Maintaining cerebral blood flow
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General discussion
Control of CBF involves an array of regulatory mechanisms including autoregulation of cerebral perfusion pressure, cerebrovascular responsiveness to CO₂, neurovascular coupling and endothelium-mediated signaling. On top of that, there is mounting evidence for a linkage between the heart and the brain. The finding that cardiac failure relates to low CBF, indicates a distinct role for the heart in maintaining cerebral perfusion. This thesis aimed to delineate the incompletely explored link between the heart and the brain from a physiological point of view. Data presented in this thesis support application of LBNP as a stimulus to challenge the systemic circulation to study the effect of a varying CO on CBF(ν) in healthy humans in a reproducible and safe way. Moreover, LBNP was found to be compatible with its application in the MRI scanner enabling quantification of CBF at the brain tissue level. We further consider quantification of CBF by TCD valid under strictly defined circumstances only. Finally, our data support the hypothesis that (mild) alterations in systemic blood flow relate to CBFν, which becomes particularly apparent with ageing.

One of the major issues that needed to be addressed from the onset of this project was concerned with the question: ‘How to disentangle the separate contribution of CO on brain (tissue) perfusion from other regulation mechanisms, such as the cerebral autoregulation?’ This at first required identification of physiological interventions that acutely and reversibly alter CO in a controllable manner while enabling simultaneous monitoring of CBF at the tissue level or in large brain-feeding arteries. Lowering central blood volume by either passive head-up tilt or LBNP decreases CO in a robust and reproducible manner while being patient-friendly and relatively easy applicable (Chapters 4.1 and 4.2). As passive head-up tilt is incompatible with the horizontal orientation and static set-up of an MRI scanner, supine LBNP had the potential to serve as MRI compatible alternative. Implementation of LBNP in a MRI setting was, however, not that easy as hoped for. Head movement in response to the application of sub-atmospheric pressure by conventional LBNP appeared to be substantial, rendering accurate quantification of CBF with ASL-MRI not possible. A newly designed compact LBNP box (Chapter 4.3) minimizes head movement and may therefore be designated a useful device to study the separate effects of alterations in CO on CBF as measured by ASL-MRI. Now application of LBNP became feasible in a MRI setting, this provides new opportunities to study the cerebral hemodynamic response to central hypovolemia with high spatial discrimination and from a multi-parametric view. This may also be of benefit in clinical conditions such as in patients with steno-occlusive disease and possibly focal regions of impaired hemodynamics.

Notwithstanding technical improvements of devices and interventions applicable in both the laboratory and MRI environment, disentangling the distinctive influence of systemic blood flow on brain (tissue) perfusion continues to be complex. Besides a
possible distinct effect of CO on blood supply to the brain, CO is inherently incorporated in systemic BP control as the ratio of BP and peripheral vascular resistance (BP = CO x vascular resistance). The implication of this mathematical dependency is that deliberately induced changes in CO, are intrinsically accompanied by changes in BP and peripheral vascular resistance and vice versa. As the autoregulatory plateau is not entirely flat, changes in BP affect CBF independently from CO, even within what has previously been indicated as the autoregulatory range. In addition, physiological interventions like LBNP and exercise in particular, are accompanied by (small) changes in PaCO₂ for instance due to altered respiration patterns. Thus, understanding the mechanisms involved in CBF responses requires accounting for concurrent changes in both BP and CO₂ as ‘confounding variables’, which by nature cannot be eliminated in living humans. Nevertheless, we alleged further evidence that alterations in CO directly affect CBFv independently from BP and CO₂ and that this relationship becomes more obvious when growing older (Chapters 6.1 and 6.2). Disclosure of a distinct influence of CO on CBF with aging implies that cardiac function and preload becomes important for CBF control later in life irrespective of intact cerebrovascular autoregulatory integrity. The importance of a normal functioning heart in aging subjects is in conflict with the increasing prevalence of cardiac dysfunction in the elderly population. This underscores the need for a fundamental understanding of the relationship between cardiovascular diseases and cognitive functioning. Presently, we may only speculate on the mechanisms behind the effect of aging on the heart-brain relationship; for instance, enhanced vasoconstriction of the cerebral vasculature at older age and/or the increase in preload-dependency of the aging heart. Also a reduced venous compliance in older vs. younger individuals may be proposed as it limits recruitment of blood to sustain the central blood volume in case of fluid or blood loss. Whatever the mechanisms involved, the interrelation between the heart and the brain impinge upon the thus far rather monodisciplinary approach by clinicians. An acute drop in CO is usually a manifestation of common clinical conditions like dehydration, blood loss, myocardial infarction and/or arrhythmia. Our and others data suggest that the impact of such a reduction in CO on the perfusion of the brain should be recognized, especially in the elderly population even without clinical manifestation of cardiovascular disease.

Most of the studies in this thesis report on healthy young and older volunteers. These studies provide the groundwork to expand research to clinical heart-brain axis studies, which will enhance our understanding how the heart affects the brain under (chronic) pathophysiological conditions. Specifically, the importance of systemic hemodynamics for maintaining CBF is probably more prominent when mechano- and chemoregulatory mechanisms have become affected. As soon as intrinsic CBF control does no longer function properly, for instance in patients with small vessel disease or malignant hypertension, the brain becomes more vulnerable to hyperperfusion and even more to
hypoperfusion given the hysteresis in the cerebral pressure-flow relationship. We may speculate that under those circumstances CBF may depend more heavily on CO, thus disclosing an even more tight heart-brain relation. On the other hand, in patients with chronic heart failure the sensitivity of cerebrovascular control mechanisms to secure CBF may change when CO fails to contribute sufficiently. To investigate these hypotheses, we started two new research projects that integrate intra- and extracranial components of CBF control. In one we are studying patients with mild vascular cognitive impairment before and after 14 weeks of extensive aerobic exercise and in the other we are studying patients with severe aortic valve stenosis before and after aortic valve implantation. Both aerobic exercise and aortic valve implantation are considered to improve cardiac fitness and/or function and are expected, according to our hypothesis, to increase cerebral perfusion. Simultaneous quantification of cerebral autoregulatory integrity in these patient groups likely provides additional information on CBF control and whether this may or may not change after improvement of cardiac function.

In 1945, Kety and Schmidt were the first to determine global CBF in man by the use of nitrous oxide according to Fick’s principle. Techniques to measure CBF have continuously been evolved and refined since. Part of the research described in this thesis was concerned with the quantification of CBF by TCD from which the widely used assumption of constant diameter linking CBFv to CBF, has been challenged in the past. Advances in high-resolution MRI at 7 Tesla, enabled us to provide further evidence for a direct vasodilatory effect of CO₂ on large intracranial arteries (Chapter 5.1), suggesting that the vasoactive effects of CO₂ are not limited to small cerebral vessels. In addition, vasoconstriction of the MCA in response to sympathetic activation by dynamic handgrip exercise (Chapter 5.2), strengthens the current concept of sympathetic control of large intracranial vessels. Although, the sympathetic nervous system on CBF control in humans remains debated, our finding suggest a distinct role for the autonomic nervous system in preventing hyperperfusion during elevations in arterial pressure. From aforementioned observations, the question arises whether TCD determined changes in CBFv reflect those in CBF when quantified in the same brain-feeding artery (from now on denoted as MCA blood flow), as the assumption of constant diameter is not met under a variety of circumstances. We observed that under high hypercapnic conditions, TCD measured CBFv underestimates underlying changes in MCA blood flow whereas it slightly overestimates the MCA blood flow response during exercise-induced sympathetic activation. It is not unlikely that, for instance, with heavy exercise this offset will become even larger. However, given the conditions of the studies described in this thesis, we nevertheless feel confident that the observed changes in CBFv measured by TCD largely tracked those in MCA blood flow. The next question we addressed was whether flow velocity changes in a large brain-feeding artery do represent brain tissue...
flow. We demonstrated that whole-brain CBF measurements by ASL-MRI do not support the claim that changes in CBFv measured in the MCA reflect those in CBF at the tissue level in the underlying flow territory or within the activated brain region in response to small muscle group exercise (Chapter 5.3). There was an order of magnitude difference in the cerebrovascular response between these two modalities. Shunting of arterial blood directly to the venous side through arteriovenous anastomosis might be an explanation for this discrepancy. However, the presence of pre-capillary arteriovenous shunts has not been evidenced yet, indicating the need to further explore the relation of arterial blood flow and tissue perfusion of the brain.

**CONCLUDING REMARKS**

‘Should we consider the cardiovascular system as an integral component of CBF control?’ that is the question this thesis has primarily aimed to answer. Given the findings presented in this thesis we conclude that in healthy individuals CO is important for CBF control, especially when growing older. Since cardiac dysfunction is a feature of the aging population, this underscores the need to better understand, diagnose and treat cardiovascular diseases in relation to the perfusion of the brain and, in turn, cognitive performance. The finding that TCD determined changes in CBFv measured in a large brain-feeding artery do not match those in CBF at the tissue level as quantified with ASL-MRI, calls into question the nature of cerebral perfusion from which implications could be far reaching for either or both measurement modalities. We experienced that different viewpoints from different disciplines elicits refreshing and important (research) questions. This indicates that collaborating with various expertise fields is required to provide full insight into the increasingly important research fields studying the connection between the heart and the brain. Although this thesis provided the groundwork, we are situated at the very beginning of a more integrative understanding how the brain manages its perfusion especially at conditions where the heart dysfunctions such that clinical studies on the heart-brain connection are imperative.