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**Author:** Sabayan, Behnam  
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The structural and functional integrity of the brain depends on the adequate and constant supply of energy and oxygen through cerebral blood flow. Hence, factors playing role in generation, delivery and regulation of brain blood flow may contribute in the pace of aging in the brain. Accelerated brain aging presents with pathological changes which impair cognitive function. This thesis aimed to show that cardiovascular and hemodynamic factors are related to the structural and functional features of brain aging. Findings of this thesis might open new avenues in prevention and progression of the accelerated brain aging.

Chapter 1 provides a background on the demographic, biologic and cardiovascular aspects of brain aging. In Chapter 2, we showed that higher blood pressure is associated with lower cognitive decline in very old age. This association was more prominent in older people with higher disability in their activities of daily living. This has brought us to the next step to test whether levels of cognitive and functional disability moderate the association between high blood pressure and stroke in very old age. The findings presented in the Chapter 3 indicate that higher blood pressure is associated with lower risk of stroke in very old subjects with higher degrees of disability.

Chapter 4 expands our current knowledge on the association of higher visit-to-visit blood pressure variability with impaired brain structure and function. Previously it has been shown that increased blood pressure variability is related to higher risk of stroke. Consistently, we showed that visit-to-visit blood pressure variability might put subjects at a higher risk for accelerated brain aging. In Chapters 5, 6 and 7, we focused on the association between level of cardiac function and brain aging. We observed that a strong association exists between a graded decrease in cardiac function and lower brain volumes and cognitive performance. Furthermore, we observed that in very old age, subjects who have both low blood pressure and left ventricular dysfunction have a higher risk for cognitive decline. These findings support the hypothesis that strategies to preserve cardiac function might also prevent abnormal brain aging in older subjects.

Disturbances in cerebrovascular hemodynamics have been implicated in the pathogenesis of cognitive impairment. Several studies have investigated whether patients with dementia have a lower cerebral blood flow and higher cerebrovascular resistance. In a meta-analysis (Chapter 8) we demonstrated that in patients with two most common forms of dementia; Alzheimer’s disease and vascular dementia have profound disturbances in their cerebrovascular hemodynamics. However, the severity of disturbances was higher in patients with vascular dementia.
Chapter 9 deals with the identification of very old subject at risk for stroke using cognitive assessment. This chapter shows that in late life, conventional cardiovascular risk factors lose their predictive value while impaired cognitive function better predicts risk of stroke. This finding highlights that the assessment of cognitive function might be an easily accessible tool to recognize older subjects at risk of stroke.

In Chapter 10, we showed that increased serum markers of endothelial dysfunction are associated with lower levels of cerebral blood flow in older subjects at risk for cardiovascular disease. This is in line with previous lab findings indicating that endothelial cells play an important role in regulation of cerebral blood flow. Furthermore, it supports the hypothesis that cardiovascular risk factors accelerate process of brain aging, through promotion of the endothelial dysfunction and decrease in cerebral blood flow.

The brain is a key regulator of homeostasis. Previous studies have shown that subjects who carry a higher load of cerebrovascular damages have a shorter survival independent of cardiovascular risk factors and diseases. Given the significance of cerebral blood flow in the maintenance of brain structure and function, in Chapter 11, we showed that older subjects with lower cerebral blood flow have a shorter survival. This observation merits future studies investigating how preservation of cerebral blood flow influence health and survival in old age.

Chapter 12 reviews the key findings of this thesis and discusses them in the context of current knowledge and evidence. Based on the findings of this thesis, we suggested pathophysiological models on the contribution of cardiovascular and hemodynamic factors in development and progression of brain aging.