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

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CHAPTER 10

General discussion

The studies presented in this thesis laid further groundwork for integrative and multi-disciplinary studies of the Rembrandt Project "Go with the Flow" and the heart-brain connection in general. At the core of the Rembrandt project is the multi-disciplinary approach. This approach allowed us to challenge existing dogma in *TCD as measure for cerebral blood flow changes* and create new opportunities for future research with *Lower Body Negative Pressure in the MRI*. These topics will be discussed in the next paragraphs.

TCD AS MEASURE FOR CEREBRAL BLOOD FLOW CHANGES

The non-invasive nature of TCD, together with its high temporal resolution, portability and affordable setup has made it into a widely-used research and clinical tool [1]. Since the introduction of TCD [2] three decades ago the few basic assumptions of TCD, that couple velocity measurements to cerebral blood flow, have been continuously under discussion [3]. In this thesis, we have aimed to validate two important aspects of TCD: assumption of diameter constancy and whether TCD reflects cerebral blood flow changes.

The first aspect, diameter constancy, assumes that the diameter of the vessel that is insonated by TCD remains constant during physiological challenges. Earlier studies have directly and indirectly measured diameter changes, see e.g. a recent editorial on this topic [3]. In this thesis, we showed with high resolution MRI that this assumption does not hold up during challenges such as: high levels of hypercapnia (**chapter 4**), systolic-diastolic pressure differences **(chapter 5**) and rhythmic handgrip exercise (**chapter 6**). However, these modulations of the velocity are small when compared to differences that are considered clinically relevant. For example, in stroke patients the difference in (TCD measured) cerebrovascular reactivity at three months follow-up between two patient cohorts was approximately 30% [4]. The diameter change observed in our studies would account for approximately one fifth of those CBF-changes as predicted from velocity measurements by TCD, thus potentially overestimating (or underestimating) the differences between groups rather than within groups. This thesis challenges the long-held assumption of diameter constancy, which obscures the interpretation of experimental data as well as the (comparison of) different responses between groups, e.g. patient cohorts.

Measurements obtained with TCD are often interpreted as changes in CBF, i.e. tissue perfusion. TCD is often used to probe CBFv changes at the level of the Circle of Willis, hence obtaining an aggregated measurement over the entire flow territory of the insonated vessel. In **chapter 7** we showed that during handgrip exercise, the ASL CBF did not increase in the flow territory, whereas the TCD CBFv increased by 10% in the corresponding artery. When looking into more detail the ASL determined CBF appeared to increase more locally in the precentral region (motor cortex). This is too small a region to trigger a detectable increase in the mean total MCA flow territory CBF, attributed to neural activation. The expected change in CBFv extrapolated from such a small region (1.5%) still remains within the detection limit of TCD, which is approximately 1%

(unpublished pilot data). However, the change as measured with TCD (10%) overestimates the change as determined with ASL by one order of magnitude. Although, as also stated in the previous paragraph, we did show that during handgrip exercise the MCA-diameter changes significantly (2% area change, **chapter 6**), this is much smaller than the velocity difference (10%). Previous TCD studies have shown significant changes in MCA-velocity occur following emotional or sensory stimulation [1,5], and that hemispheric dominance of hand movement originating in small cortical regions can be detected [6,7]. These results illustrate that TCD does detect velocity changes in response to cognitive or motor challenges, it is as yet uncertain whether these are exclusively related to changes in local or global CBF or whether diameter changes also explains some of these detected velocity changes. This discrepancy between large artery blood flow and tissue perfusion raises fundamental questions (see **chapter 7**) for which present literature does not provide straightforward explanations.

With respect to the question whether we can still apply TCD to measure CBF changes, the results of the present thesis seem to be very clear: i.e. TCD velocity changes are not always a valid proxy for CBF changes at the tissue level for two reasons. First, during physiological challenges constancy of vessel diameter cannot always be assumed, which introduces a level of bias and uncertainty in the TCD determined "perfusion" responses. Second, the coarse spatial resolve TCD obscures localized changed in CBF, and unlikely reflects focal changes in tissue perfusion. This should, however, not be considered as a rejection of TCD for physiological brain research, but more as a strong call to first elucidate these inconsistencies to avoid that misinterpretations on (the control of) cerebral perfusion will enter the scientific literature, thereby obscuring the true mechanisms. Further research and especially more multi-modality studies that combine the strengths of TCD and e.g. ASL-MRI are required to elucidate how cerebral perfusion and blood velocity in large cerebral arteries are related.

LOWER BODY NEGATIVE PRESSURE IN THE MRI

Head-up-tilt (HUT) is the most commonly employed orthostatic challenge for the clinical evaluation of patients with syncope of unknown origin [8,9]. Currently, cerebral hemodynamic responses to HUT are assessed by TCD, which lacks spatial differentiation. Non-invasive MRI CBF-measurements using supine LBNP as challenge might provide insight in the underlying neuronal activation processes and enable identification of areas of hemodynamic impairment during orthostatic stress.

Applying LBNP in the MRI is a challenge, both for practical and safety reasons. A practical concern is that subject motion during the application of pressure during LBNP is inevitable. Such motion occurs in sync with the applied stimulus, i.e. both motion- and stimulus effects overlap each other in time. This creates ambiguity as to whether the measured data reflect an effect of LBNP, is the result of subject motion, or a mixture of these two. In the context of the Rembrandt Project, we

have applied LBNP in the MRI [unpublished data] and observed considerable head movement of 1–2 cm (see Figure 10.1). Head motion during LBNP causes large changes in the raw (i.e. unsubtracted) ASL-signal (see Figure 10.1a). Post-processing software (e.g. SPM, FSL) can be used to correct for head motion. However, the translations and rotations are mostly through-plane (z-direction), complicating the post-processing correction due to the relatively large thickness of the imaging slices. Moreover, motion-induced signal deviations are mostly non-linear, both in (image)-space and time [10], which further complicates corrections by post-processing. Another major concern is that (head) motion will also displace the ASL labeling plane with respect to subjects' anatomy, such that changes in artery anatomy, blood velocities, arterial transit time, main magnetic field (B_0), shimming and coil loading could influence the labeling efficiency and the subsequent CBF quantification. Since ASL relies on the subtraction of label and control images, the CBF calculation would still remain unaffected as long as label and control conditions are being affected by a similar offset in signal intensity. However, due to the effects discussed earlier, this is not the case in reality, and the result is large errors in the measurement of the CBF-response to LBNP. To remedy the subject motion during LBNP, we built and tested, in collaboration with the Instrumental Design Department of the LUMC, a prototype of a compact LBNP box [11]. By restricting the area of negative pressure to the pelvic region and the upper-legs, less downward force is present during the periods of negative pressure, thereby minimizing motion. Using the compact box a strong reduction in head motion was achieved while maintaining similar systemic hemodynamic responses. This could prove to be an important step to bring the LBNP research to the field of MRI. Finally, another solution would be to repeat the survey scans during the different levels of LBNP, to adopt the planning of the ASL scans as well as to repeat the MR-calibration scans during these conditions. Whereas this will make the CBF-measurement by ASL less dependent on the induced motion, it severely limits the time-efficiency of the study-protocol and might lead to unwanted increases in the total time that LBNP is applied.

LBNP in MRI has been used for a variety of experiments, such as assessing muscle metabolism using MR spectroscopy [12,13], for performing cardiac MRI [14-16], assessing the diameter of the large brain-feeding arteries [17] and for probing autonomic and baroreflex function in the brain [18,19]. In the Rembrandt Project, we have applied LBNP to investigate the relation between cardiac output and brain perfusion, leading to the observation that subject motion during moderate levels of LBNP can adversely affect the obtained measurements of the brain [unpublished results]. In contrast, we have successfully applied LBNP in MRI to investigate the effect of sympathetic stimulation on renal perfusion [20]. Nevertheless, the potential of LBNP in the MRI remains to be proven.

In the Rembrandt Project we showed [21] that humans differ in their cardiovascular response patterns to LBNP that are reproducible over time in one and the same individual. Currently, real-time (continuous non-invasive) blood pressure measurements, and especially the derived cardiovascular parameters such as stroke volume and peripheral resistance, are not available in the MRI environment. This hampers the classification of the underlying cardiovascular response

in MRI research. Generally, such real-time cardiovascular monitoring is important for subject safety, as sudden changes in blood pressure or heart rate are suggestive of for the occurrence of (near) syncope. Therefore, both safety and response classification underline the importance of advancing integrative cardiovascular monitoring in an MRI environment, to facilitate correct interpretation of the cerebrovascular response within the framework of the human heart-brain axis.

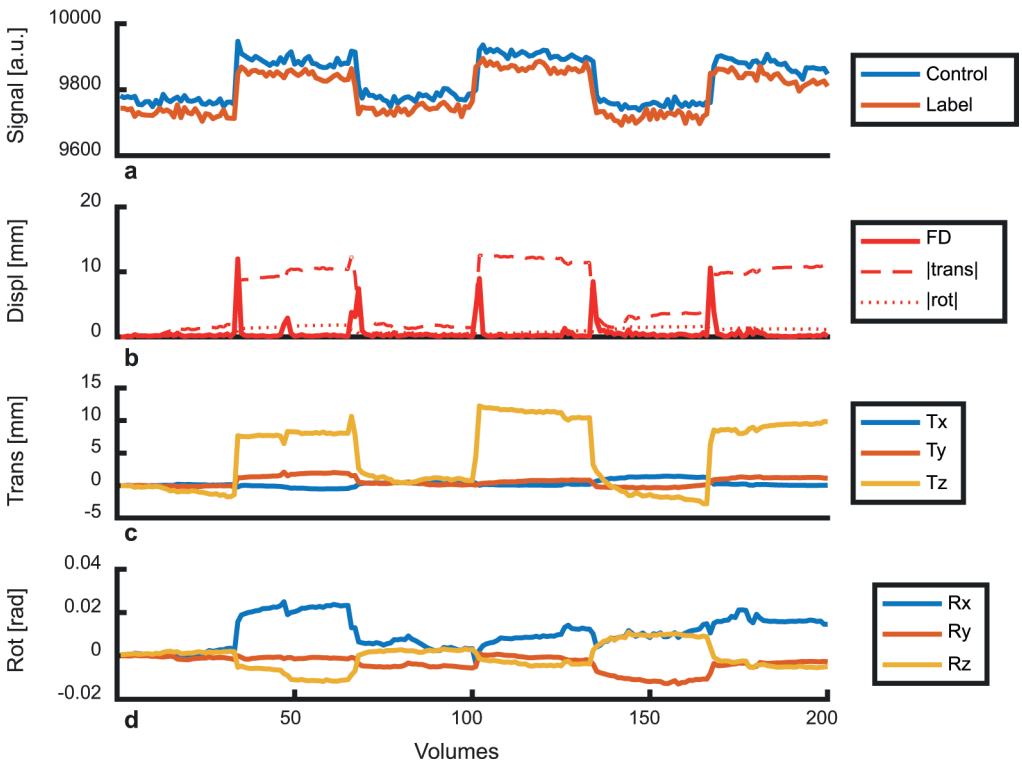

Figure 10.1 | Representative MRI signal and head displacement during three consecutive LBNP challenges in one subject. **a**) Global signal for control and label conditions **b**) Framewise Displacement (FD) and absolute translations and rotation; **c**) Relative Translations along x-, y- and z-axis; z-axis is toward the box D) Relative rotations. Global signals are averaged over the entire brain, excluding the skull.

CONCLUDING REMARKS

In the Rembrandt Project "Go with the flow", we have integrated the fields of cardiovascular physiology and brain MR imaging to investigate the heart-brain axis, and the fruits of the multi-disciplinary approach in this thesis have been plentiful. Learning from other fields of expertise creates insight and challenges traditional assumptions. In this thesis, we have used MRI to verify

an often-debated assumption of TCD (**chapters 4**–**6**). Moreover, the cardiovascular physiology underscores (to the cerebrovascular MRI community) that the brain does not stop at the neck, but has a body than can respond differently to the same LBNP challenge [21]. This underlines the importance of implementing continuous cardiovascular monitoring in the MRI-scanner to enable the study of the brain and body in an integrated fashion. Also, when bringing physiological challenges, such as LBNP, to the MRI-scanner, limitations of MRI become evident, demanding multi-disciplinary and creative solutions [11]. Combining fields of expertise in the Rembrandt Project has provided fuel to challenge the validity of currently used methods to measure global and regional cerebral blood flow during exercise (**chapter 7**). TCD seems not to reflect changes in tissue perfusion, but on the flip-side, ASL-perfusion MRI fails to explain why a large and obvious increase in blood velocity is observed in the MCA during exercise. This has far-reaching implications for the translation of the concept of cerebral autoregulation (mainly developed in the TCD domain) to the field MRI; i.e. both modalities seem to measure different aspects of cerebral hemodynamics. The observations in our work challenged existing dogma, and gave insight in the assumptions of the employed techniques which contribute to better understanding of underlying (patho-)physiological mechanisms. Also, these findings provide a starting point for evaluating the integrative response of heart and brain which may help guiding future treatment decisions and the development of treatment and interventions strategies in both heart and brain dysfunction.

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