Role of cardiac biomarkers in cognitive impairment and functional decline

Mahin Rad, S.

CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Discussion

In this thesis, the current knowledge on the heart-brain connection was extended by providing further evidence for potential mechanisms linking suboptimal cardiac function with cognitive impairment and functional decline. Another important aspect of this thesis is the preliminary results on the role of cardiac hormones in cognitive impairment, indicating a complex interplay between the heart and the brain that might extend beyond vascular factors. This chapter reviews the key findings of this thesis, discusses them in the context of current knowledge and provides perspectives for future research.

ECG-derived Markers of Cardiac Dysfunction, Cognitive Impairment and Functional Decline

Cardiac autonomic dysfunction as reflected in heart rate and heart rate variability

Elevated heart rate and reduced heart rate variability are markers of cardiac autonomic dysfunction[1]. These markers reflect failure of the autonomic nervous system in regulation of cardiovascular homeostasis[2]. The prognostic importance of high heart rate and low heart rate variability have been demonstrated for a wide range of pathogenic states and for mortality. For example, low heart rate variability has been linked to inflammation[3], insulin resistance[4] and cardiovascular factors[2, 5]; and high heart rate has been related to atherosclerosis and endothelial dysfunction[6]. Interestingly, it has been hypothesized that high heart rate and low heart rate variability are potential markers of frailty and functional decline[7]. One potential mechanism linking these markers with functional decline might be through the detrimental effect of cardiovascular factors on both cardiac autonomic control and functional status[5, 8]. In Chapter 2, we show that higher heart rate and lower heart rate variability are directly linked with higher risk of functional decline independent of cardiovascular risk factors and comorbidities. These findings highlight the link between cardiac autonomic imbalance and development of functional decline in future, even in

subjects with preserved functional status at baseline. In this setting, future research should determine whether interventions aimed at preservation of cardiac autonomic control are beneficial for functional status. In **Chapter 3**, we tested whether cardiac autonomic dysfunction – as measured by heart rate variability – also relates to cognitive decline in older subjects. **Chapter 3** shows that lower heart rate variability associates with worse performance and steeper decline in executive function of older subjects at high cardiovascular risk. Our findings indicate a direct link between low heart rate variability and accelerated cognitive decline, independent of several cardiovascular risk factors, co-morbidities and medication use. The observed direct link between low heart rate variability and cognitive decline might be attributed to a chronic failure of the autonomic nervous system in sustaining adequate cerebral perfusion[9]. A long lasting cerebral hypo-perfusion may in turn hamper the neurovascular integrity of the brain and contribute to brain functional decline[10]. On the other hand, given that low heart rate variability was mainly associated with decline in executive function, the potential mediating effect of unmeasured vascular factors needs to be further addressed in future research. Nevertheless, our findings points toward a potential role of cardiac autonomic disturbance in accelerated cognitive brain ageing and functional decline in older subjects.

Cardiac structural changes as reflected in left ventricular hypertrophy

Cerebral blood flow provides the brain with an adequate and constant supply of oxygen and nutrients[11]. Long-term cerebral hypo-perfusion has been shown to negatively affect the structural and functional integrity of the brain in animals[12]. In humans, the effect of cerebral hypo-perfusion on the brain has been frequently studied in congestive heart failure patients[13]. Patients with advanced heart failure have around 30% lower cerebral blood flow compared to normal healthy subjects[14]. Furthermore, cognitive impairment, memory problems and confusion are common in heart failure patients[15]. Recent studies suggest that not only heart failure, but also a graded decrease in cardiac functioning associates with features of brain ageing[16]. It was shown that each unit lower cardiac output associates with 3.9 mL lower total brain volume and grey matter volume[17]. In addition, cardiac index (cardiac

output/body mass surface) was shown to positively correlate with total brain volume and information processing speed, while it was negatively correlated with lateral ventricular volume[18]. Whether subjects with a suboptimal cardiac function free of heart failure are at increased risk of dementia is yet to be determined. In **Chapter 4**, we show that left ventricular hypertrophy measured from 12-lead ECG recordings associates with accelerated cognitive decline, even in subjects free of heart failure. While the effect of cardiovascular factors and cognitive impairment has been mainly attributed to a sequence of pathologic events[19], we provided evidence on the direct link between cardiac dysfunction and cognitive impairment independent of cardiovascular risk factors and co-morbidities. These findings shed light on the potential role of early structural changes in the heart – as reflected in left ventricular hypertrophy – in development of cognitive impairment. The complex mechanism(s) underlying these associations, however, needs to be further studied to allow for the development of targeted treatment strategies in future.

Cardiac electrical abnormality as reflected in spatial QRS-T angle

Growing evidence indicates that cardiac electrical abnormalities are linked with future risk of cerebrovascular accidents[20]. In fact, ECG markers such as pathologic Q waves and QRS/QT duration have emerged as potential predictors of stroke[20-22]. In addition, ventricular depolarization abnormality – as reflected in abnormal Q-waves – has been related to a higher load of cerebral small vessel disease[23]. A well-established tool for characterization of cardiac electrical changes is the spatial QRS-T angle[24]. The power of spatial QRS-T lies in its ability to assess ventricular repolarization abnormalities secondary to depolarization changes[25]. Particularly, a widened spatial QRS-T angle reflects greater heterogeneity of cardiac electrical activity due to either distortion of cardiac ionic channels or micro-myocardial damage that distorts the spread of electrical forces through the myocardium[26]. The prognostic utility of wide spatial QRS-T angle has been shown in a variety of pathologic states such as ventricular arrhythmias, sudden cardiac death and cardiovascular mortality[24]. On the other hand, an abnormally wide QRS-T angle >90° has been associated with ischemic stroke[27]. In **Chapter 5** of this thesis, a wider spatial QRS-T angle was found to associate with accelerated decline in

executive and memory function of older subjects at high cardiovascular risk. The observed association was independent of cardiovascular diseases, occurrence of cardiovascular events during follow-up, medication use and other ECG markers of cardiac electrical abnormality. Therefore, we postulated that localized pathologic changes in the heart as reflected in wide spatial QRS-T angle may result in subtle hemodynamic disturbances[24]. These hemodynamic disturbances may in turn contribute to cerebral small vessel disease and ultimately parenchymal brain damage and cognitive impairment[28, 29]. These findings extend the current knowledge on the heart-brain connection by showing a link between subtle alterations in the electrical activity of the heart and accelerated cognitive decline in old age. In this setting, effective characterization of cardiac electrical abnormalities may provide a deeper understanding of the pathologic pathways connecting cardiac dysfunction with accelerated cognitive decline.

Neuro-hormonal Aspects of the Heart-Brain Connection: Beyond Vascular Factors

The physiological connection between the heart and the brain comprises a complex interaction of vascular, neuronal and hormonal factors[16, 30]. Nevertheless, studies of the heart-brain connection have mostly focused on vascular factors and there is limited research on the effect of hormonal mediators. Natriuretic peptides have long been known as cardiac hormones that are released into the systemic circulation in response to cardiac wall stretch and systemic overload[31]. Growing evidence, however, indicates that natriuretic peptides are not only present in the systemic circulation, but are also abundant in the central nervous system[32]. In fact, animal studies showed that natriuretic peptides are locally expressed in the central nervous system and their receptors are located in numerous regions of the brain[33]. These remarkable findings have opened a new area of research focusing on the biological roles of natriuretic peptides in the central nervous system of animals and humans[34]. In Chapter 6 of this thesis, we provided a comprehensive overview of the existing literature on

the role of natriuretic peptides in the central nervous system of animal species and human subjects. The available biological and clinical evidence points toward the essential involvement of natriuretic peptides in multiple key functions of the brain including inflammation and oxidative stress, synaptic transmission, brain fluid homeostasis and the stress response of the central nervous system through the hypothalamus-pituitary-adrenal axis[32-34]. Furthermore, we postulated a cross-talk between central and systemic levels of natriuretic peptides such that increased levels of natriuretic peptides in the systemic circulation might result in reduced action of central natriuretic peptides[35]. Finally, given the involvement of natriuretic peptides in several key pathways that are also disturbed during the course of cognitive impairment[32, 36], we hypothesized that natriuretic peptides could be novel markers for diagnosis and/or treatment of cognitive impairment. To substantiate this hypothesis, in Chapter 7 we performed pilot experiments using the post-mortem human tissue and cerebrospinal fluid of non-demented controls and Alzheimer's disease human subjects. Given the limited evidence on the gene expression and localization of natriuretic peptides in the brain of human subjects, we first provided detailed cellular mapping of natriuretic peptides and their receptors in the brain of non-demented controls, as well as of their gene expression in the brain of healthy humans. Our results indicate the presence of natriuretic peptides and their receptors in various neuronal structures such as neuronal cytoplasm, neuronal processes and Nissl bodies. Furthermore, we showed that natriuretic peptides and their receptors are abundantly present in cerebral leptomeningeal and cerebral parenchymal vessels. We also demonstrated the gene expression of natriuretic peptides and their receptors in the central nervous system of healthy human subjects indicating the local production of natriuretic peptides in the brain. Taken together, these findings provide further evidence on the biological importance of natriuretic peptides in the central nervous system of human subjects. In particular, our findings of presence of natriuretic peptides in both neuronal and cerebral vessels suggest a potential role of natriuretic peptides in regulation of the blood-brain barrier integrity and/or neurovascular coupling. When comparing between controls and Alzheimer's disease patients, we showed that the level of natriuretic peptide receptor type A (NPR-A) is higher in the brain of Alzheimer's disease patients, while its ligand

– natriuretic peptide type B – is decreased in the cerebrospinal fluid of Alzheimer's disease patients. This is consistent with our earlier provided hypothesis indicating up-regulation of NPR-A which might occur in response to decreased natriuretic peptides activity in the brain[35]. An increased understanding of the complex role of natriuretic peptides in the brain of human subjects is needed to further disentangle the potential involvement of natriuretic peptides in cognitive impairment.

Conclusions and Future perspectives

The demographic shift in the life expectancy of the populations worldwide has resulted in a rapid rise of seniors with multiple age-related medical conditions[37]. Cognitive impairment and functional disability are prevalent disorders of old age[38]. Nevertheless, current strategies in reducing the progression of cognitive impairment and functional decline have been largely unsuccessful[39]. Therefore, there is an urgent need for identification of effective risk factors in an early stage[40]. The findings from Chapter 2, 3, 4 and 5 of this thesis points toward a direct link of suboptimal cardiac dysfunction – as detected by ECG – with cognitive impairment and functional decline in old age. In particular, we show that cardiac autonomic dysfunction, cardiac structural changes and subtle cardiac electrical abnormalities may contribute to accelerated cognitive decline. Moreover, we show that cardiac autonomic dysfunction also relates to a higher risk of functional decline in older subjects. The findings from this thesis are timely given the growing research and awareness on the role of cardiovascular pathologies in relation to cognitive brain ageing and functional decline[41]. As such, detection of cardiac changes in an early stage prior to manifestation of overt cardiovascular diseases may provide effective strategies in risk stratification of subjects at increased risk of dementia[28]. In line with this, several ECG-markers of cardiac dysfunction such as left ventricular hypertrophy and atrial fibrillation have already been implemented in risk stratification of stroke patients[20, 42]. Whether such markers provide accurate prognostic information for subjects at increased risk of cognitive impairment and functional decline is a

matter of future research. Furthermore, we performed our analyses using a well-established cohort of older subjects at high risk for cardiovascular diseases[43]. Although cardiovascular diseases are common in old age, the generalizability of our findings to healthy elderly subjects should be determined in future research. On the other hand, the observational nature of our studies does not imply causality. Therefore, future intervention strategies are needed to determine the effect of improved cardiac hemodynamic in decelerating the peace of cognitive and functional decline.

Another important aspect of this thesis is the hypothesis proposed along with preliminary findings about the potential role of natriuretic peptides in cognitive impairment as presented in Chapters 6 and 7. We proposed natriuretic peptides as novel markers for cognitive impairment and provided indications about their local production in the brain of human subjects. Importantly, our results extend the findings from animal studies[32, 34] to human subjects and provides evidence on the abundant distribution and localization of the natriuretic peptide family in the brain of human subjects. On the basis of our findings, we also postulate a potential up-regulation of natriuretic peptide receptors in the brain of Alzheimer's disease patients. It is important to mention that the biological role of natriuretic peptides in the brain of human subjects is largely unexplored and therefore remains mostly unknown[32]. Therefore, it is critical to carry out more research in unrevealing the biological pathways that are critical for functioning of natriuretic peptides in the human brain. On the other hand, while our findings are based on post-mortem experiments, future research should focus on exploring the implication of our findings *in vivo.* Given our findings about the abundant distribution of natriuretic peptides in the vascular structures, research aiming at unravelling the potential contribution of natriuretic peptides in regulation of blood-brain barrier integrity and/or neurovascular coupling is needed. Finally, we should keep in mind that the brain is a complex organ and multiple pathways act together to maintain the structural and functional integrity of the brain[37, 44]. This extraordinary level of complexity calls for more sophisticated approaches for a deeper understanding of the mechanisms underlying neurodegenerative disorders in the brain.

References

1. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50:823-830
2. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol*. 2010;141:122-131
3. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J*. 2004;25:363-370
4. Festa A, D'Agostino R, Jr., Hales CN, Mykkanen L, Haffner SM. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. *Diabetes Care*. 2000;23:624-628
5. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the european society of cardiology and the north american society of pacing and electrophysiology. *Eur Heart J*. 1996;17:354-381
6. Custodis F, Schirmer SH, Baumhakel M, Heusch G, Bohm M, Laufs U. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol*. 2010;56:1973-1983
7. Chaves PH, Varadhan R, Lipsitz LA, Stein PK, Windham BG, Tian J, et al. Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women. *J Am Geriatr Soc*. 2008;56:1698-1703
8. Mathers C, Fat DM, Boerma J. *The global burden of disease: 2004 update*. World Health Organization; 2008.
9. Elias MF, Torres RV. The renaissance of heart rate variability as a predictor of cognitive functioning. *Am J Hypertens*. 2017
10. van Buchem MA, Biessels GJ, Brunner la Rocca HP, de Craen AJ, van der Flier WM, Ikram MA, et al. The heart-brain connection: A multidisciplinary approach targeting a missing link in the pathophysiology of vascular cognitive impairment. *J Alzheimers Dis*. 2014;42 Suppl 4:S443-451
11. Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature*. 2010;468:232-243
12. Sarti C, Pantoni L, Bartolini L, Inzitari D. Cognitive impairment and chronic cerebral hypoperfusion: What can be learned from experimental models. *J Neurol Sci*. 2002;203-204:263-266
13. Jefferson AL. Cardiac output as a potential risk factor for abnormal brain aging. *J Alzheimers Dis*. 2010;20:813-821
14. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke*. 2001;32:2530-2533
15. Almeida OP, Flicker L. The mind of a failing heart: A systematic review of the association between congestive heart failure and cognitive functioning. *Intern Med J*. 2001;31:290-295

16. van der Velpen IF, Yancy CW, Sorond FA, Sabayan B. Impaired cardiac function and cognitive brain aging. *Can J Cardiol*. 2017
17. Sabayan B, van Buchem MA, Sigurdsson S, Zhang Q, Harris TB, Gudnason V, et al. Cardiac hemodynamics are linked with structural and functional features of brain aging: The age, gene/environment susceptibility (ages)-reykjavik study. *J Am Heart Assoc*. 2015;4:e001294
18. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, et al. Cardiac index is associated with brain aging: The framingham heart study. *Circulation*. 2010;122:690-697
19. Edwards JD. The importance of identifying early changes in cardiac structure and function for the prevention of cognitive impairment and dementia. *J Alzheimers Dis*. 2017;58:285-288
20. Agarwal SK, Soliman EZ. Ecg abnormalities and stroke incidence. *Expert Rev Cardiovasc Ther*. 2013;11:853-861
21. Soliman EZ, Howard G, Cushman M, Kissela B, Kleindorfer D, Le A, et al. Prolongation of qtc and risk of stroke: The regards (reasons for geographic and racial differences in stroke) study. *J Am Coll Cardiol*. 2012;59:1460-1467
22. Ikram MA, Hollander M, Bos MJ, Kors JA, Koudstaal PJ, Hofman A, et al. Unrecognized myocardial infarction and the risk of stroke: The rotterdam study. *Neurology*. 2006;67:1635-1639
23. Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, et al. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. *Stroke*. 2008;39:1421-1426
24. Voulgari C, Pagoni S, Tesfaye S, Tentolouris N. The spatial qrs-t angle: Implications in clinical practice. *Curr Cardiol Rev*. 2013;9:197-210
25. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. Qrs-t angle: A review. *Ann Noninvasive Electrocardiol*. 2014;19:534-542
26. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial qrs-t angle predicts cardiac death in a general population. *Eur Heart J*. 2003;24:1357-1364
27. Gandhi K, Aronow WS, Desai H, Palaniswamy C, Singh T, Amin H, et al. Patients with ischemic stroke have a higher prevalence of a planar qrs-t angle >90 degrees than patients with transient ischemic attack. *Med Sci Monit*. 2010;16:CR588-592
28. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42:2672-2713
29. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, et al. Cerebral white matter lesions and the risk of dementia. *Arch Neurol*. 2004;61:1531-1534
30. Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. *World J Cardiol*. 2015;7:204-214
31. Hodes A, Lichtstein D. Natriuretic hormones in brain function. *Front Endocrinol (Lausanne)*. 2014;5:201
32. Cao LH, Yang XL. Natriuretic peptides and their receptors in the central nervous system. *Prog Neurobiol*. 2008;84:234-248

33. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. *Endocr Rev*. 2006;27:47-72
34. Prado J, Baltrons MA, Pifarre P, Garcia A. Glial cells as sources and targets of natriuretic peptides. *Neurochem Int*. 2010;57:367-374
35. Pemberton CJ, Yandle TG, Espiner EA. Immunoreactive forms of natriuretic peptides in ovine brain: Response to heart failure. *Peptides*. 2002;23:2235-2244
36. Hu WT, Holtzman DM, Fagan AM, Shaw LM, Perrin R, Arnold SE, et al. Plasma multianalyte profiling in mild cognitive impairment and alzheimer disease. *Neurology*. 2012;79:897-905
37. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, et al. Defining optimal brain health in adults: A presidential advisory from the american heart association/american stroke association. *Stroke*. 2017;48:e284-e303
38. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimers Dement*. 2013;9:63-75 e62
39. Korczyn AD. Why have we failed to cure alzheimer's disease? *J Alzheimers Dis*. 2012;29:275-282
40. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362:329-344
41. Hooghiemstra AM, Bertens AS, Leeuwis AE, Bron EE, Bots ML, Brunner-La Rocca HP, et al. The missing link in the pathophysiology of vascular cognitive impairment: Design of the heart-brain study. *Cerebrovasc Dis Extra*. 2017;7:140-152
42. Unverzagt FW, McClure LA, Wadley VG, Jenny NS, Go RC, Cushman M, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology*. 2011;77:1729-1736
43. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The design of a prospective study of pravastatin in the elderly at risk (prosper). Prosper study group. Prospective study of pravastatin in the elderly at risk. *Am J Cardiol*. 1999;84:1192-1197
44. Iadecola C. Neurovascular regulation in the normal brain and in alzheimer's disease. *Nat Rev Neurosci*. 2004;5:347-360