Changes in total cerebral blood flow and morphology in aging

Spilt, A.

Summary and conclusions

Chapter 11

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In chapter two we studied the reproducibility of flow measurements in the basilar artery and the internal carotid arteries using phase contrast MRI. Two types of flow measurement were performed. One used retrospective gating based on the peripheral pulse and the other averaged the flow during several heart cycles. The reproducibility was assessed by measuring the flow in a group of volunteers repeatedly. The flow measurements in the volunteers were performed with and without repositioning and at two different occasions. This showed that this flow measurement was reproducible in the short term as well as in the long term. Accuracy was assessed by measuring the flow in a phantom. The results demonstrated that both triggered and non triggered measurement of cerebral blood flow are accurate. Both triggered and non triggered flow measurements slightly underestimated the flow.

The conventional manual segmentation of vessel contours is tedious, time-consuming, and leads to significant inter- and intraobserver variabilities. In order to perform reliable measurements of total cerebral blood flow an automated method was developed and tested in chapter three. Two automatic methods for segmentation of vessel contours are provided and tested against the manual method. The automatic segmentation approaches were based on fitting a 3D parabolic velocity model to the actual velocity profiles. In the static method, the velocity profiles were averaged over the complete cardiac cycle, whereas the dynamic method takes into account the velocity data of each cardiac time bin individually. The results demonstrated that the automatic dynamic method performed significantly better than the manual method. This method was incorporated in our analysis software (Flow®).

In chapter four, the phase contrast MRI technique for assessing total cerebral blood flow was compared with cerebral perfusion imaging in terms of their ability to measure the cerebrovascular reserve capacity. The cerebrovascular reserve capacity was defined as the percentage increase in TCBF (in the phase contrast method) or rCBV after the administration of a drug with cerebral vasodilating properties (acetozolamide). Acetozolamide is a drug causing cerebral vasodilatation and recruitment of collaterals. This results in an increase in CBF and CBV. The TCBF was measured with the method used in chapter 2. The rCBV was derived from the perfusion images performed during the administration of an intravascular contrast agent. Both methods were shown to be reproducible but there was a lack of agreement between the two methods. This lack of agreement can be explained by the different parameters used in phase contrast MRI (TCBF) as compared to perfusion MRI (rCBV).

In chapter five the influence of hypoxia on the cerebral blood flow was studied as well as the influence of inhibition of the NO synthase during normoxic and hypoxic conditions on cerebral blood flow. Hypoxia caused an increase of TCBF. We showed that the increase in TCBF under hypoxic conditions is diminished when a nitric oxide synthase inhibitor (NG-monomethyl-L-arginine; L-NMMA) is administered. Under normoxic conditions this inhibitor has no effect. This demonstrated that hypoxia induced cerebral vasodilation is mediated by NO.

The basal cerebral blood flow decreases with aging. In chapter six we showed that the inhibition of NO with L-NMMA has no influence on the cerebral blood flow in the young. On the other hand it does influence cerebral blood flow in elderly subjects. This points out that the NO pathway is activated in the elderly to sustain cerebral blood flow under normal conditions, whereas in the young this mechanism is only active under stress conditions (e.g. hypoxia). This suggests that in the elderly there is less reserve left of the cerebrovascular reserve capacity, which may make the elderly more vulnerable for decreases in blood flow than younger subjects.

The cerebral blood flow is diminished in subjects with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as is shown in chapter seven. We did not find a difference in the cerebrovascular reserve capacity between subjects with CADASIL and subjects without CADASIL. So, apparently in CADASIL baseline CBF is diminished although the ability to compensate for the lower CBF is intact. The reason why the lower basal CBF is not compensated needs to be elucidated.

In chapter eight we compared quantitative MTI parameters of the whole brain between a group of elderly individuals with minimal WMH, a group of elderly individuals with abundant WMH, and a group of young healthy volunteers. No differences were observed between the two groups of elderly, whereas both elderly groups differed significantly from the group of young individuals. To further reduce the influence of WMH on these results, we performed quantitative MTI analysis on normal appearing white matter selectively, and again we did not find a difference between the two groups of elderly subjects. These data suggest that age-related changes in normal appearing brain tissue are based on a different pathogenesis than WMH.

In chapter nine we studied different types of WMH with MTI to assess whether the differences that are known to occur in WMH from histological studies can also be identified with quantitative MRI sequences. We demonstrated that WMH in a periventricular location have different MTR characteristics as compared to deep white matter hyperintensities. Furthermore, there was a difference between frontal and occipital periventricular WMH. These data demonstrate that WMH, although looking similar on conventional T_2 weighted sequences, show different rates of tissue destruction. Therefore it is not surprising that WMH lesion load assessment based on T_2 weighted images show a limited correlation with functional measures, since they do not take into account the existing differences in tissue destruction in those lesions.

Finally, in chapter ten we studied two groups of elderly: a group of elderly with very good cognition and a group of equally old subjects with dementia. In these groups we compared indicators of structural brain damage and total cerebral blood flow. The load of WMH as well as quantitative MTI measures were found to be significantly different between these two groups. In addition, total cerebral blood flow was observed to be significantly lower in the patients with dementia. This study demonstrates that a variety of structural and functional changes may be responsible for dementia. The influence of these changes on each other and on the final functional outcome (cognition) remains to be elucidated.