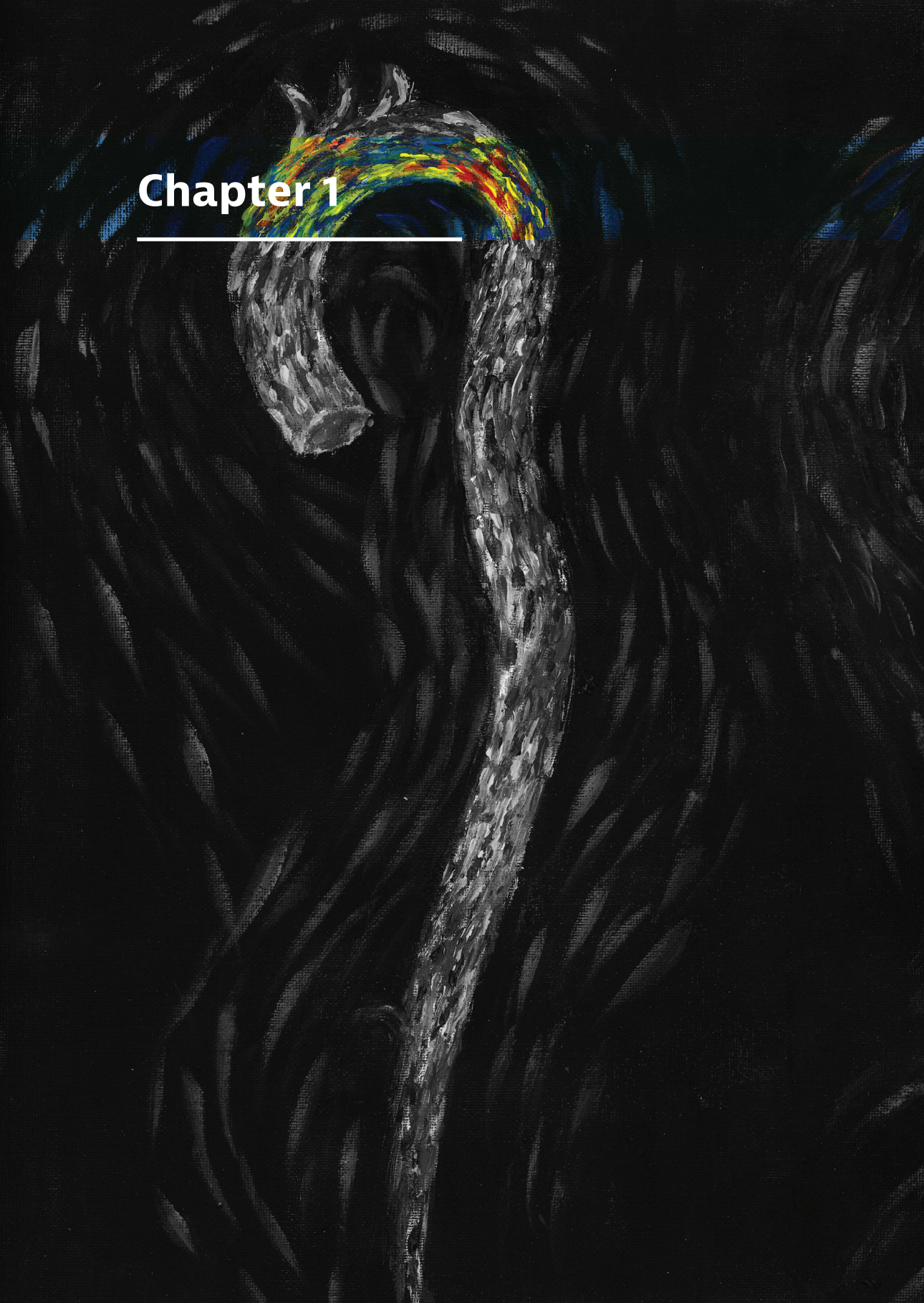
Advanced MRI in aortic pathology and systemic interactions

Hout, M.J.P. van


Chapter 1

General introduction, aim and outline of the thesis

General introduction

Cardiovascular disease is the leading cause of death in the world, which will likely further increase with the worldwide ageing population. Therefore, improving the accuracy of cardiovascular risk assessment will aid in the efficacy and efficiency of cardiovascular treatment. Considering the aorta is the largest artery in the human body, the aorta likely plays a central role in cardiovascular risk. Furthermore, interactions of the vasculature with other organ systems are of great importance in healthy aging.

Aortic structure and function

The aorta has a central location in the body and serves as a conduit to transport blood to the body while absorbing the pulsatile pressure of the cardiac output. During the cardiac cycle, at systole the aorta will expand to absorb the pulsatile pressure created by cardiac output and during diastole the aorta will recoil to maintain blood pressure and sustain organ perfusion.

The aortic vessel wall consists of three layers: the inner layer or tunica intima, the middle layer or tunica media, and the outer layer or tunica adventitia [1, 2]. The tunica intima is a monolayer of endothelial cells that nest on a membrane of collagen fibers. The media is the thickest layer and is composed of concentric layers of smooth muscle cells, interlaced with an extracellular matrix of elastin and collagen. The adventitia is a thinner layer composed of more loosely structured collagen fibers in which the nerve endings and blood supply of the aorta is located [3]. In the media, the ratio of elastin to collagen is high in the thoracic aorta (60:40) and decreases gradually towards smaller arteries outside of the thorax (30:70) [2]. Elastin fibers can stretch up to 300% of the resting length, however are fragile and can break at low amounts of stress [2]. Collagen on the other hand, is a lot stiffer but at the same time also a lot stronger compared to elastin, which provides essential support to the aorta. The high elastin to collagen ratio in the proximal aorta is necessary to absorb the pulsatile pressure of the cardiac output. With age the elastin to collagen ratio decreases, leading to increased arterial stiffness and elevated systolic blood pressure.

Elevated aortic stiffness reduces the cushioning effect of the aorta leading to an increase in systolic blood pressure and propagation of the pulsatile pressure into the smaller peripheral vessels and organs. This propagated pulsatile pressure may lead to end organ damage of for example brain tissue, which is proposed as one of the underlying conditions for cognitive decline with aging [4].

Changes in aortic structure and function

Aging is a complex process of various factors, including inflammation, oxidative and mechanical stress, which lead to medial degeneration and subsequent aortic dilatation and stiffening [5]. Besides age, several cardiovascular risk factors, such as diabetes and hypertension, have shown to reduce aortic elasticity [6]. Additionally, obesity is an increasing worldwide problem and an important risk factor that can lead to several other cardiovascular risk factors as diabetes and hypertension. The distribution of adipose tissue can be categorized into visceral and subcutaneous depositions, which are known to have different properties and may impact cardiovascular function differently [7].

Furthermore, connective tissue disorders such as Marfan syndrome can also lead to increased arterial stiffness [8]. In the case of Marfan syndrome, abnormal connective tissue is caused by mutations in the FBN-1 gene leading to a deficiency in fibrillin-1. Fibrillin-1 normally forms into microfibrils, which construct a scaffold for elastin in elastic fibers [9]. A reduction in Fibrillin-1 therefore leads to a reduction in elastic fibers and subsequent increased aortic stiffness. Additionally, Fibrillin-1 is involved in the binding of transforming growth factor- β (TGB-β). A decrease in Fibrillin-1 leads to more circulating TGB-β, causing extracellular matrix remodeling and aortic dilatation [10].

Increased aortic diameters will usually not lead to symptoms, however at certain diameters (depending on additional risk factors such as connective tissue disorders) the risk of aortic dissection or rupture increases significantly and pre-emptive surgery may be indicated [11, 12]. Patients with elevated aortic dimensions or increased risk for developing aortic aneurysms such as Marfan patients therefore require frequent imaging.

Imaging of aortic morphology

Transthoracic echocardiography (TTE), computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used imaging modalities for the follow-up of aortic dilatation. TTE is a widely accessible modality that enables quick assessment of the aortic root and ascending aorta, however image quality is operator dependent, depends on acoustic window, and imaging of a large part of the descending aorta is not possible [13]. CT is a technique that can rapidly visualize the entire aorta, however it exposes the patient to ionizing radiation, requires iodinated contrast agents [14], and does not provide functional information. MRI is capable of providing morphological assessment of the entire aorta as well as information on aortic stiffness and flow, including the impact of flow on the vessel wall [14]. Furthermore, MRI does not use ionizing radiation and can be performed without contrast agents for luminal enhancement. For MRI the main disadvantages are the availability, longer scan time and the required technical expertise. Guidelines on pre-emptive aortic surgery largely rely on the aortic diameter, so it is crucial to accurately assess aortic dimensions [11, 12]. However, there are significant differences in the measurements of aortic diameters between and within different imaging modalities. Given the potential impact of over- or underestimation of aortic dimensions on individual patient care, universal guidelines on how, when and where to measure the aorta are essential.

Currently, risk of aortic dissection or rupture is mainly determined by aortic diameter and diameter growth rate, while it has been shown that >50% of aortic dissections occur before pre-emptive surgical thresholds are reached [15]. It is therefore likely that there are other factors at play, currently not used in the guidelines for pre-emptive surgery, which could aid in the risk assessment for aortic dissection. Promising research has suggested that aortic elongation and curvature, as well as MRI derived parameters such as flow displacement and vascular stiffness could aid in dissection risk assessment [16-19].

Assessment of cardiovascular function and flow

Since the aorta functions as a conduit that absorbs the pulsatile pressure of the cardiac output, assessment of aortic stiffness is an important marker of aortic function. Different techniques to assess aortic stiffness have been developed.

For example, the augmentation index (AIx) is a quick analysis tool to estimate aortic stiffness. The AIx is calculated from the brachial pressure waveform, and uses a transfer function to approximate the central pressure waveform [20]. The waveform is made up of two peaks, one from the cardiac output and a second from the peripheral pulse wave reflection. AIx is defined as the percentage increase in pulse pressure caused by the peripheral reflection. The great advantage of the AIx is the ease of assessment, which makes it suitable for large population studies. The disadvantage is that it indirectly assesses arterial stiffness based on the wave reflection instead of direct assessment of wave propagation, therefore if wave reflection decreases as for example with age arterial stiffness may be underestimated. This may limit the accuracy of AIx in older patients.

Pulse wave velocity (PWV) is an extensively studied measure of arterial stiffness and an independent marker for cardiovascular risk [21, 22]. PWV is the velocity at which the systolic pressure wave propagates through the aorta and is calculated by dividing the aortic path length by the time it takes the systolic pressure wave to travel this distance.

Various techniques have been developed to assess PWV, of which carotid-femoral PWV (cf-PWV) and MRI-PWV are widely used in clinical research due to their own unique advantages. Cf-PWV uses applanation tonometry, which provides a quick and easy to use assessment of PWV. Cf-PWV, however is less accurate as compared to MRI-PWV due to its inability to accurately assess aortic length [23]. MRI is able to provide accurate non-invasive assessment of PWV using velocity encoding and has been validated against gold standard invasive pressure measurements [24]. Besides prediction of cardiovascular events, MRI-PWV has shown potential in predicting aortic dilatation. In Marfan patients, normal MRI-PWV has shown to predict absence of aortic diameter growth at 2-year follow-up [16]. However, the long-term prognostic capabilities of MRI-PWV on aortic diameter growth remains to be investigated.

MRI-PWI has shown great potential for clinical use, however normal and reference values are currently scarce, which is limiting clinical implementation. Furthermore, although MRI provides many advantages, MRI is relatively expensive, time consuming and requires technical expertise, thereby making it less widely available. Therefore, widespread application of MRI based measures as PWV can be difficult. An adequate estimation model for MRI-PWV, similar to the estimated glomerular filtration rate (eGFR) in the estimation of kidney function, could aid in the widespread clinical implementation of MRI-PWV.

Besides quantification of aortic stiffness, MRI is also capable of analyzing aortic blood flow using 2D or 3D velocity encoding resulting in respectively in-plane or 4D flow analysis. This allows for calculation of flow displacement in the ascending aorta, a marker of flow eccentricity which has been associated with ascending aortic dilatation in bicuspid valve patients [19]. However, little is known about the value of flow displacement in the prediction of aortic dilatation outside of the bicuspid valve patient population. Also, 4D flow allows for the calculation of wall shear stress, a marker that has been linked to aortic dissection expansion in patients with type B aortic dissection [25]. In these patients 4D flow analysis allows for measurement of true and false lumen flow, which may aid in risk assessment of false lumen dilatation [26]. Analysis of blood flow patterns such as vorticity and helicity may aid in optimization of risk stratification of aortic dilatation and dissection in the near future [27].

MRI is an imaging modality with a broad range of (cardiovascular) applications. Using cardiac magnetic resonance, cardiac function, valvular function and cardiac volumes can be analyzed. MRI of the brain can reveal signs of cerebral small vessel disease, a combination of cerebral abnormalities such as white matter lesions and brain atrophy that are related to cognitive decline and even dementia [28]. As such, large population studies using MRI of multiple organ systems creates the potential of studying complex systemic interactions of the cardiovascular system with other organ systems.

Aims of this thesis

In short, MRI derived parameters of aortic morphology and function can provide fundamental information on cardiovascular function and risk, however translation of these parameters into clinical practice can be challenging. Furthermore, these MRI derived parameters could provide critical insight into the complex systemic interplay of cardiovascular function.

Therefore in part 1 we aim to define essential basic measures of aortic morphology and function using MRI. These reference values and standardized measurement methods are critical for the clinical application of these measures. Second, in part 2 we aim to expand the clinical applicability of MRI based measures of aortic function by developing prediction models and predict outcome based on aortic morphology, function and flow. Finally, in part 3 we aim to assess systemic interactions of MRI based measures of cardiovascular function.

Outline of this thesis

Part 1: Defining the basics

Before we can use aortic measures in clinical practice, we first need to define the basics. Aortic diameter is an important clinical measure that is used on a daily basis for assessment of dissection risk and timing for pre-emptive surgical interventions. In chapter 2 we describe how, when and where to measure the aorta using MRI.

PWV is an established prognostic marker for cardiovascular events, however very limited studies to define normal and reference values have been performed. To provide a reference for clinical practice, in chapter 3 we define normal and reference values for MRI-based PWV in middle-aged population.

Part 2: Prediction of arterial stiffness and outcome

As PWV is a marker for cardiovascular risk, widespread use could improve cardiovascular risk assessment and subsequent treatment strategies. MRI provides the most accurate non-invasive PWV assessment, but has as disadvantage that it is relatively time consuming and expensive and requires technical expertise. Therefore, in chapter 4 we develop a prediction model based on clinical and anthropometric measures using linear Ridge regression as well as Deep Neural Network to estimate PWV (ePWV).

In chapter 5 we assess the long-term prognostic value of regional PWV, ascending aorta curvature radius and ascending aorta flow displacement on aortic remodeling in Marfan and non-syndromic thoracic aneurysm patients. Chapter 6 further highlights the potential of flow derived parameters through a case-report regarding the application 4D flow in a type B aortic dissection of a Marfan patient, just two weeks before retrograde progression to a type A dissection.

Part 3: Systemic interactions of cardiovascular function

As stated above, arterial stiffness increases with age and is also effected by various cardiovascular risk factors such as obesity. Interestingly, studies have suggested that different types of body fat distribution (e.g. visceral and subcutaneous adipose tissue) may impact cardiovascular function differently. Therefore chapter 7 investigates the impact of visceral and general obesity on vascular and left ventricular function in a large population cohort. In chapter 8 we aimed to investigate the association between cardiovascular function and cerebral small-vessel disease to provide novel insights into the complex heart-brain axis, which can potentially guide preventive strategies in cognitive decline in older people.

Finally, chapter 9 presents the main conclusions of this thesis and their clinical implications, as well as a proposal for future perspectives.

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