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Blood pressure in old age : exploring the relation with the structure, function and hemodynamics of the brain

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The background of the entire page is a grayscale marbled pattern, resembling natural stone or marble. It features a complex network of dark, irregular veins and blotches of varying shades of gray and white, creating a textured and organic appearance.

Chapter 8

Summary and general discussion

The main purpose of the work in this thesis was to explore the role of blood pressure in relation to cerebral structure, neurocognitive functioning and hemodynamics of the brain in old age. Therefore, we sought to determine whether discontinuation of antihypertensive therapy in persons aged 75 years and over with mild cognitive deficits and using antihypertensive medication (the Discontinuation of ANtiHypertensive Treatment in Elderly people [DANTE] population) would improve their cognitive and psychological functioning. The assumption was that the increase in blood pressure after the discontinuation of antihypertensives would lead to a direct increase in cerebral blood flow and, as a consequence, to an improvement in cerebral functioning. An additional objective was to investigate possible underlying mechanisms in the relation between blood pressure and neurocognitive functioning. To enable this, brain MRI was used to determine whether (lower) blood pressure was associated with (micro) structural damage, cerebral small vessel disease and blood flow in the brain, and also whether the presence of cerebral (micro)structural damage was related to neurocognitive functioning.

Summary

Lower blood pressure and cerebral (micro)structure

In **Chapter 2** it was determined whether a lower blood pressure was associated with cerebral structural damage as reflected in total (cortical) grey matter, white matter and subcortical brain volumes in the DANTE population. It was shown that a lower blood pressure was associated with smaller volumes of the thalamus, putamen, and hippocampus, and that these smaller volumes were related to decreased neurocognitive functioning.

Subsequently, we identified whether blood pressure was related to cerebral small vessel disease and to cerebral microstructural integrity. The findings, described in **Chapter 3**, show that current blood pressure was not associated with overt signs of cerebral small vessel disease comprising white matter hyperintensity volume, lacunar infarcts and cerebral microbleeds. Nevertheless, a lower blood pressure appeared to be associated with a lower microstructural integrity specifically in the grey matter.

Discontinuation of antihypertensive treatment and cognitive, psychological and general daily functioning

It was further evaluated whether temporary discontinuation of antihypertensive treatment improves cognitive, psychological and general daily functioning in older persons aged 75 years and over with mild cognitive deficits who were using antihypertensive treatment (the DANTE population). The hypothesis was that increasing blood pressure by discontinuation of antihypertensive treatment would improve cognitive, psychological and general daily functioning. The results, described in **Chapter 4**, indicate that discontinuation of antihypertensive treatment indeed increases blood pressure. However, the four-month discontinuation of antihypertensive treatment did not improve cognitive, psychological and general daily functioning. Similarly, in subgroups of older persons with orthostatic hypotension, a higher age, decreased cognitive or general daily functioning, more signs of overt cerebral small vessel disease, or lower cerebral blood flow, also showed no effect of the discontinuation of antihypertensive treatment on cognitive, psychological and general daily functioning.

Blood pressure and cerebral hemodynamics

The aim of **Chapter 5** was to assess whether blood pressure was associated with cerebral blood flow. In our study population no association was found between blood pressure and cerebral blood flow; also, there was no relation between changes in blood pressure on standing and cerebral blood flow. Similarly, in subgroups of older persons with more signs of overt cerebral small vessel disease, diminished cognition, or diabetes mellitus, blood pressure was not related to cerebral blood flow. Although the longitudinal data showed that after four-months discontinuation of antihypertensive medication blood pressure did increase, cerebral blood flow remained unaffected.

Cerebral (micro)structure and cognitive functioning

In **Chapter 6** it was determined whether microstructural integrity was associated with features of cerebral small vessel disease and brain atrophy, and whether microstructural integrity was associated with cognitive and psychological function, independent of cerebral small vessel disease. Data show that a lower cerebral white matter microstructural integrity was associated with signs of overt cerebral small vessel disease as well as with worse executive cognitive functioning, psychomotor speed, memory and overall cognition. These associations were independent of

periventricular and subcortical white matter hyperintensities and the presence of lacunar infarcts or cerebral microbleeds, but strongly attenuated after adjusting for brain volume. In addition, in **Chapter 7** we evaluated the association of age and cerebral small vessel disease with the expression of structural covariance networks, representing specific patterns of grey matter atrophy. In this study the association between the expression of structural covariance networks and cognitive functioning and the role of the presence of cerebral small vessel disease in this association was also assessed. The results indicate that a lower expression of grey matter structural covariance networks is associated with higher age and with signs of cerebral small vessel disease comprising white matter hyperintensity volume, lacunar infarcts and cerebral microbleeds. Decreased expression of specific networks including, the temporal, occipital lobe and cerebellum, was related to decreased cognitive functioning, independently of cerebral small vessel disease.

General discussion

Integration of our study findings into current knowledge

The relation between blood pressure and structure, function and hemodynamics of the brain is complex. The findings described in this thesis indicate that a lower blood pressure, rather than a higher blood pressure, is indeed associated with cerebral (micro)structural damage. Nevertheless, in contrast to these findings, the DANTE study Leiden further revealed that an increase in blood pressure, due to the discontinuation of antihypertensive treatment, did not improve cognitive functioning. Also, increased blood pressure did not increase cerebral blood flow.

It is true that, to date, observational evidence suggests that in frail older persons a lower, rather than a higher blood pressure, is associated with an increased risk of cognitive decline.¹⁻⁴ Moreover, specifically in older persons with more cerebral small vessel-related damage, a lower blood pressure may compromise cerebral blood flow and may thereby result in lower cognitive functioning.⁵⁻⁷ Consequently, uncertainty arose about the desirability of lowering blood pressure with antihypertensive medication in frail older persons, and older persons with established cerebral small vessel disease.^{2,5,6} Although in the DANTE population overt signs of small vessel disease were relatively high compared with other

studies among older persons, our results show that also in subgroups of more vulnerable persons, discontinuation of antihypertensive medication had no (immediate) effect on cognitive functioning. Besides, blood pressure was not associated with cerebral blood flow, and the increase in blood pressure after discontinuation of antihypertensive medication did not improve cerebral blood flow after four months.

Thus, the findings of the studies in this thesis seem to be contradictory. Although associations were demonstrated between a lower blood pressure and cerebral damage, there was no indication that cognitive functioning and cerebral blood flow increased after blood pressure increased. An important reason for our finding that a lower blood pressure is associated with (micro)structural damage, might be that both are the result of cardiovascular damage due to the harmful effects of a higher blood pressure earlier in life. Furthermore, it is possible that a short-term increase in blood pressure cannot immediately increase cerebral blood flow and thereby improve cognitive functioning. Essential to our hypothesis was the idea that an increase in cerebral blood flow would improve cognitive functioning. However, because the increase in blood pressure did not result in an increase in cerebral blood flow, this could not lead to an improvement in cognitive functioning. Possible explanations for this are that i) because of a still intact cerebral autoregulation it is not possible to increase cerebral blood flow by increasing blood pressure, or ii) that hypoperfusion is related to irreversible neurovascular damage⁸ and, therefore, cerebral blood flow cannot be increased by a higher blood pressure in already damaged areas. On the other hand, because in old age a lower blood pressure is associated with worse health outcomes, and a short-term increase in blood pressure showed no immediate cognitive improvement, a continuously lower blood pressure due to the use of antihypertensive medication may be associated with an additional or a faster decline in cognitive functioning in the long term.

Strengths and limitations

The DANTE study Leiden is the first trial to assess in a large sample of older persons whether discontinuation of antihypertensive treatment leads to improved cognitive functioning. Notably, our study population of older persons using antihypertensive medication and with mild cognitive deficits, has been underrepresented in randomized clinical trials to date (e.g. the HYVET trial⁹)

that showed that antihypertensive medication, and thus lowering instead of increasing the blood pressure, improves cognition. Moreover, the design of the DANTE study Leiden allowed to collect an extensive battery of MRI data both at baseline and at four-months follow-up. These additional MRI data of the DANTE population enabled us to study the relation between cerebral (micro)structure and cerebral blood flow cross-sectionally and to assess whether cerebral blood flow would increase over a four-month period as a result of the increased blood pressure.

Despite the strengths of the design of the DANTE study Leiden, the exclusion of persons with severe cardiovascular disease may have resulted in a population with a possibly intact cerebral autoregulation, thereby making it impossible to increase cerebral blood flow. Importantly, due to the cross-sectional nature of our studies on the association of blood pressure and (micro)structural damage, and on the association of (micro)structural damage and cognition, it remains undetermined whether these are temporal or causal relationships.

Implications for clinical practice and future studies

The DANTE study Leiden showed no short-term advantage of discontinuation of antihypertensive treatment on cognition and cerebral blood flow. Therefore, the clinical value and implications of this study are modest. However, the DANTE study Leiden was methodologically innovating, as it was the first study to examine discontinuation of lifelong medications in older persons.¹⁰ Moreover, this thesis showed that microstructural integrity and the expression of structural covariance networks are important factors that, in addition to cerebral small vessel disease, seem to play an important role in the cognitive health of older persons. These data are certainly of interest to clarify the cerebral mechanisms involved in cognitive functioning, and an important field for additional basic and clinical studies.

Several issues require further investigation. It is still possible that very old, frail persons with cognitive impairment, severe cerebral small vessel disease and, most importantly, impaired cerebral autoregulation would benefit from (long-term) discontinuation of antihypertensive therapy and increased blood pressure. Also, life-course studies in large populations, such as ongoing population-based cohort studies (including the Rotterdam study and the LifeLines study) have a unique opportunity to investigate over longer periods of time whether a temporal relation

exists between blood pressure on the one hand and cerebral damage/functioning and cognition on the other. These studies might elucidate blood pressure changes throughout life and the ways in which cerebral hemodynamics, cerebral damage and cognition are related to these changes. In addition, to further disentangle the relation of blood pressure with cerebral damage and cognition, it is worthwhile to take into account the role of cardiac function in this relation. Aging is associated with stiffening of the aorta and with pulsatility, which is generated by the left cardiac ventricle and increased by aortic stiffening.¹¹ An increased or more intense pulsatility can damage high-flow organs, such as the brain.¹² In this respect, it has been proposed that the cerebral arterioles regulating cerebral blood flow may be damaged by excessive intracranial pulsatility and are an essential factor in causing cognitive decline in older people. In a longitudinal study among older persons (mean age of 88 years), arterial stiffness (as measured by carotid-femoral pulse wave velocity) was predictive of cognitive decline whereas blood pressure alone was not.¹³ It is also reported that a higher pulsatility is associated with lower brain volumes, increased cerebral small vessel disease and worse cognitive functioning.^{14;15} For that reason, measures of cardiac function, such as pulsatility, could be included in future studies.

In conclusion, the studies in this thesis suggest that, in older persons, a lower blood pressure is involved in (micro)structural brain damage which, in turn, is related to lower cognitive function. Although the findings described in the thesis parallel the suggestions that a lower blood pressure at old age might be harmful, increasing the blood pressure did not improve cerebral blood flow or reverse cognitive deficits in the short term.

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