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Author: Sabayan, Behnam
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Key Findings and General Discussion
Increasing life span and decreasing birth rate have given rise to a rapid increase of the aged population in many countries, both in absolute and relative terms. This demographic transition has resulted in increasing number of older people with disorders linked to the accelerated brain aging such as dementia. Different lines of evidence from epidemiological, pathological and neuroimaging studies indicate that exposure to cardiovascular risk factors are closely related to structural and functional changes in the brain. This cumulative evidence on the role of vascular factors in acceleration of brain aging has been reflected in the statements by the American Heart Association / American Stroke Association (AHA/ASA) and the National Institute of Health (NIH) emphasizing that cardiac diseases and vascular pathologies should be considered as potentially modifiable risk factors for cognitive impairment and dementia. Despite achievements in the understanding of the brain structure and function, the mechanisms by which cardiovascular factors contribute in brain aging are not fully understood.

The aims of this chapter are to (1) review the key findings of this thesis in the context of current knowledge and evidence (2) present pathophysiological models on potential contribution of cardiovascular and hemodynamic factors in development and progression of brain aging, (3) address the methodological issues and (4) provide directions for future research.
Lowering blood pressure: a double-edged sword for the aging brain

Higher midlife blood pressure increases risk of cognitive impairment and stroke, whereas studies on late-life hypertension have shown mixed findings\textsuperscript{5, 6}. There is a complex interaction between blood pressure and the brain. Long-lasting hypertension damages cerebral vessels through hemodynamic stress and puts subjects at high risk for cerebral small vessel disease and stroke\textsuperscript{7}. Once vascular pathologies are established and the brain tissue is extensively damaged, the brain fails to play a central role in regulation of blood pressure\textsuperscript{8}. If this situation coincides with a decrease in cardiac function, a drop in blood pressure may further decrease brain perfusion and accelerate brain aging\textsuperscript{9}. In line with this notion, life course studies have shown that men who develop dementia experience a steeper increase in systolic blood pressure from midlife to late life, followed by a steeper decrease in late life\textsuperscript{10}. The dynamic connection between the brain and blood pressure has made it difficult to give a single answer to the clinical question whether lowering blood pressure can protect the brain in late life. A limited number of clinical trials investigated the effect of antihypertensive medications in prevention of dementia and stroke in the oldest old. Most of these studies showed some benefits\textsuperscript{11, 12}. However, such trials generally recruited healthy participants with low levels of co-morbidities and frailty. This has raised a concern whether findings of these studies can be generalized to general populations of very old people in which functional disability and multi-morbidity are relatively common\textsuperscript{13}. In the second and third chapters of this thesis the association of high blood pressure with risk of cognitive decline and stroke in very old subjects is examined. The findings indicate that higher blood pressure is not associated with adverse brain outcomes. In addition, in subjects with disability, high blood pressure might be even beneficial. These results possibly imply that the biological age rather than chronological age should be a basis for treatment of high blood pressure in older people. In very old people with higher degrees of frailty and morbidities, higher blood pressure might be needed to ensure perfusion of different organs including the brain\textsuperscript{14, 15}.

Limitations of the hypertension hypothesis in old age: significance of variability

Although hypertension has been recognized as a strong risk factor for cerebrovascular damage, current evidence shows that the predictive value of high blood pressure for stroke attenuates with age\textsuperscript{6}. Based on the common hypoth-
esis of hypertension, the main determinant of blood pressure-related end organ damage is higher levels of blood pressure. However, recent data suggest that other parameters such as blood pressure variability also contribute in increasing risk of vascular events. Blood pressure fluctuates around average values over short and long period of times. Exaggerated minute-to-minute and diurnal blood pressure variability has been mentioned as a cardiovascular risk indicator. Apart from short-term blood pressure variability, a substantial variation in blood pressure exists when a subject is observed over months with repeated clinical visits. Recent studies have shown that visit-to-visit blood pressure variability, independent of average blood pressure, is associated with higher risk of stroke, carotid artery atherosclerosis and cerebral small vessel disease in older subjects. In the fourth chapter of this book, it is demonstrated that higher visit-to-visit blood pressure variability has a strong relationship with cognitive impairment, manifestations of cerebral small vessel disease and lower hippocampus volume. Higher blood pressure variability might reflect a long-term hemodynamic instability that puts stress on the vascular endothelium and leads to alterations in brain structure and function. Furthermore, increased fluctuations in systemic blood pressure might result in repeated episodes of cerebral hypoperfusion causing neuronal injury and accelerated brain aging. Increase in age is associated with a decrease in cardiac function, alternations in the mechanical and the structural properties of the vessels and diminished activities of blood pressure regulatory mechanisms. Therefore, it seems that standard blood pressure measurements are not adequate for the evaluation of cardiovascular risk in older people. Most of the current guidelines put emphasis on reduction of blood pressure in older subjects and less attention has been paid to management of blood pressure variability. Further studies are needed to evaluate whether strategies to lower blood pressure variability can contribute in preservation of the brain structure and function in older subjects.

**Blood pressure dysregulation, cerebrovascular dysfunction and brain aging: A pathophysiological model**

Normal regulation of blood pressure is necessary for adequate organ perfusion and prevention of vascular damage. In the presented pathophysiological model, hypertension, hypotension and blood pressure variation contribute in cerebrovascular damage and promote cerebral hypoperfusion (figure 1). Hemodynamic stress imposed by hypertension damages large and small cerebral vessels and results in endothelial dysfunction. Impaired function of the vascular endothelium leads to efflux of abnormal proteins and waste metabolic products.
In addition, neurovascular unit loses its capacity to adjust the regional perfusion according to the metabolic demands of neurons. Long-lasting cerebral hypoperfusion results in neuronal energy crisis which ultimately lead to neuronal cell death. Extensive brain tissue damage may perpetuate the situation by further dysregulation in blood pressure and cerebral blood flow.

**Impaired cardiac function: an emerging risk factor for brain aging?**

Experimental studies in animal models have shown that chronic cerebral hypoperfusion results in neuronal energy crisis, glial cell activation, accelerated amyloid beta accumulation and blood brain barrier disruption which all contribute to development of neuronal dysfunction and injury. Likewise, human studies have revealed that lower cerebral blood flow is associated with higher risk of developing white matter lesions and brain atrophy. It is known that the heart
plays a pivotal role in generation and regulation of cerebral blood flow\textsuperscript{24, 25}. Despite activities of multiple regulatory mechanisms, it has been shown that patients with New York Heart Association (NYHA) class III/IV heart failure have about 30% lower total cerebral blood flow compared to healthy controls\textsuperscript{26}. On the other hand, interventions to improve cardiac functioning such as cardiac transplantation have been shown to restore cerebral hemodynamics to the normal levels\textsuperscript{24}. Patients with congestive heart failure frequently present with cognitive impairment\textsuperscript{27}. Decline in cerebral blood flow and hemodynamic abnormalities have been suggested to mediate the association between congestive heart failure and cognitive impairment\textsuperscript{25}. A large prospective study showed that congestive heart failure in older people independent of cardiovascular comorbidities associates with higher risk of dementia\textsuperscript{28}. Recent reports suggest that not only presence of congestive heart failure but also a graded decrease in cardiac functioning might be a risk factor for brain aging\textsuperscript{29}. Findings of the chapters five, six and seven of this thesis show that the association between cardiac function and impaired cognition is not limited to patients with heart failure. These data suggest that a graded decrease in cardiac function as reflected in cardiac hemodynamics and serum NT-proBNP level, a marker of ventricular dysfunction, is associated with cognitive decline in general populations of old and very old subjects as well as in older subjects at risk of cardiovascular disease without heart failure. In line with these results, role of the heart-brain axis in brain aging has been suggested\textsuperscript{30}. Long-lasting decline in cardiac functioning in interaction with pathologies in the systemic and cerebral circulations results in chronic brain hypoperfusion (figure 2). Chronic brain hypoperfusion gives rise to neuronal energy crisis and this ultimately leads to neuronal cell death. This cascade of events may put subjects at risk of accelerated brain aging.

**Cognitive impairment in old age: a red flag for future stroke**

Postmortem and neuroimaging studies have confirmed that not only patients with vascular dementia but also patients with Alzheimer’s disease carry a high load of brain vascular pathologies\textsuperscript{31}. In this thesis, it is demonstrated that patients with Alzheimer’s disease and vascular dementia have a pronounced disturbance in their cerebrovascular hemodynamics (chapter eight). Accordingly, it has been suggested that cognitive impairment might reflect covert brain vascular pathologies, predisposing subjects to higher risk of stroke\textsuperscript{32}. A number of longitudinal studies have investigated whether cognitive impairment is associated with increased risk of stroke and whether cognitive assessment can be considered as a tool for identification of subjects at high risk of stroke\textsuperscript{33, 34}.
Figure 2. Proposed pathophysiological model on the link between abnormalities in the heart-brain axis and accelerated brain aging. Long-lasting decline in cardiac functioning in interaction with pathologies in the systemic and cerebral circulations results in chronic brain hypoperfusion. Chronic brain hypoperfusion gives rise to neuronal energy crisis and this ultimately leads to neuronal injury and cell death. This cascade of events renders subjects vulnerable for development of accelerated brain aging.
Most of these studies reported that middle aged or younger elderly subjects with lower cognitive performance were at a higher risk for developing stroke. In the ninth chapter of this thesis, we showed that lower cognitive function measured by mini-mental-state examination (MMSE) was associated with risk of first-time stroke in the oldest old. Furthermore, MMSE score appeared to be a better predictor for stroke when compared to the well-established Framingham stroke risk score. Collectively, available data suggest that older subjects with cognitive impairment should be considered among high-risk groups for development of future stroke.

**Vascular endothelium; roles in regulation of cerebral blood flow**

Cerebral autoregulation is the inherent ability of the brain to maintain a relatively constant level of cerebral blood flow despite fluctuations in perfusion pressure\(^{35}\). Changes in cerebral vascular tone play a key role in regulation of cerebral blood flow. Vascular tone in the cerebral circulation is regulated by several mechanisms\(^{36}\). One major mechanism involves endothelial factors\(^{37}\). Endothelium produces and releases potent relaxing and contracting factors that regulate tone of underlying vascular muscle and may also influence vascular growth\(^{38}\). Cardiovascular risk factors such as hypertension and diabetes have been linked to a decline in cerebral perfusion and it has been postulated that endothelial dysfunction due to chronic exposure to these risk factors is responsible for a decline in cerebral blood flow\(^{39}\). In line with this hypothesis, data presented in the tenth chapter of this thesis demonstrate that two serum markers of endothelial activation (von willebrand factor and tissue plasminogen activator) are associated with lower levels of cerebral blood flow. Given the critical role of cerebral perfusion in the maintenance of brain structure and function, preservation of the vascular endothelium can be a potential approach for delaying brain aging.

**Cerebral blood flow; a determinant of survival in old age**

The brain has an extraordinary metabolic demand\(^{40}\). This high metabolic demand is met by adequate and constant levels of cerebral blood flow that deliver energy, nutrient and oxygen to the brain\(^{41}\). Normal function of the brain is crucial for maintenance of health and homeostasis\(^{42}\). The brain is involved in regulation of stress response, circadian rhythm, endocrine system, fluid and elec-
trolyte balance, body energy expenditure and several other key pathways that act in concert to keep our body in a steady state\textsuperscript{43, 44}. It has been shown that animal models with a state of hypoperfusion live shorter and develop weight loss\textsuperscript{45}. In human, development of stroke is associated with disturbances in autonomic control, impaired sleep cycles and immune response\textsuperscript{46, 47}. In the eleventh chapter of this thesis, the association between cerebral blood flow and 12-year survival in older people at risk for cardiovascular disease is investigated. The observed associations of cerebral blood flow with all-cause; cardiovascular and non-cardiovascular mortality might highlight the importance of cerebral perfusion in maintenance of health and survival in older people. Interestingly, all these associations were independent of socio-demographic and cardiovascular risk factors. There are a limited number of studies investigating the link between decreased brain blood flow and mortality. For instance, a recent study showed that lower cerebral blood flow is a strong predictor for mortality in patients with heart failure\textsuperscript{48}. This finding might further highlight the importance of sufficient cerebral blood flow in maintenance of health and survival. Strategies to slow down decline of cerebral blood flow might decelerate rate of brain aging and improves survival in older people.

**Methodological considerations**

Scientific background, accurate observation, experimentation and applicability have been regarded as the fundamental elements of clinical research\textsuperscript{49}. In this thesis, we build up our hypotheses based on the current evidence on the link between cardiovascular factors and age-related disorders of the brain. While findings of this thesis are in line with growing evidence exist supporting a role for vascular factors in brain aging, cardiovascular aging can be a cause or an epiphenomenon for brain aging\textsuperscript{50, 51}. Hence, further life-course studies are needed to show the temporal relationship between dysregulations in cardiovascular system and changes in the brain structure and function. Such studies might unravel how early life events influence the susceptibility of the brain to cardiovascular and hemodynamic abnormalities. Findings presented in this thesis come from three well-established cohorts of older subjects. Despite strengths in the design, inclusion of participants and availability of a wide range of variables, observational nature of these studies limits causal inference from the results. Therefore, interventional studies are needed to test whether correction of cardiovascular and hemodynamic abnormalities can decelerate process of brain aging.

It is important to keep in mind that the translation of findings from clinical studies to clinical practice has been always a challenge\textsuperscript{52}. While clinical studies
usually look at outcomes in a population under study, in real life clinicians need to make decision for individual subjects. In this thesis we emphasized on the associations independent of sociodemographic and cardiovascular factors which might serve as potential confounders. Nonetheless, large proportions of older subjects have multiple cardiovascular risk factors and co-morbidities. These cardiovascular factors might individually or in interaction with each other contribute to brain aging. Further sophisticated analyses are warranted to account for cumulative contribution of multiple factors in development and progression of brain aging.

Future directions

Despite major efforts have been made, our understanding about etiology of abnormal brain aging is still limited. Current evidence indicates that the brain aging is a complex and multi-facet phenomenon. This complexity has been reflected in the etiology of age-related disorders of the brain like dementia. It is well-described that a combination of factors act in concert in the pathogenesis of cognitive impairment and no single mechanism can explain the pathologic features observed in the brain of patients with dementia. In this setting, studies which targeted specific brain pathologies, such as amyloid β deposition, have failed to show any improvement in cognitive function. Future studies might be needed to focus on strategies which cover multiple aspects of brain aging. It has been shown that long-lasting cerebral hypoperfusion promotes oxidative stress, activation of inflammatory pathways, endothelial dysfunction, and amyloid β deposition. Therefore, optimization of brain perfusion by prevention of pathologies in the heart-brain axis and neurovascular unit might modulate pace of aging in the brain. In addition, findings of this thesis suggest that the association between cardiovascular factors and features of brain aging, like cognitive performance, might be not only age dependent but also functional status dependent. This calls for future studies investigating individualized approach in treatment of cardiovascular risk factors in order to preserve brain structure and function.
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