mean CBF over a large area of the brain, that is, the flow territory perfused by the insonated artery. The second modality, MRI, provides techniques such as arterial spin labeling (ASL) and blood-oxygen-level dependent (BOLD) imaging which enable the measurement of whole brain CBF and oxygenation changes at the microvascular level. MRI is a complex, costly and time-consuming procedure that offers a non-invasive measure of brain perfusion and oxygenation at a high spatial resolution. A combination of TCD and MRI-based quantifications of CBF has the potential to complement each other in obtaining a more complete understanding of brain perfusion at both the macro- and microvascular level. In the following paragraphs we will discuss both modalities into more detail.

Middle cerebral artery blood flow velocity

Measuring CBF*v* in the basal cerebral arteries by TCD was introduced in the early eighties of the twentieth century by Aaslid and coworkers [87] and has found wide acceptance in both clinical and research settings. The ultrasound probe emits a high-pitched sound wave through the intact scull, which is then reflected from erythrocytes moving through ultrasound beam. The CBFv is recorded from the Doppler shift spectrum of the reflected sound waves [88]. Mean CBFv reports the velocity associated with the maximal frequency of the Doppler shift ("the envelope"), rather than the cross-sectional average velocity that defines the blood flow through the artery [89]. The average velocity can be obtained from the intensity-weighted mean flow velocity or the total signal power, but is sensitive to small changes in insonation angle of the artery [89]. Therefore, the maximum velocity is preferred as reported entity.

A TCD system (DWL Multidop X4, Sipplingen, Germany) with a pulsed ultrasound frequency of 2 MHz can be used to satisfactory penetrate the skull. As the bone of the temporal region is thin and therefore the best promising area for ultrasound insonation [87]. CBF*v* measurements were localized in the proximal segments of the left or right middle cerebral artery (MCA). The ultrasound probe is placed on the temporal region of the skull just above the zygomatic arch (Figure 3.1). At an insonation depth between 45 and 60 mm, the signal is optimized. Subsequently, the probe is secured in position by a head-band.

The relation between calculated vs. actual CBF*v* depends on angle of insonation [90]. When the angle increases from 0° to 30°, its cosine will decrease from 1 to 0.86 resulting in a maximum error up to 15% [88]. By immobilizing the probe by a head-band, we minimized the influence of a potential change in angle as might occur during the experiments. An important issue of TCD whether blood flow velocity accurately reflects the actual underlying blood flow. Changes

in blood flow velocity reflect those in blood flow when the cross-sectional area of the insonated vessel remains constant (blood flow = blood flow velocity x cross-sectional area).

Vessel diameter does not change significantly during moderate variations in mean BP or CO_2 tension according to direct observations made during craniotomy [91]. Also orthostatic stress, as stimulated by lower body negative pressure (LBNP), does not induce detectable changes in the diameter of the MCA as observed with 3 Tesla MRI [92]. These findings suggest that the MCA diameter does not change and that changes in TCD-determined CBFv will track those in CBF. In three studies presented in **chapters 4-6**, we examined these assumptions under influence of carbon dioxide and sympathetic stimulation using high-resolution MRI at 7 Tesla.

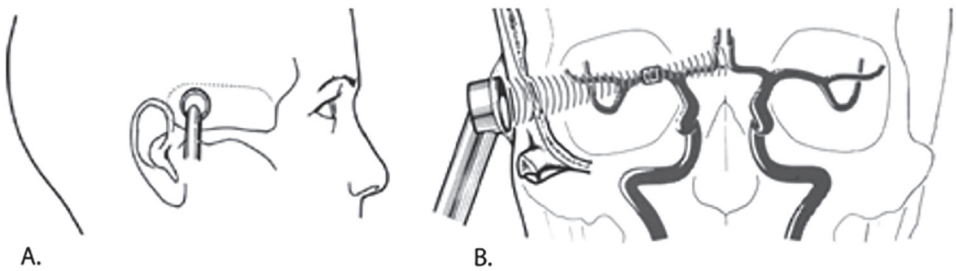

Figure 3.1 | The ultrasound probe is placed on the temporal region of the skull (dotted line indicates the 'temporal window') just above the zygomatic arch **A**). A frontal view of the ultrasound probe directed toward the MCA **B**). The cilindrical sample volume is indicated by a circle over the MCA, i.e. observation region; the distance from the middle of the cylinder to the probe corresponds to the depth setting. Reproduced from J Neurosurg [87].

Whole brain blood flow

Since the proposal of ASL two decades ago [93], the non-invasive quantification of regional CBF with MRI has progressively developed into a well-accepted and clinically suitable technique. ASL MRI is based on the detection of a tracer that is delivered to and cleared from the tissue by blood flow [94], and usually expressed in ml/min/100g tissue [95,96]. With ASL, an endogenous tracer is created by inverting the proton spins of blood, mainly located in water molecules (H_2O). Magnetic labeling of arterial blood water spins is done by a long series of radiofrequency pulses (in pseudo-continuous ALS) that are applied in a plane perpendicular to the neck. Subsequently, labeled protons in the arterial blood water act as (almost) freely diffusible tracers. From the labeling location the labeled protons migrate within 1–2 seconds via the arterial vessels and capillaries into the brain tissue where the label accumulates, thereby altering the local tissue magnetization. The change in tissue magnetization is measured by acquiring multiple image slices covering the whole brain and a comparison to an identical control scan in which the inflowing blood was

not labeled. A 3-dimensional perfusion map can be obtained by subtracting the labeled image volume from the control image volume (no label) (Figure 3.2).

The ASL-signal, i.e. the difference in signal intensity between label and control images, is small (~1%). To obtain a sufficient signal-to-noise ratio (SNR), many repetitions of the control and label pairs are acquired during 3–5 minutes. The ASL technique applied here is pseudo-continuous ASL, as the recommended standard for use in a clinical setting [96] and which has been recently compared with $15H_2O$ positron emission tomography (PET) CBF measurements [97]. Background suppression RF pulses were used to enhance the SNR of the CBF signal. In addition, the imaging module was extended with an extra echo block to obtain the BOLD fMRI signal with minimal additional scan time [98]. The BOLD signal is mainly sensitive to the concentration of deoxy-hemoglobin, and also depends on blood flow, blood volume and tissue properties, such as diffusion. This makes this method less specific than ASL. Changes in ASL or BOLD determined regional are often used as proxy for neuronal activation [99]. **Chapter 7** describes a comparative study of the determination of the CBF changes upon small muscle group exercise as measured by either ASL MRI or TCD.

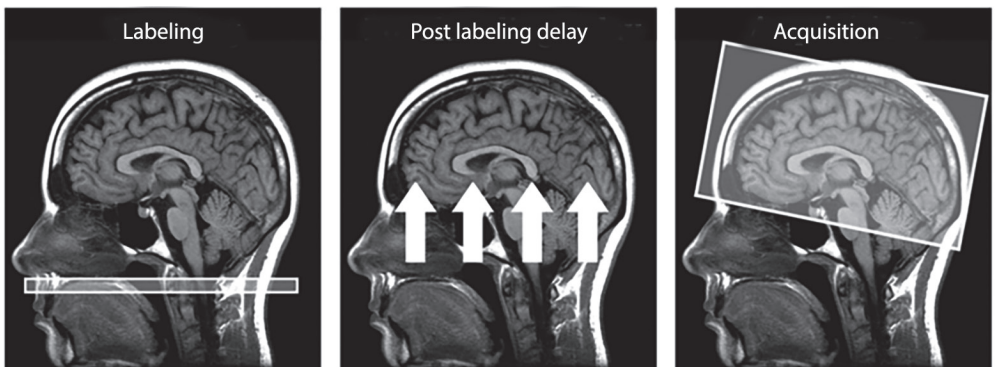

Figure 3.2 | Principle of arterial spin labeling. Arterial blood flowing to the brain is magnetically labeled in the neck by applying radiofrequency pulses. The labeled protons (i.e. water in arterial blood) flow to the brain tissue, where the labeled water protons mix and accumulate in the extravascular space and tissue. To allow the protons to reach the brain tissue, a delay time is applied (i.e. post labeling delay, PLD) after which the images are acquired, often with full brain coverage. The static brain tissue is subtracted by acquiring a separate set of control images. The control images are obtained without labeling the arterial blood. A full brain quantified ASL measurement requires multiple measurements of label and control images, and takes 3–5 minutes.

RESPIRATION

Brain perfusion is highly sensitive to changes in $PaCO_2$ (see section on Chemoregulation). To enable a correct interpretation of the CBF and CBFv responses, it is highly recommended to also monitor (changes in) $PaCO_2$. The partial pressure of CO_2 in exhaled air (designated as end-tidal

CO_2; $PetCO_2$) is generally used as a non-invasive proxy for $PaCO_2$ and therefore measured in the studies described in this thesis.

Partial end-tidal carbon dioxide pressure

$PetCO_2$ is continuously monitored, via a nasal cannula, by a sampling infrared capnograph (Tonocap, Datex-Ohmeda, Madison, USA or Datex Normocap 200, Helsinki, Finland). This technique is based upon the absorption of infrared radiation by CO_2, with the amount of absorbed radiation having a nearly exponential relation to the CO_2 concentration. Detecting a change in infrared radiation levels, using photo-detectors, allows for the calculation of the CO_2 concentration in the gas sample.

Physiological challenges

The present thesis discusses various physiological methods (including orthostatic stress tests, small muscle group exercise and inhalation of a gas mixture containing CO_2) that were applied to address autonomic cardio- and cerebrovascular control. This section summarizes these methods with respect to their known physiological mechanism and the way in which they were performed.

Orthostatic stress tests

Passive head-up tilt (HUT), lower body negative pressure (LBNP) and orthostasis (standing up) all lead to a gradual translocation of blood from the intra-thoracic region into the lower parts of the body. As a result, CO decreases and a series of cardiovascular regulating mechanisms and reflexes come into action to maintain arterial blood pressure and cerebral perfusion.

Passive head-up tilt

Passive HUT is performed with the subject lying supine and safely strapped on a tilt table (custom built by AMC Medical Technological Development / Dr. Kaiser Medizintechnik, Bad Hersfeld, Germany) and then either mechanically or manually tilted to a semi-supine (30°), semi-upright (45°) and/or almost completely upright (70°) position. Tilting back from 70° HUT to the supine position leads to central blood volume repletion and mimics a fluid challenge.

The bulk blood volume translocates between upper and lower body because the hydrostatic indifference point for intravascular pressure (i.e. point in the vascular tree at which pressure remains constant independent of body position) is located at the level of the diaphragm [100]. Moreover, blood volume measurements by electrical impedance suggest that the indifference point for volume as is even lower, positioned between the navel and iliac crest [101,100]. As a consequence, in upright position, roughly 70% of the blood volume is located below the level [100] of the heart . The translocated blood is mainly being contained in the (compliant) veins and venules and, therefore, does not contribute to the effective arterial blood volume [100,102]. This shift in blood volume distribution is estimated to be 300–800 ml of which 50% takes place within the first few seconds [34,103,104]. The central blood volume is challenged further by an estimated

10% or ~500 ml reduction after 5 min and 15% or ~750 ml reduction after another 5 minutes in the HUT position [105].

Lower body negative pressure

During LBNP, sub-atmospheric pressure is applied to the lower limbs in a supine subject such that blood redistributes from the upper parts of the body into the compliant compartment of the lower extremities. In preparation for LBNP, the lower body of the subject is positioned inside an LBNP box (Dr. Kaiser Medizintechnik, Bad Hersfeld, Germany / Dept. Instrumental Development, LUMC) and sealed at the level of the iliac crest [106]. An advantage of this technique compared to passive HUT, is its utilization within the static and horizontal setup of the MRI-scanner.

Standing up

The presumed mechanism behind the gravitational translocation of blood from the intra-thoracic region to the veins in the legs during passive HUT is similar to that when humans stand up from the supine position. However, the active change in posture during standing-up produces a hemodynamic response that is different from what happens with passive tilt during the first 30 s of upright posture [107].

Small muscle group exercise

Rhythmic handgrip exercise is a form of small muscle group exercise that increases HR and CO, with modest changes in blood pressure [108]. An advantage of rhythmic handgripping is that it can be performed in the supine position while ensuring minimal (head) motion, which makes it a suitable exercise method during MRI monitoring. Moreover, a mild to moderate handgrip exercise level can be maintained for a longer period of time to achieve the steady state needed for acquisition of ASL-measurements, which typically take about 3–5 minutes. To standardize the workload between individuals, the subjects were first instructed to squeeze a handgrip dynamometer (fOrb Gripforce, Current Designs Inc., Philadelphia PA, USA) to the maximum extent possible for 2–3 s without tensing the entire body. The so-measured maximum force was taken as 100%. The exercise experiments consisted of 0.5 Hz intermittent handgrip contractions performed for the first minute at 80% of the maximum force followed by 4 minutes at 60%. The decreasing force protocol was used to achieve a steady-state in minutes 3 to 5.

Inhalation of a gas mixture containing CO_2

In order to quantify the cerebral vasomotor reactivity, a wide range of PetCO2 was established by, respectively, inhaling a gas mixture containing 5% CO_2 and 95% O_2 (carbogen) through a mouthpiece for 2 minutes, followed by 2 minutes of breathing room air and hyperventilating for approximately 2 minutes.

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