Role of cardiac biomarkers in cognitive impairment and functional decline

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CHAPTER 1

GENERAL INTRODUCTION

Burden of Cognitive Impairment and Functional Decline in Old Age

The recent increase in life expectancy and decreased birth rate have resulted in a rapid rise of older individuals worldwide[1]. In particular, 8.3% of the Europes' population are aged above 75 years, and this proportion is projected to increase up to 10.7% by 2030[2]. Such population ageing has a profound impact on the burden of age-related disorders such as dementia and functional disability[3]. In fact, currently 47 million people are living with dementia worldwide, while these numbers are expected to rise to 75 million by 2030[2]. Despite these alarming public health projections, current treatment strategies have largely been unsuccessful in delaying the progression of cognitive impairment and functional decline[4]. Consequently, such ageing-related disorders create an important challenge for medicine, public health services and society[1].

Mounting evidence suggest that cognitive impairment and functional decline have a long preclinical phase[5]. In fact, several older subjects develop mild cognitive impairment years before progression to dementia[6]. As such, effective identification of risk factors in an early stage may provide an opportunity for the timely start of disease modifying interventions[5]. This premise, however, necessitates elucidating the link between the pathological processes and the onset of clinical symptoms[5,7].

Cardiac Function and Cognitive Impairment: Pathophysiological Perspectives

Over the past couple of decades, a large number of preclinical and clinical studies have focused on identifying the main causes of dementia[8]. Despite huge investments, strategies targeting the neurodegenerative changes in the brain of demented subjects have proven to be unsuccessful[9]. While Alzheimer's disease is the most common type of dementia, vascular dementia is largely recognized as an independent contributor to cognitive impairment[10]. Interestingly, it has been shown that neuro-vascular damage is a common feature in Alzheimer's disease[4]. Meanwhile, vascular dementia and Alzheimer's disease have also been

shown to be highly prevalent in heart failure patients[11, 12]. Furthermore, vascular damage such as atherosclerosis and peripheral arterial disease are shown to be predictors of functional decline[13, 14]. Together, these findings suggest a potential contribution of cardiac and vascular disturbances to cognitive impairment and functional decline in old age[15].

Cardiac and vascular contributions to cognitive brain ageing have been captured in the heart-brain connection hypothesis[16]. This hypothesis states that cardiac and vascular pathologies affect the hemodynamic status of the brain resulting in cerebral hypo-perfusion, neuronal crisis and dysregulation of the neurovascular unit[17]. Ultimately, this might lead to neuronal injury and impairment of the structural and functional integrity of the brain[18]. In fact, animal studies showed a negative influence of cerebral hypo-perfusion on structure and function of the brain[19]. In human subjects, the detrimental effects of cerebral hypo-perfusion have been frequently studied in heart failure patients[20]. It was shown that heart failure patients are at increased risk of dementia[21], and restoration of cardiac function improved cerebral blood flow and cognitive function[22, 23]. On the other hand, recent findings suggest that the link between cardiac dysfunction and cognitive impairment might not be limited to overt cardiac damage[17]. Instead, it has been suggested that individuals with suboptimal cardiac function might also be at increased risk of dementia[24]. This is supported by studies demonstrating a link between graded decrease in cardiac function and features of brain ageing[25, 26]. However, there has been lack of studies on the link between subclinical cardiac dysfunction and cognitive impairment, and the mechanisms underlying this association remain largely unknown.

The physiological connection between the heart and the brain is rather complex and not limited to vascular and hemodynamic factors[17]. Particularly, neuronal and hormonal mediators act in concrete to maintain homeostasis of the cerebro- and cardiovascular systems[27, 28]. It is known that the autonomic nervous system regulates the adoptive response of the cardiovascular system to the rapidly changing external stimuli[28]. Furthermore, cardiac hormones and hormones released from the hypothalamus-pituitary-adrenal glands act in a tangible feedback loop to regulate body fluid homeostasis, blood pressure, stress responses

and inflammation[29]. Notably, increased levels of plasma cardiac hormones have been shown to associate with dementia and cognitive impairment, even in the absence of overt cardiac damage[24, 30]. However, the pathological mechanism linking cardiac hormones with cognitive impairment remains largely unknown.

Building on this background, the aim of this thesis was to explore the link between cardiac biomarkers, cognitive impairment and functional decline in older subjects with a focus on non-invasive markers that are routinely available in clinical practice.

Cardiac Biomarkers Derived from Electrocardiogram

Heart Rate and Heart Rate Variability

The autonomic nervous system is a branch of the peripheral nervous system that plays an important role in regulation of cardiovascular homeostasis[28]. Particularly, the sympathetic and parasympathetic branches of the autonomic nervous system innervate the sinoatrial node and regulate heart rate[31]. By modulating the heart rate, the autonomic nervous system keeps blood pressure within an optimal range and ensures adequate perfusion to vital organs[32]. This cardiac autonomic control is frequently assessed by means of heart rate variability[7]. Heart rate variability is characterized as the beat to beat variations in consecutive heart beat intervals that represents the synchronized action of the autonomic nervous system on the sinoatrial node[33] (Figure1). Importantly, increased heart rate and reduced heart rate variability indicate a disturbed cardiac autonomic control and decreased resilience to stressors[34].

Heart rate variability is usually measured from a 12-lead electrocardiogram (ECG) recording by means of “time domain” or “frequency domain” methods. The “time domain” methods are among the most commonly used measures of heart rate variability[7]. Their measurement depends on detection of the QRS complexes and normal-to-normal (NN) RR intervals. The NN interval refers to the interval between the neighboring QRS complexes that

are generated from the sinoatrial node. The most simple "time domain" measures include the mean NN interval, the mean heart rate, and the difference between the longest and shortest NN interval. More complex "time-domain" measures include the standard deviation of NN intervals (SDNN), heart rate variability triangular index, standard deviation of the average NN intervals (SDANN) and the square root of the mean squared differences of successive NN intervals (RMSSD)[7].

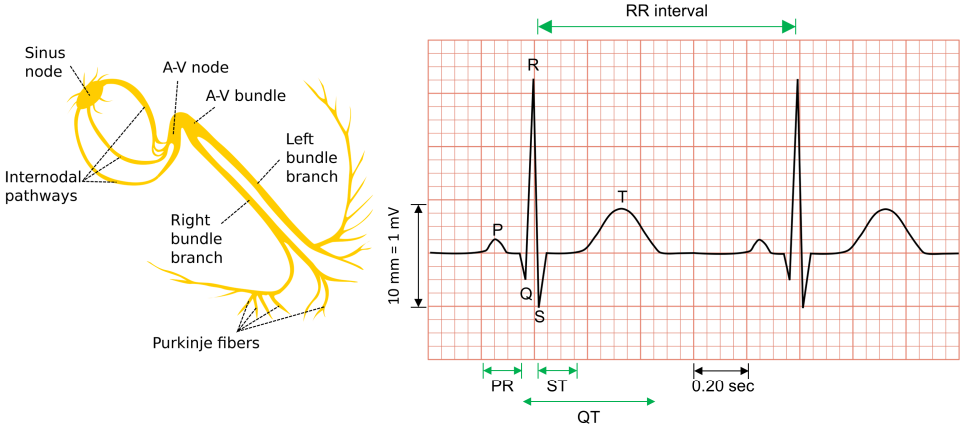

Figure 1. Cardiac conduction system and electrocardiogram waveforms. The figure shows a schematic view of the components of the electrical conduction system of the heart and an ECG-recording. The electrical impulses generated from the sinus node travel to the A-V node. After a delay, the electrical impulses spread through the cardiac ventricles via bundle branches and Purkinje fibers. The ECG captures these electrical impulses in forms of ECG-waveforms. The P wave represents depolarization of atrium; the QRS complex represents depolarization of ventricles and the T wave captures repolarization of ventricles. Sources: Wikipedia and the cardiovascular physiology website (http://www.cvphysiology.com).

Left Ventricular Hypertrophy

The cardiac wall tissue consists of an elastic network of myocyte cells encompassed in a collagen matrix that connects the myocytes and supports the coronary vasculature[35]. An

increase in the cardiac workload results in a range of changes in the cardiac tissue architecture that manifests as thickening of the cardiac wall structure[36]. For example, a chronic increase in cardiac workload such as that in hypertension leads to thickening of the cardiac left ventricle walls. This cardiac structural remodeling known as left ventricular hypertrophy may in turn hamper diastolic function and decrease cardiac output[36]. Particularly, left ventricular hypertrophy is considered a precursor of clinical heart failure in the form of diastolic heart failure[37]. As such, a long lasting hemodynamic stress manifested in cardiac structural remodeling can be detected by means of assessment of left ventricular hypertrophy[8].

There are different ECG-markers for measurements of left ventricular hypertrophy that are frequently based on the amplitude of R and S waves. Since the duration of the QRS complex is frequently increased in left ventricular hypertrophy[38], the QRS complex is incorporated in the calculation of a number of ECG markers[39]. The Sokolow-Lyon product is among such markers that is commonly used in evaluation of left ventricular hypertrophy patients from ECG[39, 40]. In practice, the Sokolow-Lyon product is defined as the sum of S wave in the V1 lead plus the R wave in V5 or V6 leads, multiplied by the duration of the QRS complex[40]. Of note, most ECG markers for left ventricular hypertrophy have a high specify ranging from 85% to 90%[39].

Spatial QRS-T angle

The cardiac action potential consists of waves of depolarization and repolarization. During a cardiac cycle, the loss of electrical charges in cardiac cells result in depolarization (excitation), that is followed by a period of electrical inactivity and repolarization (relaxation), i.e. restoration of electrical charge in the cardiac cells[41]. The depolarization and repolarization waves are generated through a cascade of ionic movements between the intra- and extracellular spaces that result in cardiac muscle contraction/relaxation[42]. An important feature of the cardiac action potential is the ventricular gradient: heterogeneous restoration of electrical charges in the ventricles[43]. This phenomenon is a result of delayed repolarization in the endocardium (inner cardiac tissue layer) compared to the epicedium (outer cardiac

tissue layer)[43]. In fact, the depolarization waves start in the endocardium and travel toward the epicardium, while the repolarization begins in the epicardium rather than the endocardium. As a result, the electrical changes generated by depolarization (QRS axis) and the electrical changes generated by repolarization (T-wave axis) are in opposing directions, forming an angular shape. This angle is known as the QRS-T angle. The QRS-T angle has been originally measured by means of vectorcardiogram in three orthonormal leads of X,Y and Z and referred to as the spatial QRS-T angle[43, 44](Figure 2). Using modern computerized methods, the spatial QRS-T angle can be reconstructed using information derived from a 12-lead ECG[45].

The spatial QRS-T angle provides novel additional information about the function of cardiac ventricles that is not captured with a routine 12-lead ECG. Importantly, cardiac pathophysiological changes such as ischemia, fibrosis, ionic channel disturbances or infarction result in an abnormally wide spatial QRS-T angle indicating localized non-physiological changes[43]. Hence, a wide spatial QRS-T angle might indicate early hemodynamic stresses to the cardiac ventricles.

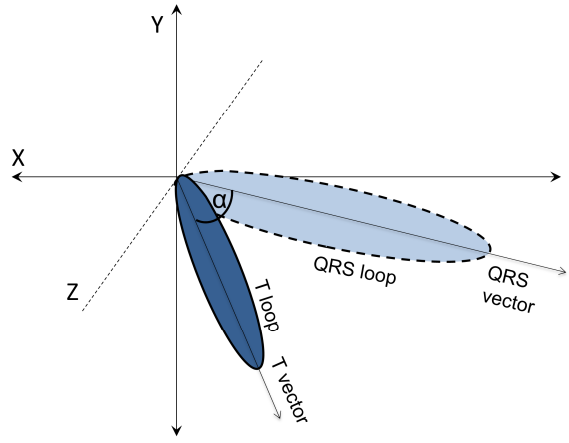

Figure 2. Spatial QRS-T angle in a three dimensional space. Figure shows orthonormal leads of X, Y and Z in a 3-dimentional space. Using T loop and QRS loop, the main T and QRS vectors (arrows) are calculated. The T vector shows the mean direction of ventricular repolarization and the QRS vector shows the mean direction of ventricular depolarization. The angle between the T and QRS vectors (α) represents the spatial QRS-T angle. Adopted from *Vahedi, Farzad, et al. Journal of Applied Physiology 113.3 (2012): 368-376.*

Cardiac Biomarkers Derived from Plasma and Brain Tissue

Natriuretic Peptides

Natriuretic peptides (NP), often referred to as cardiac hormones, are cardiac biomarkers that are used in clinical practice for diagnosis of heart failure and cardiac wall stress[46]. They consist of a family of structurally related peptides that are released into the circulation in response to cardiac wall stretch and volume overload[47]. The opposing action of NP on the renin–angiotensin–aldosterone system and their vasodilatory effect contribute to natriuresis, diuresis and lowering the blood pressure[24] (Figure 3).

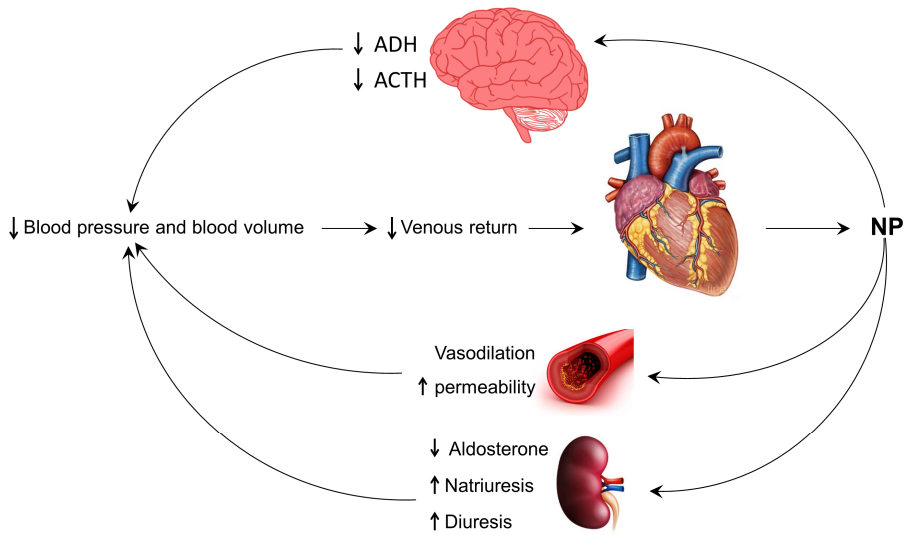

Figure 3. The main physiological functions of the natriuretic peptides in the systemic circulation. Natriuretic peptides are released into the circulation in response to volume overload. Upon release, they stimulate the natriuretic peptide receptors that are located on the kidney, vessel walls and the brain. Consequently, this results in activation and/or deactivation of several biological pathways in the systemic circulation as well as in the brain. NPs: natriuretic peptides, ADH: antidiuretic hormone, ACTH: Adrenocorticotropic hormone. Adopted from: *Moro, Cedric, and Max Lafontan. American Journal of Physiology-Heart and Circulatory Physiology 304.3 (2013): H358-H368.*

Furthermore, a gradual increase in the plasma levels of NP indicates a graded decrease in cardiac function and severity of heart failure[24, 48]. Several studies have shown that higher plasma levels of NP associate with cognitive impairment, even in subjects free of heart failure[30, 49, 50]. Interestingly, growing evidence suggests that the role of natriuretic peptides is not limited to the cardiovascular system, but that they might as well be essential in regulation of brain homeostasis[51]. Differential evidence from animal and human models suggests the presence and expression of natriuretic peptides in brain tissue and cerebrospinal fluid[52]. In fact, natriuretic peptides might be involved in regulation of several brain functions such as neurovascular integrity, synaptic transmutation and neruo-inflammation[51]. However, the role of centrally acting natriuretic peptides in the brain of human subjects remains unknown.

Outline of this thesis

Chapter 2 tests the association of resting heart rate, heart rate variability and functional decline in older subjects. **Chapter 3** explores the independent link between heart rate variability and cognitive function in older subjects. **Chapter 4** is devoted to studying the relation between left ventricular hypertrophy and cognitive function; and **Chapter 5** assesses the relation between spatial QRS-T angle and cognitive function in older subjects. **Chapter 2, 3, 4 and 5** are performed using participants of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) cohort who are at increased risk of cardiovascular disease[53]. The physiology of natriuretic peptides and the role of centrally acting natriuretic peptides in relation to cognitive impairment is described in **Chapter 6**. **Chapter 7** explores the distribution of natriuretic peptides in the brain of post-mortem human subjects and their relation to Alzheimer's disease. **Chapter 8** summarizes the main findings of this thesis and discusses the future perspectives.

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