Advanced imaging of the aortic valve and thoracic aorta

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Advanced imaging of the aortic valve and thoracic aorta

Moving beyond diameters

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op
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Voor mijn meisjes

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General introduction

01

Chapter

THE ANATOMY OF THE AORTIC VALVE AND THORACIC AORTA

The aorta is the largest artery in the human body. During the average lifetime it transports approximately 250 million liters of oxygenated blood from the heart to the tissues. The vessel is divided into five main anatomic segments: the bulb-shaped aortic root, the ascending aorta, the aortic arch (from the brachiocephalic trunk to the left carotid artery), the descending thoracic aorta (from the left carotid artery to the diaphragm), and the abdominal aorta (Figure 1)(1). The latter terminates at the level of the lumbar vertebrae by bifurcating into the left and right common iliac arteries.

The aortic vessel wall consists of three layers (Figure 2a)(2). The tunica intima is in direct contact with the blood flow and comprises a basement membrane lined with a single layer of endothelial cells. The thick tunica media consists of smooth muscle cells and elastic laminae, and provides the elasticity needed for the aorta to modulate its circulatory role and to endure the pulsatile cardiac output. The outer layer (or adventitia) is mainly composed of collagen. Although this layer is thin, it provides great tensile strength. Furthermore, it contains the vasa vasora, which nourish the major part of the aortic vessel wall.

AORTIC DISSECTION: CLASSIFICATION AND EPIDEMIOLOGY

Acute aortic syndromes (AAS) comprise a spectrum of medical emergencies that have similar presentations but distinct demographic and pathophysiological characteristics(3). Among various AAS, aortic dissection is the most prevalent(4). It is characterized by a tear in the intimal layer of the vessel wall, which allows blood to enter and create an alternative (or ‘false’) lumen (Figure 2b). While propagating, dissection can restrict blood flow into aortic side branches and cause severe end-organ ischemia(5). The disease can quickly lead to death when the intimal tear progresses into the coronary arteries, aortic valve, pericardium, or in case of complete aortic rupture(6, 7).

Aortic syndromes are classified according to the location and extent of involvement of the aorta(8). The Stanford classification system, which is most widely used, divides dissections into type A (in case of involvement of the ascending aorta) and type B (all other dissections). Population studies have reported an annual incidence of 2.6-5.9 dissections per 100.000 inhabitants per year(9-12).

Approximately two-thirds of those are classified as type A(13). The disease more often develops in men (68%), while women are generally older at the time of presentation (67 vs. 60 years)(13, 14). Systemic hypertension and aortic dilatation are common precipitating factors and present in 77% and 92% of cases, respectively(14, 15). Fifty percent of younger dissection patients (under age 40 years) are diagnosed with an underlying genetically mediated connective tissue disorder (such as Marfan or Loeys-Dietz syndrome)(16). Despite its relatively low incidence, aortic disease is among the top 15 most lethal diseases in patients aged ≥ 50 years(17). It was reported to be the cause of 1.035 out of 153.363 (0.7%) deaths in the Netherlands in 2018(18). Studies using post-mortem computed tomography (CT) have reported that more than half of patients with acute type A aortic dissection (ATAAD) experience circulatory arrest before arrival at the hospital(19, 20). Of those who reach the hospital alive and undergo emergency surgery, 20-44% die postoperatively due to malperfusion syndromes such as cerebral, visceral or spinal ischemia(9, 21-24).

THORACIC AORTIC ANEURYSM: DEFINITION AND ETIOLOGY

Aortic dilatation is the primary anatomic risk predictor for the occurrence of ATAAD(25). Large studies have established normal values for the diameters of different aortic segments and demonstrated their correlation with age, gender, and body surface area (BSA)(26-31). Thoracic aortic aneurysm (TAA) is defined as a focal dilatation $\geq 50\%$ of one or more segments of the aorta within the thoracic cavity(32). Most likely, these involve the ascending aorta (60%) or descending aorta (40%)(33). Aneurysms of the aortic arch and thoracoabdominal aorta are less prevalent (both 10%)(33).

The pathophysiology of ascending aortic aneurysm formation is characterized by degeneration of the medial layer of the vessel wall. This process involves loss of smooth muscle cells and elastin content, which occurs – to some extent – as a normal consequence of aging(34). Excessive loss of structural integrity can result in weakening of the aortic vessel wall and subsequent luminal dilatation(35). Most TAAs are degenerative (i.e., sporadic) in nature and occur in association with hypertension(36-39). Medial degeneration in young patients is classically associated with connective tissue disease, familial thoracic aortic aneurysm and dissection syndrome, or presence of a bicuspid aortic valve (BAV)(40-44). Although rare, aneurysms can also form as a consequence of aortic infection or systemic autoimmune processes(45). Atherosclerosis underlies aneurysm formation of the descending and abdominal aorta but is a less common cause of ascending aortic aneurysms(37-39).

THORACIC AORTIC ANEURYSM: LINK WITH AORTIC VALVE DISEASE

The aortic valve is the door to the aorta and opens up to three billion times in a lifetime. There is an evident association between narrowing of the aortic valve (either congenital or acquired) and ascending aortic aneurysm formation. The coexistence of both is generally referred to as 'poststenotic dilatation' and occurs in patients with calcific aortic stenosis (AS), stenotic and non-stenotic BAV, and following aortic valve replacement(46, 47). Prevalence is higher in patients with bicuspid valves compared to those with tricuspid valves (83% vs. 15-33%)(47). There has been controversy as to whether BAV aortopathy is due to a vessel wall defect or whether it is caused by abnormal hemodynamic stress on the vessel wall. On the one hand, BAV disease shows similarities with Marfan's syndrome, since the vessel walls of both patient groups exhibit cystic medial necrosis and decreased amounts of fibrillin-1(48). Fibrillin-1 deficiency predisposes to aortic dilatation by causing smooth muscle cell detachment and disruption of the extracellular matrix(49, 50). On the

other hand, there is evidence that increased wall stresses play a role in the pathophysiology of poststenotic dilatation. Early studies showed that patients with mild AS accompanied by a thrill develop aneurysms at the point downstream of the maximal vibration(51, 52). It was postulated that these aneurysms represented structural fatigue as a consequence of the 'acoustic energy resulting from flow turbulence'. More recently, simulation studies have shown that flow through a bicuspid valve is intrinsically eccentric and turbulent, even in the absence of a significant transvalvular pressure gradient(53). The occurrence of a dilated aorta with an abnormal tricuspid valve further supports the concept of a hemodynamic cause, as opposed to an inherent tissue weakness(47, 54). Emerging imaging techniques (such as four-dimensional flow magnetic resonance [4D flow MR]) afford a detailed visualization of flow patterns in the heart and great vessels and can shed light on the pathogenesis of poststenotic aortic dilatation(55).

PREVENTIVE TAA MANAGEMENT: ROLE OF CARDIOVASCULAR IMAGING

The association between maximal aortic diameters and the risk of natural complications has been well-described(56). The risk of type A dissection is $<1\%$ per year in the mildly dilated aorta (40-55 mm) but increases to 6.9% once the diameter reaches 60 mm(57, 58). To avoid expansion towards this critical point, societal guidelines recommend pre-emptive extirpation of aneurysms ≥ 55 mm (or ≥ 50 mm in patients who are at increased risk for adverse outcomes)(25, 59-61). Patients with asymptomatic TAAs who do not meet criteria for prophylactic surgery should undergo conservative management. This includes lifestyle modification, aggressive blood pressure control to limit further dilatation, and genetic counseling to identify inheritable vascular syndromes(25, 59). Furthermore, all TAA patients require periodic imaging for follow-up of aneurysm diameters and re-assessment of surgical criteria(25, 59-61). Ultrasound, computed tomography (CT), and MR are all reasonable first-line modalities for TAA surveillance. Transthoracic echocardiography (TTE) is particularly useful for evaluation of the aortic valve, aortic root, proximal ascending aorta, and upper abdominal aorta(62). The distal ascending aorta, arch, and descending aorta are often incompletely imaged by TTE and require assessment by CT or MR. Since each technique has pros and cons in terms of resolution, acquisition time, radiation exposure, contrast agent administration and costs, the choice of study should be individualized and based on patient characteristics and the diagnostic questions to be answered(1). Current cardiovascular guidelines recommend (semi-)annual CT or MR in all TAA patients, but are not substantiated by data demonstrating the need for this approach(59, 61).

Despite the association between aortic size and the relative risk of complications, it has been shown that the majority of dissections occur in aortas with diameters below the cut-offs for prophylactic surgery(15, 63-66). The explanation for this so-called 'aortic size paradox' lies in the right-skewed distribution of TAA sizes, with a relatively large pool of patients with small aneurysms(67). The aortic size paradox has fueled the debate about the actual value of diameter measurements and underlines the need for research aiming to improve individual risk profiling. Advanced genetic testing, blood biomarkers, and novel imaging techniques are currently being investigated as potential additional markers of disease activity. **Chapter 2** of this thesis reviews emerging imaging methods that hold promise to predict aortic disease at an early stage.

GAPS IN KNOWLEDGE

Guidelines for management of aortic disease provide well-substantiated recommendations for diagnosis and treatment of (suspected) dissection. However, evidence on prevention of AAS and the role of imaging herein is limited. Although the decision as to refer patients for pre-emptive

aneurysmectomy depends on aortic diameter measurements, it is unknown how (and how often) these should be measured. Moreover, an increasing body of literature demonstrates that diameter measurements are incapable of predicting the majority of dissection cases. In elderly patients, radiologic reports often mention that the aorta is 'elongated', yet the role of aortic elongation in the pathophysiology of dissection has not been investigated. Also, no previous study has assessed the potential of aortic volumetry in prediction of acute adverse events. Although volume measurements have shown high reproducibility and have been adopted in many medical fields (such as to assess tumor sizes in oncology), their use in predicting aortic disease has not been evaluated. Hemodynamic imaging by means of 4D flow MRI has contributed to the unraveling of the pathophysiological mechanism in BAV disease, but has not been applied in patients with calcified tricuspid valves. The added value of this technique in prediction of TAA progression is yet unknown.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to assess novel anatomic and functional imaging parameters that may help to predict acute aortic syndromes and add value in the preventive management of aortic disease.

Chapter 1 is the general introduction and outline of this thesis. **Chapter 2** reviews considerations regarding aortic diameter measurements and highlights emerging imaging techniques that have shown promise to improve dissection risk assessment.

Societal guidelines recommend annual or semi-annual CT or MR for all TAAs ≥ 40 mm. However, these recommendations are not backed up by data showing the necessity of this approach. **Chapter 3** aims to determine a standardized imaging interval for TAA patients by evaluating growth rates and predictors for disease progression.

Modern acquisition and post-processing techniques facilitate high-resolution three-dimensional imaging of the aorta, which – in turn – affords measurements of aortic volume and length. At surgery, the dissected aorta often looks markedly elongated in its course through the thorax. **Chapter 4** investigates the normal evolution of longitudinal aortic dimensions during life. By using a propensity-matched strategy, **Chapter 5** investigates the potential role of aortic elongation in the pathophysiology of dissection. **Chapter 6** compares the diagnostic accuracies of maximal aortic diameter, length and volume for prediction of acute type A dissection.

Over recent years, four-dimensional (4D) flow magnetic resonance (MR) has emerged as a non-invasive imaging technique that enables the comprehensive assessment of intra-cardiac and -aortic hemodynamics. **Chapter 7** aims to validate 4D flow-derived velocities and pressure gradients in the aortas of patients with calcified aortic valve stenosis, by comparing them to the clinical reference standard (transthoracic echocardiography).

To assess the role of aberrant hemodynamics in aneurysm formation, **Chapter 8** compares flow patterns and hemodynamic markers (including wall shear stress) between TAA patients and healthy controls.

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Predictive imaging for thoracic aortic dissection and rupture: moving beyond diameters

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Chapter

ABSTRACT

Acute aortic syndromes comprise a group of potentially fatal conditions that result from weakening of the aortic vessel wall. Pre-emptive surgical intervention is currently reserved for patients with severe aortic dilatation, although abundant evidence describes the occurrence of dissection and rupture in aortas with diameters below surgical thresholds. Modern imaging techniques (such as hybrid PET-CT and 4D flow MRI) afford the non-invasive assessment of anatomic, hemodynamic and molecular features of the aorta, and may provide for a more accurate selection of patients who will benefit from preventative surgical intervention. In the current review, we summarize evidence and considerations regarding predictive aortic imaging and highlight evolving imaging modalities that have shown promise to improve risk assessment for the occurrence of dissection and rupture.

KEYWORDS

Aorta, aortic dissection, aortic aneurysm, type A dissection, aortic rupture.

KEY POINTS

- Guidelines for the preventative management of aortic disease depend on maximal vessel diameters, while these have shown to be poor predictors for the occurrence of catastrophic acute aortic events.
- Evolving imaging modalities (such as 4D flow MRI and hybrid PET-CT) afford a more comprehensive insight into anatomic, hemodynamic and molecular features of the aorta and have shown promise to detect vessel wall instability at an early stage.

INTRODUCTION

'Upon examining the heart, its pericardium was found distended with a quantity of coagulated blood, nearly sufficient to fill a pint cup; the whole heart was so compressed as to prevent any blood contained in the veins from being forced into the auricles; therefore the ventricles were found absolutely void of blood; and, in the trunk of the aorta, we found a transverse fissure on its inner side, about an inch and a half long, through which some blood had recently passed...'

In 1760, King George II of Great Britain died unexpectedly while 'straining on the toilet', and so became subject of the first ever case report on acute type A aortic dissection(1). At autopsy, the King's personal physician described findings of an intimal vessel wall tear and subsequent cardiac tamponade, which – as we now know - is one of the most feared complications of dissection. Along with pathophysiologically distinct entities like aneurysm rupture and intramural hematoma (IMH), dissection belongs to the spectrum of acute aortic syndromes (AAS). Despite best efforts, these have proven challenging to predict, and annual incidence rates have been stable at approximately 10 per 100.000 over the past decades(2, 3). Cardiovascular imaging plays a central role in the preventative management of aortic disease, since guidelines traditionally depend on diameter criteria for stratification towards prophylactic surgical intervention(4, 5). In the current review, we summarize evidence and considerations regarding predictive aortic imaging and highlight modern imaging techniques that have shown promise to improve risk assessment for the occurrence of dissection and rupture.

BEST CURRENT PRACTICE – AORTIC DIAMETERS

Normal Diameters

The aorta is the largest artery in the body and runs from the aortic valve until the abdominal bifurcation. From proximal to distal, it consists of the aortic root, ascending aorta, aortic arch, descending thoracic aorta, and abdominal aorta (Figure 1). Cross-sectional diameters are influenced by gender, patient habitus, and hypertension, and increase in an indolent manner by approximately 0.1 mm/year(6). Reference values for the different anatomic segments have been established by multiple imaging modalities, including echocardiography, CT, and MRI(7-9). Imaging guidelines provide specific measurement recommendations for each of these techniques and emphasize that there exists no standardized method across modalities(10). Therefore, diameters can vary slightly depending on trigger time (end-systolic vs. end-diastolic) and edge selection (leading edge-to-leading edge vs. inner edge-inner edge vs. outer edge-outer edge). In general, it is stressed that measurements should be performed perpendicular to the aortic centerline (i.e., on double oblique images), and that measurement location and methodology should be specified in order to provide for accurate follow-up in individuals with an indication for repetitive imaging(11-13).

Thoracic aortic aneurysm (TAA)

An aneurysm is defined as a localized arterial dilatation of ≥ 2 standard deviations (SDs) above the expected vessel diameter(14). The underlying pathophysiological mechanisms differ partially for aneurysms at various locations along the aorta. Whereas TAA results from excessive degeneration of the medial layer of the vessel wall (also known as cystic medial necrosis), the formation of abdominal aortic aneurysms (AAA) is mainly associated with atherosclerosis(15). However, the net result – extensive remodeling of the extracellular matrix of the vessel wall with loss of vascular smooth muscle cells (VSMCs) and elastin content – is similar for all aneurysms(15).

Figure 1. Three-dimensional CT reconstruction of a healthy thoracic aorta. The ascending aorta runs from the sinotubular junction until the first branch vessel (brachiocephalic trunk), while the aortic arch is defined as the segment that contains the three branch vessels. The descending thoracic aorta is divided into two parts: a proximal part (from the left subclavian artery to the level of the pulmonary artery), and a distal part (from the pulmonary artery to the diaphragm).

Progressive aortic dilatation is a well-acknowledged risk factor for the occurrence of both acute dissection and rupture. While these natural complications are rare in ascending aortic aneurysms of moderate size (yearly rupture or dissection risk of 0.08%, 0.22% and 0.58% at diameters of 45, 50 and 55 mm, respectively), a sharp step-up in their occurrence – to 6.9% yearly – is observed when the diameter exceeds 60 mm (Figure 2)(16-18). In descending thoracic aneurysms, a similar 'hinge point' is identified at 70 mm(18). In order to avoid aneurysm expansion beyond these critical points, the general consensus is to refer patients for pre-emptive surgery at 55 mm (ascending aorta) or 55 to 60 mm (descending thoracic aorta, depending on the eligibility for an endovascular approach)(4, 5, 19). More frequent surveillance imaging and lower surgical cut-offs apply to patients with connective tissue diseases (such as Marfan syndrome), who are at increased risk for negative outcomes(5). In these patients, surgery is indicated at diameters ≥ 50 mm, or even ≥ 45 mm in the co-presence of additional risk factors (growth rate >3 mm/year, familial history of dissection, or severe valvular regurgitation). Patients with bicuspid aortic valve (BAV) and concomitant risk factors are also considered for surgery at a lower than normal threshold (≥ 50 mm), although evidence for this approach is lacking(4, 5, 20). Admittedly, BAV is overrepresented in large dissection

Figure 2. Lifetime probability of dissection or rupture at various sizes of the thoracic aorta. Note the 'hinge points' at 6 cm (ascending aorta) and 7 cm (descending thoracic aorta), at which the natural complication risk suddenly escalates. Reprinted, with permission, from Elefteriades et al., *J Am Coll Cardiol* 2010;55(9):841-57.

cohorts, but the higher number of aortic events in this patient group cannot be seen independent from its increased TAA prevalence(17, 21). At any given TAA diameter, the yearly aortic complication risk for bicuspid and tricuspid valves has shown to be comparable(22).

Aortic size paradox

Despite the evident link between TAA formation and unfavorable outcomes, the vast majority of dissections occur in aortas with diameters below the threshold for preventative surgery – the so-called 'aortic size paradox'. Retrospective studies have shown that only 30-41% of patients with type A and 18% of patients with type B dissection had diameters ≥ 5.5 cm at the time of presentation(23-26). Since the aorta dilates by about one-third of its size directly after dissection onset, the number of events that could have been prevented by current diameter cut-offs is probably even lower(27-29). Nevertheless, it is questionable if lowering the thresholds for surgical intervention would bear a long-term mortality benefit. Given the large population at risk, it would more likely expose a considerable number of patients with smaller TAAs – and thus, minimal yearly risk of natural complications – to the 3.7-8.3% mortality risk associated with elective surgery(30). In conclusion, it could be stated that the aortic diameter predicts rupture and dissection on a populational level, but is an insufficient parameter to identify individuals at risk. For this reason, recent research interests have shifted to the deciphering of additional risk factors for AAS, in an attempt to enhance personalized risk assessment and clinical decision-making.

MODERN PERSPECTIVES – MOVING BEYOND DIAMETERS

Aortic elongation and volume

One drawback of maximal diameter measurements is that they do not adequately represent the three-dimensional process of aortic growth. Aneurysm lengthening and cylindrical deformation are two scenarios of positive remodeling that are not necessarily accompanied by an increase of maximal diameters(31). Since more advanced acquisition and post-processing techniques are required to assess the three-dimensional geometry of the aorta, data on its length and volume is relatively scarce. Similar to its diameters, normal aortic length has shown to increase with age(32, 33). With the vessel being confined within the thoracic cavity, this lengthening process

Figure 3. Scatter plot depicting the length of the ascending aorta in patients with acute type A dissection (red) and healthy controls (grey). In the majority of dissection patients, the aorta was evidently lengthened (mean difference of 2.0 cm when compared to propensity-matched healthy controls).

naturally causes the artery to become more tortuous(32). Driven by observations that the intimal entry tear runs in the transverse direction in the majority of cases (i.e., results from disruptive stretch in the longitudinal direction), recent studies have investigated the role of excessive elongation in the pathophysiology of dissection(34, 35).

They found that increased vessel curvature significantly elevates the forces acting on the aortic wall and that vessel length serves as independent risk factor for the occurrence of both type A and type B dissection (Figure 3)(36-39).

To date, the added value of volume measurements in the management of thoracic aortic disease is not fully understood. Several AAA studies have suggested improved sensitivity for detection of aneurysm growth by reporting that substantial volume expansion can occur even while the maximal diameter remains stable(40-43). This finding is important, since it implicates (rapid) growth in regions proximally or distally from the widest portion of the aneurysm sac. Volumetry has also shown improved intra- and interobserver variability when compared to diameter measurements, which is another argument in favor of its use in clinical aneurysm follow-up(44). Although no causal link with adverse outcomes has yet been established, the cited studies have demonstrated that aortic length and volume can be measured on routinely obtained CT using commercially available software packages. This widespread availability makes them feasible predictive parameters for use in a clinical setting, although longitudinal – and, preferably, prospective – studies are now required as the next step in their validation process.

Figure 4. (A) Streamline visualization of a BAV patient, showing a pronounced eccentric and helical flow pattern. The adjacent WSS map (B) shows elevated wall stress in the greater curvature of the aorta, at the location of impingement between the eccentric jet and the vessel wall.

Aortic hemodynamics

The role of hemodynamics in the pathogenesis of aortopathy has been subject of a long-standing debate. Especially in BAV patients, who exhibit enlarged aortic diameters even in the absence of valvular dysfunction, there has been controversy regarding the origin of aneurysm formation(45). Two theories explain the accelerated aortic growth rates and high prevalence of TAA in this patient group: i) a genetic theory, which rests on evidence that BAV is a congenital condition with considerable genetic heterogeneity, and ii) a hemodynamic theory, in which abnormal flow patterns and turbulence cause elevated wall stress and subsequent vessel remodeling(46). Several genes (such as *NOTCH1*, *ACTA2*, and *GATA5*) have been associated with abnormal development of the aortic valve(46, 47). Given that the aortic cusps and the medial layer of the ascending aorta are embryologically linked (i.e., both originate from the neural crest), it is conceivable that the genes responsible for BAV formation can also affect the development of the aortic vessel wall. Other arguments in support of the genetic theory include observations that BAV aortopathy is not uncommon in children and adolescents, and that progressive diameter increase can occur even after replacement of the aortic valve(48, 49). Initially, the histologic presence of cystic medial necrosis was also presented as an argument for disease inheritability, as this was believed to resemble findings in those with Marfan syndrome(50). However, later work has demonstrated that medial degeneration is a common feature of all TAAs and dissected aortas, regardless of their underlying etiology(15, 51).

Over the past few years, the hemodynamic theory has become increasingly popular, along with the evolvement of functional imaging modalities that afford a more comprehensive insight into aortic hemodynamics. In flow MRI, phase-contrast (PC) techniques are used to generate image contrast between moving protons (such as in blood) and stationary protons (most soft tissues). The underlying concept is based on the feature of protons to accumulate an MRI phase shift that is proportional to the speed at which they move along a magnetic gradient field. Phase-contrast MRI is traditionally performed using a manually positioned two-dimensional (2D) acquisition that encodes velocity in one principal direction. This approach generates time-resolved velocity maps, which can be used to quantify flow rates and velocities of blood moving through the imaging slice. As such, it enables evaluation of a broad spectrum of cardiovascular diseases, including assessment of shunt fractions and valvular regurgitant volumes. Over recent years, methodological advances have facilitated the acquisition of time-resolved, three-dimensional, three-directionally encoded velocity data. This technique, commonly known as 4D flow MRI, affords a uniquely detailed flow visualization within the heart and large vessels and allows post-hoc flow quantification at any location within an acquired volume(52). Furthermore, the obtained velocity data can be used for estimation of various flow-derived hemodynamic parameters, including wall shear stress (WSS) and normalized flow displacement. In BAV patients, 4D flow MRI has revealed markedly eccentric and helical flow with highest flow velocities and WSS located along the aortic vessel wall (Figure 4)(53, 54). For each BAV cusp fusion type, a typical WSS distribution pattern with elevated shear stress at the location of impingement between flow jet and vessel wall was identified(55). Subsequently, raphe-specific WSS patterns have shown to correspond with the phenotype of BAV aortopathy (i.e., left-right coronary cusp fusion leads to sole dilatation of the tubular ascending aorta, whereas a raphe between the right- and non-coronary cusps causes more diffuse dilatation with involvement of the aortic root, tubular ascending aorta and aortic arch)(56, 57). In a recent contribution, Guzzardi et al. have also demonstrated a more direct association between WSS and histologic changes of the aortic vessel wall(58). In their study, BAV patients who were scheduled for ascending aortic replacement underwent pre-operative WSS mapping. During surgery, paired tissue samples of aortic regions with normal and elevated WSS were collected to show that increased WSS was associated with dysregulation of the extracellular matrix and degeneration of elastin fibers (Figure 5).

Flow displacement is another 4D flow MRI parameter that has shown potential to predict progression of aortic disease. It provides a quantitative measure of flow eccentricity by calculating the distance between the location of peak systolic flow and vessel center in a 2D imaging plane(59). Like WSS, the degree and direction of flow displacement depend on the underlying aortic valve phenotype(56). As yet, it is the only 4D flow MRI parameter that has been associated with aortic growth in a (small) longitudinal cohort study. In this study (mean follow-up duration: over 4 years) BAV patients with eccentric aortic flow exhibited faster diameter growth than those with laminar flow profiles (1.2 mm/year vs. 0.3 mm/year, respectively)(60). Larger longitudinal studies that aim to acquire the clinical relevance of various 4D flow MRI parameters are currently ongoing.

Figure 5. Aortic wall specimens of regions with normal WSS (left panels) and high WSS (right panels) in three (a,b,c) patients with BAV aortopathy (40x magnification). Note the decreased number of elastin fibers (black) in the context of elevated WSS. Center panel: 4D flow MRI-based maps depicting areas with increased (red) and depressed (blue) WSS. Reprinted, with permission, from Guzzardi et al., Valve-related hemodynamics mediate human bicuspid aortopathy, *J Am Coll Cardiol* 2015;66:892-900.

Vessel wall inflammation

Immunohistochemical studies have reported extensive inflammatory activity within the aneurysmatic vessel wall(15). Whereas the presence of lymphocytes and activated macrophages is rare in the healthy aorta, elevated numbers of CD3⁺ and CD68⁺ cells were found throughout the medial layer of TAAs(51). Of note, infiltration of these cells has shown to be even more pronounced in the dissected aorta, raising the question whether the degree of inflammation can be used to discriminate between low- and high-risk patients(51). Since leukocytes demand glucose for their accelerated metabolic processes, areas of increased inflammatory activity can be detected using positron emission tomography (PET). This imaging modality depends on measurements of radioactivity emitted after administration of a radioactive tracer, most commonly the glucose derivative 18-fluoro-2-deoxyglucose (FDG; >95% of all PET examinations). FDG is transported into cells by glucose transporters and becomes phosphorylated to form FDG-6-phosphate. Unlike glucose-6-phosphate, FDG-6-phosphate is not further metabolized along the glycolytic pathway and becomes trapped within the cell in a concentration that is in

Figure 6. (A) Contrast-enhanced CT depicting type B dissection (arrow) in a patient with acute chest pain. Adjacent PET (B) and PET/CT (C) examinations revealed regions of elevated FDG-uptake in the dissected vessel wall (arrows). Adapted by permission from BMJ Publishing Group Limited, from Kuehl et al., *Heart* 2008;94:1472-1477.

proportion to that cells' glucose consumption. In animal experiments, FDG avidity has shown to be positively correlated with macrophage content of the arterial vessel wall(61, 62). A similar association has been observed in vivo in patients with abdominal aneurysms(63, 64). Furthermore, the AAA study by Reeps et al. reported FDG uptake to be associated with a decrease of collagen content and VSMCs – factors that determine the stability of the aortic wall. However, despite these promising results, studies that sought to investigate the use of FDG-PET for prediction of AAA expansion and rupture have reported conflicting results. Whereas two prospective studies have demonstrated elevated tracer uptake to be associated with disease progression, others could not establish such a relationship(65-70). As yet, only one study has investigated the use of PET/CT in thoracic aortic disease. In a small sample of hemodynamically stable patients with various acute aortic conditions (i.e., type B dissection, penetrating ulcer or IMH), this longitudinal study showed increased FDG-uptake to be associated with the risk of disease progression (Figure 6)(71). Of the eleven included patients with increased FDG uptake, nine (82%) showed progression of wall pathology under conservative treatment requiring emergency medical intervention, and three of these nine patients died. In contrast, only ten of the twenty-two (45%) PET-negative patients experienced disease progression (two deaths).

In conclusion, no clear relation between FDG-PET and clinical outcomes in thoracic and abdominal aneurysm patients has yet been demonstrated, although it should be noted that the inconsistency between studies partly relates to their small and heterogeneous study populations. Prospective studies with larger patient cohorts are warranted to assess the actual clinical value of FDG-PET. Also, future work could address the clinical value of novel radiotracers that have shown potential to target other processes within the inflammatory pathway of aneurysmal disease, such as expression of matrix metalloproteases (MMPsSense 680), active vascular calcification (18F-NaF) and chemokine receptor 4 expression (68-Ga-pentixafor)(72-74). The recent integration of PET and MRI into PET/MRI scanners has afforded the synchronized evaluation of anatomic, physiologic and molecular imaging features, and could serve as promising imaging platform in the future.

CONCLUSIONS

Excessive aortic dilatation (diameter ≥ 5.5 cm) poses a significant risk for the occurrence of acute aortic events, and patients with aneurysms beyond this size should be referred for prophylactic surgical intervention. However, the majority of acute aortic events occur in aortas with diameters below surgical thresholds. Therefore, these patients would not have qualified for preventative surgery, even when screened appropriately prior to event onset. Several modern imaging techniques (such as hybrid PET/CT and 4D flow MRI) have shown promise to detect vessel wall instability at an early stage. Studies that aim to demonstrate a causal link with the occurrence of acute aortic syndromes are currently ongoing and could lead to the integration of these techniques into clinical practice guidelines.

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A piece of white paper is torn, revealing a teal-colored surface underneath. The text 'ANATOMIC IMAGING' is printed in white, bold, uppercase letters on the teal surface. The paper is torn in a jagged, irregular shape, with the top right corner missing and the bottom edge frayed. The background is a light gray gradient.

ANATOMIC IMAGING

Part I

Determining the optimal interval for imaging surveillance of ascending aortic aneurysms

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Chapter

ABSTRACT

BACKGROUND

Cardiovascular guidelines recommend (bi-)annual computed tomography (CT) or magnetic resonance imaging (MRI) for surveillance of the diameter of thoracic aortic aneurysms (TAAs). However, no previous study has demonstrated the necessity for this approach. The current study aims to provide patient-specific intervals for imaging follow-up of non-syndromic TAAs.

METHODS

A total of 332 patients with non-syndromic ascending aortic aneurysms were followed over a median period of 6.7 years. Diameters were assessed using all available imaging techniques (echocardiography, CT and MRI). Growth rates were calculated from the differences between the first and last examinations. The diagnostic accuracy of follow-up protocols was calculated as the percentage of subjects requiring pre-emptive surgery in whom timely identification would have occurred.

RESULTS

The mean growth rate in our population was 0.2 ± 0.4 mm/year. The highest recorded growth rate was 2.0 mm/year, while 40.6% of patients showed no diameter expansion during follow-up. Females exhibited significantly higher growth rates than men (0.3 ± 0.5 vs 0.2 ± 0.4 mm/year, $p=0.007$). Conversely, a bicuspid aortic valve was not associated with more rapid aortic growth. The optimal imaging protocol comprises triennial imaging of aneurysms 40-49 mm in diameter and yearly imaging of those measuring 50-54 mm. This strategy is as accurate as annual follow-up, but reduces the number of imaging examinations by 29.9%.

CONCLUSIONS

In our population of patients with non-syndromic TAAs, we found aneurysm growth rates to be lower than those previously reported. Yearly imaging does not lead to changes in the management of small aneurysms. Thus, lower imaging frequencies might be a good alternative approach.

KEYWORDS

Aorta; aortic aneurysm; thoracic aortic aneurysm; follow-up; dissection

KEY POINTS

- Nearly half of ascending aortic aneurysms do not grow over time.
- Female sex and aortic regurgitation predispose to more rapid aortic growth.
- Triennial imaging suffices for aneurysms with diameters between 40-49 mm.

INTRODUCTION

Acute type A aortic dissection (ATAAD) is a medical emergency that requires immediate surgery to avert fatal outcome. Dissection is commonly precipitated by aneurysm formation, and the risk for ATAAD is known to correlate with the maximal aneurysm diameter(1). This risk is less than 1% per year in mildly dilated aortas but increases to 6.9% once the diameter reaches 60 mm(2-5). To prevent dissection and rupture, prevailing guidelines recommend preventive extirpation of ascending aortic aneurysms ≥ 55 mm (or ≥ 50 mm in high-risk patients)(6-11). Patients with smaller aneurysms require serial imaging until the threshold for intervention is reached.

Although indication criteria for prophylactic surgery rely on maximal diameter measurements, the optimal interval for the follow-up of thoracic aortic aneurysms (TAAs) has not been determined. If any, current guidelines propose surveillance protocols that involve (bi)annual computed tomography (CT) or magnetic resonance imaging (MRI)(6, 7). However, these proposals are insufficiently backed up by data demonstrating the necessity for such an approach. The current retrospective longitudinal cohort study aims to 1. acquire growth rates of TAAs in the context of aortic valve morphology, 2. identify risk factors that predict the need for pre-emptive aortic repair, and 3. provide patient-specific follow-up intervals.

METHODS

Study population

We reviewed the clinical database of the Maastricht University Medical Centre (MUMC+) for patients who were referred for TAA evaluation between January 1999 and August 2019. Patients with maximal ascending aortic diameters ≥ 40 mm at baseline who underwent multiple imaging examinations during follow-up were included. Exclusion criteria comprised prior aortic or valvular surgery and a diagnosis or suspicion of hereditary connective tissue disease. The study protocol was reviewed and approved by the institutional medical ethics committee, who waived the need for informed consent due to the study's retrospective nature.

Data collection and image analysis

Data collection and image assessment were performed by two readers (B.A., M.R.). Baseline characteristics and medical history were drawn from electronic patient records. Valve morphology and baseline valvular function were determined using transthoracic echocardiography (TTE) and classified according to current guidelines(12, 13).

All TTE, CT angiography, and MRI procedures performed for evaluation of TAA dimensions were assessed to study aortic diameters. Echocardiographic diameters were measured in parasternal long-axis views at end-diastole, using the leading edge-to-leading edge technique. CT and MRI were typically performed using prospective ECG gating with end-diastolic triggering, while measurements were acquired from inner edge to inner edge. For all modalities, care was taken to perform measurements perpendicular to the long axis of the aorta. Mean aneurysm growth rates were calculated by dividing the diameter difference between the first and last imaging examinations by the time interval between the two studies. The primary endpoint was reached when a patient met the indication criterion for pre-emptive surgery. This threshold was set at ≥ 55 mm (tricuspid aortic valve (TAV) and uncomplicated bicuspid aortic valve (BAV)) or ≥ 50 mm (BAV with concomitant risk factors (arterial hypertension, aortic coarctation, family history of dissection and/or expansion rate ≥ 3 mm/year))(6, 8).

Statistical analysis

Statistical analyses were performed using SPSS version 24 (IBM SPSS Statistics, Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). The Student t-test and Mann-Whitney U test were used for comparison between groups. Categorical variables are given as frequencies and percentages, and were compared using the chi-square test. Logistic regression was performed to identify predictors for reaching the endpoint of prophylactic surgery. For the patients who reached this endpoint, it was calculated – based on mean growth rates - whether a 2- or 3-yearly imaging strategy would have delayed surgery compared to an annual surveillance approach. The diagnostic accuracy of various follow-up protocols was calculated as the percentage of subjects in whom timely identification would have occurred.

RESULTS

Baseline characteristics

In total, 332 TAA patients (25.3% female) were included (Table 1). Median age was 64.2 years (range 19-86 years). Fifty-seven patients (17.2%) had BAV. Compared to those with BAV, patients with TAV were older (65.9 vs 52.4 years, $p<0.001$) and more frequently suffered from hypertension (76.4% vs 43.9%, $p<0.001$) and hyperlipidaemia (44.0% vs 17.5%, $p<0.001$). Patients with BAV more often had moderate or severe aortic stenosis at baseline (28.1% vs 6.9%, $p<0.001$).

Median follow-up of the entire cohort was 6.7 years (IQR 4.5-10.2 years). During the cumulative follow-up of 2545.4 years, the included patients underwent 2233 imaging examinations (TTE $n=1750$, CT $n=378$, and MRI $n=105$). Mean time between two consecutive measurements was 1.3 ± 0.7 years. Of the patients who died during follow-up ($n=23$), none died of thoracic aortic disease. Two patients suffered dissection and underwent emergency surgery; both had TAV and diameters <55 mm at last follow-up contact (both <1 year before dissection onset).

Table 1. Baseline characteristics of the study population.

	TAV (n = 275)	BAV (n = 57)	p-value
Age (years)	65.9 (58.4-71.7)	52.4 (42.4-59.8)	<0.001
Sex (female)	65 (23.6%)	19 (33.3%)	0.125
Height (cm)	174.8 ± 8.6	177.2 ± 9.6	0.07
Weight (kg)	81.8 ± 14.8	83.6 ± 14.8	0.39
BMI (kg/m²)	26.6 ± 3.9	26.6 ± 4.1	0.94
BSA (m²)	2.0 ± 0.2	2.0 ± 0.2	0.19
Hypertension	210 (76.4%)	25 (43.9%)	<0.001
Dyslipidemia	121 (44.0%)	10 (17.5%)	<0.001
Diabetes	15 (5.5%)	3 (5.3%)	0.95
AS ≥ moderate	19 (6.9%)	16 (28.1%)	<0.001
AR ≥ moderate	27 (9.8%)	9 (15.8%)	0.19

Table 1. (continued)

	TAV (n = 275)	BAV (n = 57)	p-value
CABG	25 (9.1%)	1 (1.8%)	0.06
CVA/TIA	35 (12.7%)	6 (10.5%)	0.65
Malignancy	33 (12.0%)	6 (10.5%)	0.75
Haemodialysis	2 (0.7%)	0	0.52

Values are mean ± SD or median (interquartile range).
BMI: body mass index; BSA: Body Surface Area; AS: aortic stenosis; AR: aortic regurgitation; CABG: coronary artery bypass graft; CVA: cerebrovascular accident; SD: standard deviation; TIA: transient ischemic attack.

Aneurysm growth

The growth rates of the entire population were 0.14 mm/year (median) and 0.2 ± 0.4 mm/year (mean and SD). The largest observed growth rate was 2.0 mm/year, while 40.6% of patients showed no diameter increase between baseline and last follow-up (Figure. 1). Mean expansion rates were comparable between TAV and BAV (0.2 ± 0.4 mm/year vs 0.2 ± 0.3 mm/year, $p=0.819$) (Figure. 2). Women had greater expansion rates than men (0.3 ± 0.5 vs 0.2 ± 0.4 mm/year, $p=0.007$). At multivariable regression analysis, female sex and presence of at least moderate aortic regurgitation (AR) at baseline were shown to be independent predictors for more rapid aneurysm expansion (Table 2). In contrast, the presence of a BAV was not associated with higher growth rates.

Figure. 1 Histogram showing the distribution of mean growth rates among patients with thoracic aortic aneurysms. As depicted, the majority of aneurysms remain stable or grow only minimally over time.

Figure 2 Bar charts showing mean growth rates of ascending aortic aneurysms as a function of sex, valve type, hypertension, and valvular function. Female sex and presence of more than moderate aortic regurgitation (AR) were associated with higher thoracic aortic aneurysm growth rates. AS aortic stenosis, BAV bicuspid aortic valve, TAV tricuspid aortic valve; *statistically significant.

Table 2. Univariable and multivariable regression analysis showing predictors for aortic growth.

	Univariable		Multivariable	
	B	p-value	B	p-value
Age (years)	-0.003	0.108		
Sex (female)	0.134	0.007	2.142	0.033
Hypertension	0.002	0.964		
Dyslipidemia	0.030	0.492		
Valve morphology (tricuspid)	0.013	0.819		
AS ≥ moderate	-0.016	0.817		
AR ≥ moderate	0.270	<0.001	3.987	<0.001
Baseline diameter (mm)	-0.011	0.118		

AR: aortic regurgitation; AS: aortic stenosis.

Surgical repair

During follow-up, 24 patients (7.2%) reached the indication criterion for pre-emptive surgery. Among those were 9 BAV patients, who all had concomitant risk factors and were referred for aneurysmectomy at a diameter of ≥50 mm. Logistic regression revealed baseline diameter, growth rate, and the predetermined interventional threshold to be independent predictors of reaching the primary endpoint (Table 3).

Table 3. Univariable and multivariable logistic regression analysis showing predictors for reaching the threshold for prophylactic aortic repair.

	Univariable		Multivariable	
	B	p-value	B	p-value
Age (years)	-0.031	0.046	0.024	0.578
Sex (male)	0.623	0.159		
Hypertension	0.003	0.996		
Dyslipidemia	-0.089	0.839		
AS ≥ moderate	0.891	0.098		
AR ≥ moderate	1.609	0.001	2.432	0.080
Surgical threshold (≥55 mm)	-1.179	0.009	-5.610	0.004
Baseline diameter (mm)	0.302	<0.001	1.130	<0.001
Growth rate (mm/year)	3.992	<0.001	11.299	<0.001

AR: aortic regurgitation; AS: aortic stenosis.

Table 4. Diagnostic accuracy of various imaging strategies.

A. Surgical threshold: ≥55 mm

	Current diameter			Accuracy	Reduction of imaging studies*
	40-44 mm	45-49 mm	50-54 mm		
Protocol 1	Two-yearly	Two-yearly	Annually	100%	17.8%
Protocol 2	Two-yearly	Two-yearly	Two-yearly	53.3%	43.4%
Protocol 3	Three-yearly	Two-yearly	Annually	100%	20.6%
Protocol 4	Three-yearly	Three-yearly	Annually	100%	29.9%

B. Surgical threshold: ≥50 mm

	Current diameter		Accuracy	Reduction of imaging studies*
	40-44 mm	45-49 mm		
Protocol 1	Two-yearly	Annually	100%	8.0%
Protocol 2	Two-yearly	Two-yearly	33.3%	44.4%
Protocol 3	Three-yearly	Annually	100%	16.0%

*As compared to a once-yearly strategy.

Optimal imaging interval

Various imaging protocols were tested for their accuracy in timely identification of the necessity for pre-emptive aortic repair (Table 4). Lowering imaging frequencies to less than once annually causes delay to surgery in patients in whom the current diameter is within 5 mm of the surgical threshold. However, imaging intervals can be prolonged safely to once every 3 years, as long as the diameter is between 40 and 44 mm (BAV with risk factors) or 40-49 mm (uncomplicated BAV and TAV). The implementation of such strategies would have reduced the number of imaging examinations in the study population by 16.0% and 29.9%, respectively.

DISCUSSION

Cardiovascular guidelines provide comprehensive recommendations on which patients should be selected for preventive aortic repair. However, the management of asymptomatic non-syndromic TAAs with diameters below interventional cut-offs is less well described. Our main conclusions are: (1) the majority of TAAs remain stable or grow minimally over time, (2) the need for prophylactic surgery is determined by baseline diameter, growth rate, and the predetermined interventional threshold, and (3) 3-yearly imaging follow-up suffices for any aneurysm with a diameter >5 mm below the surgical indication criterion.

Aortic growth rates

Thus far, studies that sought to investigate aneurysm growth rates have yielded divergent results. Our findings concur with those of recent investigations, which have shown that ascending aortic aneurysms expand at slightly higher rates than the normal-sized aorta (i.e. 0.2-0.4 mm/year vs 0.1 mm/year)(14-17). As such, average TAA growth rates are markedly lower than previously assumed(18). Pioneer work from the Yale group, whose studies form the basis for many recommendations within current guidelines, demonstrated an average enlargement of 0.7-1.2 mm/year(19). Using serial CT, Hirose et al. even documented growth rates as high as 4.2 mm/year(20). However, these early studies included a substantial number of patients with connective tissue disease and chronic dissections, who were followed over a relatively short period (i.e. 6-19 months). Since short follow-up durations can cause small diameter changes and measurement inaccuracies to become translated into disproportionately high annual growth rates, it is conceivable that the expansion rates reported in these studies are somewhat overestimated. In comparison, a growth rate of ≥ 0.7 mm/year was observed in only 8.1% of our patient population.

The current study provides more insight into the individual character of TAA progression. Based on reported mean expansion rates, it has long been thought that all aneurysms grow over time(8, 19). However, our results reflect that nearly half of non-syndromic TAAs remain stable in size - even at long-term follow-up. In contrast, a small portion of patients exhibit remarkably high growth rates (up to eight times the mean) and are at risk for reaching the diameter threshold for preventive surgery. Moderate or severe AR at baseline was shown to be the most important risk predictor for rapid growth. The pathophysiological mechanism behind this observation can be regarded as a vicious circle, in which AR causes increase of left ventricular stroke volumes and elevated aortic wall stress, and further aortic dilatation leads to aggravation of AR. Importantly, we have shown that presence of BAV does not confer risk for more rapid aneurysm dilatation. This, and the observation that BAV is not associated with a higher risk of acute aortic events, may question the lower interventional thresholds that apply to this patient group(3, 21).

Our data confirm that female sex is associated with more rapid aneurysm growth(22). Moreover, outcome studies have demonstrated that female TAA patients have a three-fold higher risk of experiencing dissection, and a 40% increase in risk of mortality(19, 23). Although

the magnitude of sex-based growth differences does not merit a more frequent imaging strategy in women, it prompts deliberation as to why the natural history of aneurysms differs between genders. One theory explains the worse outcome in women by their higher vessel wall concentrations of matrix metalloproteinases (MMPs) – enzymes involved in the degradation of extracellular matrix (ECM) content. Interestingly, aneurysms with more pronounced MMP-2 and MMP-9 expression show more extensive ECM remodelling and decreased compliance(24). Future immunohistochemical and biomechanical studies could evince a causal relation between gender-associated structural differences and the more aggressive TAA behaviour in women.

Implications for imaging

Current guidelines prescribe referral for preventive surgery based on absolute diameter cut-offs. In addition, the ACC/AHA advocates elective operation of patients who exhibit growth rates >5 mm/year. Assessment of these indications requires adequate imaging surveillance, yet only two out of five available guidelines provide appropriateness criteria to this end. Based on the consensus opinion of experts, these recommend yearly or semi-annual CT or MRI(6, 7). Although others cautiously suggest lowering imaging frequencies in the case of stable disease, no previous study systematically investigated the impact of different follow-up protocols. The results of the current study reveal that yearly imaging carries no therapeutic consequences for patients with small aneurysms. On the contrary, it can add unjustifiable costs to health care and unnecessary exposure to radiation and contrast agent administration. Here, we propose a surveillance strategy that consists of 3-yearly imaging of patients with smaller aneurysms and yearly imaging of those who are in close proximity to their respective surgical thresholds. We conclude that this approach is as accurate as annual follow-up and reduces the number of requested imaging examinations by 29.9% (TAV) and 16.0% (BAV with risk factors). It is noteworthy that these percentages have been calculated using data of patients who met the endpoint of prophylactic surgery. The proposed strategy could have reduced imaging frequencies by up to two-thirds in patients with stable diameters.

Although current guidelines primarily depend on maximal diameter cut-offs, it is generally known that ATAAD can also occur in aortas that do not meet criteria for pre-emptive surgical repair(25). Recent studies have investigated the predictive potential of aortic length and volume, and found that these may improve the timely identification of patients at risk(26, 27). Furthermore, four-dimensional (4D) flow MRI is emerging as a clinically feasible imaging technique that can further improve selection of patients who may benefit from prophylactic surgery(28, 29). Future prospective studies are now needed for these novel imaging markers to find their way into clinical guidelines.

Limitations

Some limitations of the current study need to be addressed. First, our study population is not representative of patients with connective tissue diseases. These are reported to have higher aortic growth rates, and the proposed imaging intervals should not be extrapolated to this patient group(30). Second, we have only looked into growth rates of ascending aortic aneurysms. Descending thoracic and abdominal aneurysms may expand more rapidly and merit more frequent surveillance imaging. Since we included only patients who underwent imaging at ≥ 2 different time points, we were not able to adequately evaluate the risk of adverse outcomes. Third, diameters were assessed using different imaging modalities. Although leading edge-to-leading edge (TTE) and inner edge-to-inner edge (CT and MRI) measurements closely agree, incongruity between methods may have contributed to inaccuracies in calculated growth rates(31). Fourth, growth rates were calculated assuming a linear TAA growth pattern. According to Laplace's law,

wall tension is proportional to the vessel radius for a given blood pressure. Therefore, it has been hypothesised that growth rates become higher as the aorta progressively enlarges(32). However, a previous study with standardised imaging intervals could not confirm this hypothesis and found that growth rates remained steady during follow-up(15). Due to the various time points at which our patients were imaged, we were not able to investigate the relationship between aortic size and growth rate in the current study. Finally, this was a single-centre analysis. Future prospective multicentre studies are needed to confirm our results.

CONCLUSIONS

Non-syndromic ascending aortic aneurysms grow at lower rates than previously assumed. Reduction of imaging frequency to once every 3 years seems reasonable for asymptomatic patients in whom the ascending aorta is only mildly dilated.

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Aortic elongation part I: the normal aortic ageing process

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Chapter

ABSTRACT

OBJECTIVES

Differentiation between normal and abnormal features of vascular aging is crucial, as the latter is associated with adverse outcomes. The normal aortic aging process is accompanied by gradual luminal dilatation and reduction of vessel compliance. However, the influence of age on longitudinal aortic dimensions and geometry has not been well studied. This study aims to describe the normal evolution of aortic length and shape throughout life.

METHODS

A total of 210 consecutive patients were prospectively enrolled in this cross-sectional single center study. All subjects underwent computed tomography (CT) on a third-generation dual-source CT scanner. Morphometric measurements, including measurements of segmental length and tortuosity, were performed on three-dimensional models of the thoracic aorta.

RESULTS

The length of the thoracic aorta was significantly related to age ($r=0.54$) and increased by 59 mm (males) or 66 mm (females) between the ages of 20 and 80 years. Elongation was most pronounced in the proximal descending aorta, which showed an almost 2.5-fold length increase during life. The lengthening of the thoracic aorta was accompanied by a marked change of its geometry: whereas the aortic apex was located between the branch vessels in younger patients, it shifted to a more distalward position in the elderly.

CONCLUSIONS

The normal aging process is accompanied by gradual aortic elongation and a notable change of aortic geometry. Part II of this two-part article investigates the hypothesis that excessive elongation could play a role in the occurrence of acute aortic dissection.

KEYWORDS

Aortic elongation, vascular aging, aortic aging

KEY POINTS

- The thoracic aorta gradually elongates with increasing age. The proximal descending aorta is the segment in which greatest longitudinal growth is observed.
- During life, the aorta becomes more tortuous and the apex shifts to a position distal of the left subclavian artery. The length of the proximal descending aorta is the most important predictor of aortic phenotype (i.e., type I or type II).

INTRODUCTION

As the Western population grows increasingly older, physicians will more frequently encounter age-related alterations of the vascular system. It is important to distinguish normal from abnormal aspects of vascular aging, since an accelerated aging process confers risk for future cardiovascular disease (CVD)(1, 2). Prominent structural changes of the aorta include thickening of the intimal vessel wall and gradual luminal dilatation(3-7). The increase of aortic diameters has been studied extensively, given the relation of excessive dilatation with severe complications like dissection and rupture(8). In contrast to its circumferential dimensions, the longitudinal dimensions of the aorta and their evolution over time have not been well studied. It is conceivable that the aorta lengthens during life, since a tortuous deformation or even kinking is frequently observed in elderly patients. This theory was investigated by an autopsy study, which measured aortic length in post mortem specimens(9). However, in vitro measurements may not represent those in vivo due to post mortem contraction and the loss of autonomous nerve innervation(9, 10). Since advanced imaging techniques are required to study the complex three-dimensional geometry of the aorta, it was not until recently that non-invasive measurements of aortic length became feasible. One imaging study assessed the relation between age and aortic length and concluded that elongation only occurs in the proximal aorta(11). However, this study measured the length of the ascending aorta as the distance between the sinuses of Valsalva and the apex of the aortic arch. Since the morphology of the aortic arch differs between individuals(12) and may change with increasing age(13), it is unclear if these findings represent true vessel lengthening. Theoretically, tortuosity and kinking could also result from age-associated changes of thorax configuration (such as spondylosis and increased kyphosis), which may lead to confinement of the aorta in a gradually decreasing intrathoracic volume(14). Using the latest computed tomography (CT) scan techniques, the purpose of the current study is to provide an elaborate description of the evolution of longitudinal aortic dimensions and geometry during life.

MATERIALS AND METHODS

Study population

Consecutive adult patients who underwent contrast-enhanced chest CT at the Maastricht University Medical Center+ between September 2015 and September 2016 were prospectively enrolled in this single center cross-sectional study. Patients with suspected or known aortic disease and those who previously underwent cardiothoracic surgery were excluded, as were those with any other condition that might cause distortion of aortic shape (such as previous radiotherapy or pneumothorax). All scans that provided for adequate three-dimensional (3D) modeling of the thoracic aorta with automatically detected centerline were studied. Eventually, a total of 210 patients was included. CT examination was performed because of suspicion of pulmonary embolism (50.7%), pneumonia (7.1%), evaluation or follow-up of pulmonary nodules (38.9%) and other (3.3%). Baseline characteristics were drawn from the medical record. The institutional review board approved the study protocol and waived the need for written patient consent because of the observational character of the study.

Image acquisition

All CT scans were performed on a third-generation dual-source CT scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany) with 96 x 0.6 slice collimation at a rotation time of 0.25 seconds (s). Indications and protocolling were clustered in vascular ($n = 111$) and oncological ($n = 99$) workflows without dedicated ECG synchronization of the respective data sets. Tube

voltage and tube current were individually and semiautomatically adapted in all examinations (CARE kV, CARE Dose4D, Siemens), depending on patient's Body Mass Index (BMI). Iopromide (300 mg iodine/mL, Ultravist, Bayer, Berlin, Germany) was used as a contrast medium in all subjects, using an individualized approach (Contrast Dose Management, Certegra, Bayer). Image reconstruction was performed with 1 mm slice thickness and a reconstruction increment of maximal 0.7 millimeter (mm) with soft tissue kernels (Siemens Bv36/Br40), using a raw data based iterative reconstruction algorithm (ADMIRE, reconstruction strength 3).

Image evaluation

Image evaluation was performed by a single observer with 5 years experience in cardiovascular imaging. A 3D reconstruction of the thoracic aorta with fitted centerline was created automatically using dedicated software (Syngo.via, Siemens). The aorta was then manually divided by the observer into multiple anatomical segments following current guidelines (Figure 1A)(15-17). The ascending aorta was defined as the part of the aorta between the sinotubular junction (STJ) and the origin of the brachiocephalic trunk. The aortic arch was measured as the distance from the brachiocephalic trunk to the left subclavian artery. The descending aorta was defined as the segment between the left subclavian artery and the diaphragm and subdivided into two parts: a proximal part (from the left subclavian artery to the level of the bifurcation of the pulmonary trunk) and a

distal part (from the level of the pulmonary trunk bifurcation to the diaphragm). The length of each segment was measured as the centerline distance between two points. Segment tortuosity was calculated as the ratio of the centerline path length to the direct linear distance between centerline endpoints (Figure 1B). The position of the aortic apex (i.e. the most cranial position of the centerline) determined the morphology of the aorta. Type I was defined as an aorta in which the apex was located between the branch vessels (i.e. in the segment defined as the aortic arch), while in type II aorta the apex was identified at a position distally of the left subclavian artery (Figure 1).

Statistical analysis

Statistical analyses were performed using commercially available software (IBM SPSS Statistics, version 24, Armonk, New York, USA). The distribution of continuous variables was assessed for normality by the Shapiro-Wilk test and assessed visually by inspection of histograms and standardized normal probability (P-P) plots. Continuous baseline characteristics are presented as mean ± standard deviation or as median and interquartile range (IQR) in the presence of skewness. Categorical variables are expressed as frequency and percentages. Differences between genders were assessed using the independent samples t-test (or Mann-Whitney U test, if deemed appropriate) and Chi-square test for categorical variables. Linear regression tested the relationship between age and aortic length. Model assumptions on normality, linearity and homoscedasticity for multiple regression analysis were checked and variance stabilizing measures, such as log transformation and bootstrapping were applied. Check for (curvi)linearity was performed by introducing linear and quadratic terms for the quantitative predictor of age (in years minus the average, to prevent collinearity between the linear and quadratic term)(18). Logistic regression analysis was performed to obtain predictors for the two distinct aortic types. A p-value <0.05 was considered statistically significant.

RESULTS

Study population

Subject characteristics are summarized in Table I. The study sample comprised more females than males (61% vs. 39%, respectively). The median age of the total study sample was 62 years (IQR 52–72, range 23-92) and did not differ between genders. Men were significantly taller and heavier than women and, consequently, had a larger body surface area (BSA). Body mass index (BMI) was comparable between genders. Sixty-eight patients were free of any cardiovascular risk factor. The others were marked as smoker (n=82) and/or suffered from hypertension (n=69), hypercholesterolemia (n=29) or diabetes (n = 19). Of the hypertensive subjects, 62 (91%) were treated with antihypertensive medication.

Table 1. Baseline characteristics of the study population.

	Males (N = 82)	Females (N = 128)	p-value
Age (years)	65 [55-73]	61 [50-70]	0.072
Length (cm)	176 ± 8	165 ± 8	<0.001
Weight (kg)	82.0 [71.0-90.0]	70.9 [59.3-81.5]	<0.001
BMI	26.2 [23.4-28.6]	25.0 [21.7-29.7]	0.58
BSA (m²)	2.0 ± 0.2	1.8 ± 0.2†	<0.001
Hypertension	34 (41.5%)	35 (27.3%)	0.036
Dyslipidemia	15 (18.3%)	14 (10.9%)	0.47
Diabetes	13 (15.9%)	6 (4.7%)	0.15
(Past) smoker	35 (42.7%)	47 (36.7%)	0.012

BMI: Body Mass Index; BSA: Body Surface Area.

Aortic length

The entire thoracic aorta and all individual segments were, on average, significantly longer in men than in women. However, after adjustment for BSA, none of these differences persisted, indicating the influence of body proportions on aortic length. The BSA-indexed length of the entire thoracic aorta was positively related to age ($r=0.54$, $p<0.001$), as were the individual lengths of the ascending aorta ($r=0.55$, $p<0.001$) and the aortic arch ($r=0.52$, $p<0.001$, Figures 2A-C). The length of the descending aorta was also correlated with age ($r=0.45$, $p<0.001$). However, this was solely driven by notable lengthening of its proximal part ($r=0.63$, $p<0.001$, Figure 2D). No relation was found between the length of the distal descending aorta and age ($r=0.09$, $p=0.178$, Figure 2E). Between the ages of 20 and 80 years, the total length of the thoracic aorta increased by a mean of 59 mm (males) and 66 mm (females), reflecting a relative lifelong growth of approximately 125%. The extent of elongation differed markedly between individual segments: the length of the ascending aorta increased by 142%, compared to 169% (aortic arch) and 247% (proximal descending aorta).

Aortic geometry

The tortuosity ratios of the ascending aorta, aortic arch, and distal descending aorta were not significantly related to age. The tortuosity of the proximal descending aorta was moderately associated with age ($r=0.38$, $p=0.004$) and increased from mean 1.07 (at age 20 years) to 1.21 (at age 80 years). During life, the morphology of the thoracic aorta changed markedly: younger patients exhibited a type I aorta ($n=49$), whereas a type II aorta was mainly observed in the elderly ($n=161$, Figure 3 and 4). Multivariable logistic regression analysis revealed age, proximal descending aortic length, and hypertension to be independent predictors of aortic type (Table 2). The morphology of the aorta was not influenced by BSA, gender or cardiovascular risk factors other than hypertension.

Figure 2. Relation between age and BSA-indexed aortic length. BSA-indexed length of the (A) entire thoracic aorta, (B) ascending aorta, (C) aortic arch, (D) proximal descending aorta, and (E) distal descending aorta. The dashed lines mark the 95% prediction intervals. As can be derived from these graphs, elongation is most prominent in the proximal descending aorta. BSA: Body Surface Area, NS: not significant.

Figure 3. The influence of age on aortic type. Boxplot showing the age differences between aortic types: type I is more prevalent in younger individuals, while type II aorta is mainly observed in the elderly.

Table 2. Univariable and multivariable logistic regression analysis showing predictors for aortic morphology.

	Univariable		Multivariable	
	B	p-value	B	p-value
Age (years)	0.166	<0.001	0.212	<0.001
Gender	-0.360	0.296		
BSA (m²)	-1.899	0.011	-1.000	0.547
Hypertension	1.324	0.003	-1.828	0.047
Dyslipidemia	0.734	0.194		
Diabetes	0.152	0.796		
(Past) smoker	0.360	0.296		
Ascending aortic length (mm)	0.104	<0.001	-0.079	0.151
Aortic arch length (mm)	0.117	<0.001	-0.125	0.086
Proximal descending aortic length (mm)	0.227	<0.001	0.342	<0.001

BSA: Body Surface Area.

DISCUSSION

Premature vascular aging plays a major role in the development of CVD, as it forms the basis for specific pathophysiological disease mechanisms to act upon. An extensive body of literature describes the relation between common features of vascular aging, such as reduced vessel compliance and luminal dilatation, and the occurrence of cardiovascular events(19-21). Information on aortic length, however, is scarce, since older imaging techniques did not provide for an accurate and three-dimensional visualization of the thoracic aorta. Using latest CT equipment and acquisition protocols, we have assessed the longitudinal dimensions of the aorta in apparently healthy subjects. By implication, we have shown that it is possible to assess aortic length on routinely acquired CT, even if scans were not specifically acquired for a focused visualization of the aorta. The main findings of the current study are that: i) the thoracic aorta and its individual segments lengthen with increasing age, ii) the extent of elongation differs between segments, and iii) the morphology of the thoracic aorta (aortic type) changes over time. As shown, the ascending aorta only grows modestly during life, while the greatest increase in length is observed in the segment distal to the arch branch vessels. This results in a notable change of aortic morphology. Whereas the younger aorta typically looks like a candy cane (type I aorta), the older aorta unfolds and is more ‘question mark-shaped’ (type II aorta, Figure 4). Few previous studies have addressed the age-related alterations of aortic length. Sugawara et al. investigated aortic length in healthy volunteers, but concluded that elongation occurs in the ascending aorta only(11). However, their study defined the ascending aorta as the distance between the root and the apex of the aorta. As we have shown, the position of the apex changes during life and, therefore, the measurements by Sugawara et al. represent an alteration of aortic morphology rather than lengthening of the tubular ascending aorta. To avoid indistinctness, we would advocate the use of anatomical landmarks in the assessment of aortic length, as supported by current guidelines(15-17). Rylski et al. investigated gender- and age-related differences of aortic diameters and length, which were found to be largest in males(22). BSA-indexed aortic lengths (but not diameters) were comparable between genders and increased in a similar pattern when compared to the current study. We have additionally shown that the geometry of the thoracic aorta changes with increasing age and postulate that these changes could reflect an (un)successful vascular aging process. Future studies are warranted to investigate the prognostic importance of changes of longitudinal aortic dimensions.

The question arises how our results can be explained from a biomechanical point of view. It has been suggested that aortic elongation is part of a gradual remodeling process as a result of ‘material fatigue’ of the vessel wall(10, 11, 23). The lifelong exposure to pulsatile strain causes fracture and breakdown of elastin fibers, which results in structural remodeling. Besides elongation and dilatation, this theory explains age-related vascular stiffening, as the reduction of elastin content impairs vessel compliance. Two reasons provide a possible explanation for the differences in elongation between various segments. First, elastin content is highest in the aortic arch and proximal descending aorta(24, 25). Following the principles of material fatigue, one would expect these segments to be more prone to remodeling, which is in line with the findings of the current study. Second, the distal descending aorta is fixated to the spine by the intercostal arteries and endures only little longitudinal strain(26), whereas the more proximal aortic segments can move relatively freely in the longitudinal direction. Circumferential strain values, however, are comparable throughout the entire thoracic aorta(26). This provides a plausible explanation for the fact that diameter increase is more prominent than length increase in the distal descending aorta, whereas the opposite applies to the more proximal segments of the thoracic aorta(6).

Clinical perspective

Our findings evoke several clinical questions. First, future research could address the clinical implications of aortic elongation. It has been postulated that aortic length plays a role in the occurrence of aortic dissection, which is the result of an imbalance between the biological strength of the aorta and forces exerted on its wall(27). To date, the transverse diameter is the only recognized anatomical risk factor for dissection and the sole marker used in the stratification towards prophylactic aortic surgery. However, luminal diameters are considered to be a poor risk predictor for dissection, as the majority of patients (either presenting with Stanford type A or type B dissection) would not have met the threshold for preventative aortic repair(28-30). In part II of this two-part article, we will investigate the hypothesis that excessive aortic elongation could also play a role in the development of aortic dissection.

Furthermore, our findings should be taken into account in the assessment of arterial stiffness. Pulse wave velocity (PWV) is the velocity at which the arterial pulse propagates through the circulatory system and is the gold standard technique for measurements of arterial stiffness. It is measured as $PWV = \text{distance (meters)} / \Delta t$ (transit time in seconds), in which t is the time delay between the arrival of two waveforms obtained at different anatomical locations (usually at the level of the carotid and femoral arteries). The distance covered by the waves is usually assimilated to the surface distance between the two recording sites. Our results indicate that this technique only provides approximations of the distance traveled by the pulse waves, as vessel length differs between individuals and changes with increasing age. The use of 3D-imaging methods allows for exact distance measurements between two recording sites and, thus, for more precise calculations of PWV.

Study limitations

A few limitations of the current study should be addressed. First, we used a cross-sectional study design, whereas a longitudinal design could be preferred to investigate an aging process. However, to investigate aortic elongation, one would need to conduct a study with a near lifelong follow-up duration, which carries insuperable constraints for both patient and researcher.

Second, CT examinations were performed for clinical purposes, which implicates that a substantial number of subjects were exposed to cardiovascular risk factors such as hypertension and hyperlipidemia. Our study sample therefore represents a population that is encountered in daily clinical practice, rather than a population of entirely healthy volunteers. As patients aged 50 to 70 years undergo CT more frequently, these are somewhat overrepresented in our study population. The greater variance of aortic length in the elderly should be taken into consideration in the prediction of aortic length.

Third, CT acquisitions were performed without ECG synchronization. Nevertheless, in none of the included scans did we encounter motion artifacts that could hamper the accuracy of length measurements. With the acquisition parameters as described above, the entire thoracic aorta can be acquired within one rotation of the scanner tube. With rotation times as short as 250 msec, acquisition time only covers a small fraction of the R-R interval, which explains the absence of motion artifacts. Scans acquired with older scanners (and, thus, longer acquisition times) will more likely benefit from ECG synchronization.

Figure 4. Three-dimensional CT models of the aorta. Three-dimensional modeled CT images of the aorta of a 24-year old female (A) and an 85-year old female (B). In (A), a type I aorta is displayed, as the apex of the arch is located between the branch vessels. (B) depicts a type II aorta, as the apex has shifted to a position distally of the left subclavian artery.

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Aortic elongation part II: the risk of acute type A aortic dissection

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Chapter

ABSTRACT

OBJECTIVES

Prophylactic surgery for prevention of Acute Type A Aortic Dissection (ATAAD) is reserved for patients with an ascending aortic aneurysm sized ≥ 55 mm. Identification of additional risk predictors is warranted since more than 70% of patients who present with ATAAD have a non-dilated aorta or an aneurysm that would not have met the diameter criterion for preventative surgery. Aim of the current study was to evaluate ascending aortic elongation as a risk factor for ATAAD, and to compare aortic lengths between ATAAD patients and healthy controls.

METHODS

Aortic lengths and diameters of ATAAD patients were measured on three-dimensional modeled CT and adjusted to pre-dissection dimensions in this cross-sectional single center study. Binary logistic regression was used to evaluate the relation between ATAAD and aortic length and diameter. Lengths of different aortic segments were compared with a healthy control group using a propensity score matching model.

RESULTS

Two-hundred and fifty patients were included in the study (ATAAD $n=40$, healthy controls $n=210$). Ascending aortic length and diameter proved to be independent predictors for ATAAD (OR=5.3 CI 2.5-11.4, $p<0.001$, OR=8.6 CI 2.4 - 31.0, $p=0.001$, respectively). Eighty patients were matched based on propensity scores (ATAAD $n=40$, controls $n=40$). The ascending aorta was longer and more dilated in ATAAD patients when compared to matched healthy controls (78.6 ± 8.8 mm vs. 68.9 ± 7.2 mm, $p<0.001$, $34.4\text{ mm}\pm 0.32$. vs. $39.4\text{ mm}\pm 0.77$, $p<0.001$, respectively). No differences were found in the lengths of the aortic arch and descending aorta.

CONCLUSIONS

Ascending aortic length could serve as an independent predictor for ATAAD. Future studies that investigate indications for prophylactic aortic surgery should also focus aortic length.

KEYWORDS

Aortic elongation, aortic dissection, ascending aorta

KEY POINTS

- The length of the ascending aorta is increased in patients with type A dissection compared to propensity-matched controls.
- Ascending aortic length and diameter are both independent predictors for occurrence of acute type A dissection

INTRODUCTION

Acute Type A Aortic Dissection (ATAAD) is a life-threatening cardiovascular disease with an annual incidence of approximately 10 per 100.000 per year(1, 2). Mortality rates are high and range from 27% in surgically treated patients to 56% in those who undergo conservative therapy(3). Aortic dilatation is the only recognized anatomical risk factor for development of ATAAD and ascending aortic replacement is considered in patients with aortic aneurysms to prevent the occurrence of dissection and rupture(4). Current guidelines recommend preventative surgical intervention in aneurysms ≥ 55 millimeters (mm), as these carry an annual complication risk that exceeds the current surgical mortality rates(5, 6, 7). However, the sole use of aortic diameters in the risk prediction for ATAAD is questionable, since multiple studies have shown that the majority of dissected aortas exhibit diameters below this cut-off(8, 9). Modeling of dissected aortas to pre-dissection dimensions even demonstrated that 97% of ATAAD patients would fail to meet the criterion for preventative aortic repair(10). Therefore, the identification of additional risk factors is warranted in order to reduce the incidence of ATAAD. We hypothesize that excessive aortic elongation, like dilatation, could carry the risk of dissection. In part I of this two-part article, we have investigated the normal aging process of the thoracic aorta and shown that its length gradually increases with age. In daily clinical practice, the dissected aorta often appears abnormally elongated and tortuous in its course. Moreover, a transverse intimal entry tear is often observed upon inspection of the vessel wall, whereas a longitudinal burst would be expected as a consequence of severe aortic dilatation(11, 12). In our hypothesis, the transverse entry tear reflects disruptive stretch in the longitudinal direction, which may result from excessive aortic lengthening. Aim of the current study was to evaluate the potential role of elongation in the occurrence of ATAAD using three-dimensional (3-D) modeled computed tomography (CT) and to compare the aortic lengths of ATAAD patients with those of propensity-matched healthy controls.

MATERIALS AND METHODS

Study population

We retrospectively evaluated all consecutive adult patients who were diagnosed with ATAAD at the Maastricht University Medical Center+ between January 2010 and December 2016 and who underwent contrast-enhanced CT angiography (CTA). Exclusion criteria were prior aortic surgery, iatrogenic dissection, connective tissue disease (Marfan's disease, Loeys-Dietz syndrome, or Ehlers-Danlos syndrome), bicuspid aortic valve and familial thoracic aneurysm and dissection (TAAD). Results were compared with those of an apparently healthy control group, which was presented in part I of this two-part article. In brief, the control group consisted of apparently healthy adult patients who were referred for contrast-enhanced chest CT between December 2015 and December 2016. The study protocol was reviewed and approved by the local ethics committee. The need for written patient consent was waived because of the observational character of this study.

Image acquisition

The CT protocol for control patients was described in part I of this study. In the ATAAD group, scans were performed on a second-generation dual source CT scanner (Somatom Flash, Siemens Healthineers, Forchheim, Germany) with 128 x 0.6 slice collimation at a rotation time of 0.28. The scan protocol consisted of a non-contrast enhanced CT of the aorta, a retrospective ECG-triggered helical CTA of the aortic root and ascending aorta followed by a high-pitch spiral

CTA from the aortic arch to the femoral bifurcation. Tube voltage and tube current were semiautomatically adapted in all examinations (CARE kV, CARE Dose4D, Siemens) based on patient habitus. Iopromide (300 mg iodine/mL, Ultravist, Bayer, Berlin, Germany) was used as a contrast medium in all subjects, using an individualized approach (Contrast Dose Management, Certegra, Bayer). Image reconstruction was performed to achieve the same reconstruction parameters (slice thickness and increment) as in the control group.

Image analysis and modeling of aortic dimensions

Image analysis of ATAAD patients was performed by a single observer. After image acquisition, CT datasets were loaded onto a workstation for post processing (Syngo.via, Siemens). A three-dimensional model of the thoracic aorta was created and divided into three anatomical segments following current guidelines (Figure 1)(13). The ascending aorta was measured as the centerline distance between the sinotubular junction (STJ) and the origin of the brachiocephalic trunk. The aortic arch was defined as the segment that comprised the three branch vessels. The descending aorta was defined as the part of the aorta from the left subclavian artery to the aortic hiatus in the diaphragm. Luminal diameters were measured using the inner edge to inner edge approach at different levels of the aorta (STJ, halfway the ascending aorta and maximal diameter). All diameter measurements were performed on multiplanar reformatted images perpendicular to the automatically-detected vessel centerline.

To evaluate aortic diameter and length as a potential risk factor for ATAAD, we performed retrospective modeling of the aorta to obtain adjusted pre-dissection dimensions. Rylski et al. demonstrated the dimensions of the ascending aorta to increase on average with 30% (diameter) and 10% (length) after the occurrence of dissection, while the lengths of the aortic arch and descending aorta did not increase(14). Like in their study, we modeled the aorta of ATAAD patients to pre-dissection dimensions by deducting 30% and 10% of the measured aortic diameter and length, respectively(10).

Figure 1. Length measurements of different aortic segments. Length measurements of different aortic segments. A: segmental division of the aorta (yellow: ascending aorta, red: aortic arch, green: descending aorta); B: Three-dimensional length measurement of the ascending aorta; C: Multiplanar reformatted image of the thoracic aorta.

Statistical analysis

The distribution of continuous variables was assessed for normality using the Shapiro-Wilk test and assessed visually by inspection of histograms and standardized normal probability (P-P) plots. Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) in the presence of skewness. Categorical variables are presented as frequencies and percentages. Differences between groups were assessed using the Students t-test or the Mann-Whitney U-test (for continuous variables) or the Chi-square test (categorical variables). Binary logistic regression was performed to assess independent predictors for occurrence of ATAAD.

Covariates for aortic length, used for calculation of propensity scores, were identified using multivariable regression analysis. Variables with p-value<0.20 were considered to be important covariates and were used to calculate propensity scores. Differences in baseline characteristics were added to this model for balancing purposes. Propensity scores were matched using nearest neighbor matching on a 1:1 ratio. Replacement was not allowed. Caliper distance was set at 0.10. Baseline characteristics were presented both before and after propensity-score matching. All statistical analyses were performed using commercially available software (SPSS version 24, IBM, Armonk, New York, USA and R Statistics, the R Foundation, Vienna, Austria).

RESULTS

Study population

As described in part I of this two-part article, 210 patients were included in the control group. Between January 2010 and December 2016, a total of 48 patients were diagnosed with ATAAD at our institution based on findings at CT examination. Two patients were excluded because of the iatrogenic origin of their dissection. Six patients were excluded because of concomitant diagnosis of connective tissue disease or bicuspid aortic valve. The remaining 40 patients were included in the study group. Baseline characteristics of both groups before propensity score matching are presented in the supplementary data (Supplementary Data 1). The ATAAD group comprised significantly more males than the control group (63% vs. 39%, p=0.01). Furthermore, ATAAD patients had a larger Body Surface Area (BSA) and were more likely to suffer from hypertension (both p<0.01).

Aortic length and diameters

As shown in part I, the length of the ascending aorta was significantly related to age in normal controls and increased by a mean of 3 mm/decade. Figure 2 depicts the adjusted pre-dissection length of the ascending aorta of ATAAD patients when plotted against the aortic length of the healthy control group. Adjusted and non-adjusted ascending aortic diameters were presented in Table 1. Binary logistic regression analysis was performed for evaluation of predictors for ATAAD. All variables with p<0.20 in univariable analysis were included in the multivariable model to assess independent predictors (Table 2). Both ascending aortic length and diameter proved to be independently related to the occurrence of ATAAD (OR 5.3, CI 2.5-11.4, p<0.001 and OR 8.6, CI 2.3-31.0, p=0.001, respectively).

Table 1: Ascending aortic diameters in ATAAD patients.

	Non-adjusted diameters	Adjusted diameters
Mean max. diameter (mm, $\pm$ SD)	51.2 $\pm$ 0.75	39.4 $\pm$ 0.57
Stratified max. diameter		
<50 mm	17 (43%)	39 (97%)
50-55 mm	10 (25%)	1 (3%)
>55 mm	13 (32%)	0

ATAAD: Acute Type A Aortic Dissection; mm: millimeter; SD: Standard Deviation.

Table 2: Binary logistic regression analysis for occurrence of ATAAD.

	Univariable		Multivariable			
	OR	CI	p-value	OR	CI	p-value
Age	1.0	0.9-1.1	0.21			
Gender	0.4	0.2-0.8	0.01	1.9	0.6-6.0	0.25
BSA	9.0	1.9-44.2	0.01	1.2	0.1-14.5	0.89
Hypertension	3.4	1.7-6.8	<0.001	1.3	0.5-3.5	0.56
Diabetes	0.3	0.0-2.0	0.19	0.5	0.1-4.8	0.54
Adjusted ascending aortic diameter (cm)	7.8	4.1-14.6	<0.001	8.6	2.4-31.0	0.001
Adjusted ascending aortic length (cm)	31.8	11.1-90.9	<0.001	5.3	2.5-11.4	<0.001

ATAAD: Acute Type A Aortic Dissection; BSA: Body Surface Area; OR: Odds Ratio; CI: Confidence Intervals.

Propensity score matching

For covariate assessment, multivariable linear regression analysis was conducted in the control group with ascending aortic length as dependent variable. Age, gender and BSA showed to be independent predictors for ascending aortic length (Table 3). These variables were therefore included in the model for calculation of propensity scores. Hypertension was also added to the model for balancing purposes. The propensity scores pre- and post-matching and their distribution are presented in the supplementary data (Supplementary Data 2). Eventually, 40 pairs were matched. After matching, there were no persisting differences in baseline characteristics between the two groups (Table 4).

Table 3: Univariable and multivariable linear regression analyses for assessment of covariates for aortic length in healthy controls.

	Univariable		Multivariable			
	R	p-value	B	β	CI	p-value
Age	0.47	<0.001	0.25	0.46	0.18 - 0.32	<0.001
Gender	0.44	<0.001	-4.63	-0.30	-6.72 - -2.55	<0.001
BSA	0.29	<0.001	9.22	0.25	4.62 - 13.83	<0.001
Hypertension	0.33	<0.001	1.09	0.08	-0.77 - 3.52	0.21
Diabetes	0.06	0.35	1.60	-0.05	-4.62 - 1.69	0.36

BSA: Body Surface Area; R: correlation coefficient; B: unstandardized regression coefficient; β : standardized regression coefficient; CI: Confidence Intervals.

Table 4: Post-matching baseline characteristics.

	Control group (n = 40)	ATAAD group (n = 40)	p-value
Age (years)	65 $\pm$ 13	63 $\pm$ 11	0.65
Gender (male)	24 (60%)	25 (63%)	1.00
BSA (m²)	1.95 $\pm$ 0.20	1.97 $\pm$ 0.18	0.80
Hypertension	26 (65%)	25 (63%)	1.00
Diabetes	1 (3%)	1 (3%)	1.00
Medication			
Betablockers	11 (28%)	10 (25%)	1.00
ACE-inhibitors	14 (35%)	10 (25%)	0.46
Calciumblockers	10 (25%)	3 (8%)	0.07
Diuretics	9 (23%)	7 (18%)	1.00

ATAAD: Acute Type A Aortic Dissection; SD: Standard Deviation, BSA: Body Surface Area; ACE: Angiotensine Converting Enzyme.

Aortic dimensions in dissection patients

The adjusted length of the ascending aorta was significantly increased in the ATAAD group when compared to their propensity-matched healthy peers (78.6±8.8 vs. 68.9±7.2 respectively, p<0.001). Adjusted maximum ascending aortic diameter was significantly increased as well (39.4±0.57 vs 34.4±0.32, p<0.001). Aortic arch length (36.2±7.0 vs. 34.3±11.9, p=0.39) and descending aortic length (219.4±23.3 vs. 210.4±28.1, p=0.13) did not differ significantly between the two matched groups (Table 5).

Table 5: Dimensions per segment.

	Control group (n = 40)	ATAAD group (n = 40)	p-value
Adjusted ascending aortic length (mm)	68.9 ± 7.2	78.6 ± 8.8	<0.001
Adjusted max. ascending aortic diameter (mm)	34.4 ± 0.32	39.4 ± 0.57	<0.001
Aortic arch length (mm)	34.3 ± 7.0	36.2 ± 11.9	0.39
Descending aortic length (mm)	219.4 ± 23.3	210.4 ± 28.1	0.13

ATAAD: Acute Type A Aortic Dissection; SD: Standard Deviation.

DISCUSSION

Acute type A aortic dissection is a catastrophic cardiovascular disease that carries high morbidity and mortality rates(16). Although aortic dilatation is a well-known risk factor for dissection, it can also occur in normal-sized aortas. Only 32% of dissection patients in the current study exhibited diameters on post-dissection scans that would qualify for prophylactic surgery, which is in accordance with previous studies that stated that the sole use of aortic diameters is insufficient for adequate risk prediction for ATAAD(8, 9, 14). In fact, when the acute diameter expansion after dissection onset is taken into account, 97% of patients would fail to meet the indication criterion of <55mm, which is also in line with previously reported findings(10). We hypothesized that, like dilatation, aortic elongation could also carry risk for dissection and used 3-D modeled CT to show that the adjusted ascending aorta of ATAAD patients is significantly longer than would have been expected based on age, gender and body posture. Our conclusions concur with those of Krüger et al., who were the first to investigate aortic length and diameters in dissected aortas and proposed a new risk scoring system based on these two anatomical variables(17, 18). However, in their study, the normal age-related changes of longitudinal aortic dimensions were not accounted for, and non ECG-gated scans were used for length and diameter measurements. Besides the differences in aortic dimensions between ATAAD patients and healthy controls, we additionally investigated the role of ascending aortic length and diameter in the occurrence of ATAAD using a regression model. This model also included predisposing factors like age, BSA, diabetes and hypertension. Length and diameter increase both proved to be significantly associated with an increased risk for ATAAD (with every centimeter increase of ascending aortic length carrying a 5-fold risk of ATAAD occurrence). A similar significant increase in risk was demonstrated for diameter expansion. We therefore endorse the vision of Krüger et al. for a multifactorial risk scoring system for the prediction of ATAAD, which would include both

aortic length and diameter(18). Ideally, also factors like aortic curvature(19), genetic predisposition(20), and hemodynamics(21) would be included in this model.

Of note, the aortic arch and descending aorta were not elongated in ATAAD patients. In healthy controls however, elongation and tortuosity of these segments is not uncommon. The question arises if the etiology of aortic elongation, like aneurysm formation, differs per anatomical segment. It has been well-described that aneurysm disease divides itself into two entities, one involving the ascending aorta and one involving the descending aorta(22). The distinct embryological origin of the aorta's smooth muscle cells (the smooth muscle cells of the ascending aorta derive from the neural crest, while those of the descending aorta derive from somatic mesoderm) are thought to attribute to this segmental predisposition of aneurysm formation(23). Likewise, and in accordance with the findings of the current study, it is conceivable that the extent of aortic elongation varies per segment and concentrates solely in the ascending aorta in patients suffering from ATAAD.

Limitations

Some limitations of the current study should be addressed. First, we used a cross-sectional study design. To evince a clear causal relationship between aortic elongation and dissection, a prospective and longitudinal study design should be conducted. However, given the low incidence rate of ATAAD and the time span that is required to investigate an aging process like aortic elongation, it would be challenging to perform such a study. We therefore consider our study design combined with modeling of dimensions to be the best achievable alternative.

Second, we measured aortic diameters in the healthy control group using non-ECG gated CT. The accuracy of diameter measurements in the control group could benefit from ECG-gating on CT(24). However, reference values for aortic diameters are mostly based on non-triggered scans and in daily practice, the majority of diameter and circumferential measurements are performed on non-ECG-gated images(6, 25).

Finally, aortic modeling was performed using a generalized algorithm in all patients. However, the actual increase in diameter and length after dissection onset may differ between patients.

CONCLUSION

Ascending aortic diameter is an insufficient stand-alone predictor for the occurrence of ATAAD. The current study demonstrated ascending aortic diameter and length to contribute equally to the occurrence of dissection. Furthermore, we have shown that the ascending aorta of ATAAD patients is significantly longer compared to their propensity matched counterparts. No difference was found between the lengths of the aortic arch and descending aorta, implying ATAAD to have a specific pathophysiological origin in the ascending aorta.

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Age-dependent aortic elongation: a new predictor for type A aortic dissection?

EDITORIAL

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Aortic dissection is a relatively rare condition with catastrophic outcomes if left untreated. The classification of this pathology is essentially based on its anatomical location or acuity. Data from the International Registry for Acute Aortic Dissection (IRAD) revealed that in the absence of immediate surgical repair, acute type A aortic dissection (ATAAD) is associated with a 24% mortality in the first 24 hours, 29% at 48 hours, 44% at day 7 and 50% after 2 weeks. Despite major advances in diagnostic yield, the early clinical diagnosis of aortic dissection remains elusive in up to 38% of patients. Furthermore, in 28% of cases the correct diagnosis was ascertained only after postmortem examination(1). The most common risk factor associated with aortic dissection is systemic hypertension, with up to 72%. Particularly in the

elderly, other major risk factors include atherosclerosis, prior cardiac surgery and known aortic aneurysms. With younger age (<40 years), hereditary conditions of aortopathy (eg, Marfan syndrome and other genetic factors) constitute a significant fraction of cases of aortic dissection(1). Despite recent advances in identifying structural and biomechanical properties of the aorta in vivo, a variety of determinants for the evolution to an aortic dissection are still unclear. The common denominator is a weakening of the aortic tunica media, which predisposes to dissection by splitting the cohesive layers of the aortic wall. This weakening of the tunica media could be due to either a derangement or possibly a loss of structural elements in the media layer, including elastin, collagen, non-fibrous matrix and smooth muscle cells. Aortic diameter is currently the best-evaluated predictor for aortic dissection with specific 'hinge points' at which rupture or dissection is increasingly likely to occur. These hinge points are set at around 6 cm for the ascending aorta and 7 cm for the descending aorta(2), with current recommendations for preventive treatment when the diameter exceeds 5.5 cm regardless of location. For patients with Marfan syndrome or other hereditary conditions, bicuspid aortic valve or family history of aortic dissection, the threshold is set lower at 4.5 cm² or 5.0 cm³. Interestingly, a substantial number of patients dissect at an aortic diameter less than 5.5 cm. The IRAD registry showed nearly 60% of patients with type A dissection had an aortic diameter <5.5 cm and almost 40% had diameters <5.0 cm(4), suggesting that aortic diameter alone is an insufficient marker to predict the risk of dissection, and highlighting the need for better predictors. A detailed discussion on aortic dimensions and geometry in healthy individuals and in patients with ATAAD was presented in the *Heart* paper. The first article evaluated the aortic length of 210 consecutive routine non-dissected patients with contemporary CT. The length of the thoracic aorta was significantly related to age ($r=0.54$; $p<0.001$), with an increase of 59 mm in men and 66 mm in women noticed between the ages of 20 and 80 years, reflecting a longitudinal growth to approximately 125%. Such correlation was found for the ascending aorta, arch and proximal part of the descending aorta, while the distal part of the descending thoracic aorta failed to show such a relationship between age and length ($p=0.178$). Elongation was most prominent in the proximal part of the descending thoracic aorta (247%), followed by the arch (169%) and the ascending thoracic aorta (142%). Additionally, a change in geometry was noticed by a distalward shift in the aortic apex from type I to type II aorta(5). A separate back-to-back publication compared the control group with 40 patients with ATAAD and adjusted the data to predissection dimensions. Elongation of the ascending aorta and diameter proved both to be independent predictors of dissection (OR=5.3, CI 2.5 to 11.4, $p<0.001$; OR=8.6, CI 2.4 to 31.0, $p=0.001$, respectively). The ascending aorta was longer and more dilated in patients with ATAAD compared with healthy controls (78.6±8.8 mm vs 68.9±7.2 mm, $p<0.001$; 34.4±3.2 mm vs 39.4±5.7 mm, $p<0.001$, respectively). Meanwhile, longitudinal elongation in both the aortic arch and the descending aorta was not predictive(6). Current guidelines regarding replacement of ascending aorta are based on diameters only. Interestingly, of the 343 patients who had undergone CT angiography <2 years before and within 12 hours after aortic dissection onset,

334 (97%) patients had an ascending aorta diameter of <5.5 cm and 315 (92%) patients had a diameter <5 cm before dissection(7). Similar to the IRAD experience(4), more than 60% of women and 70% of men had a non-dilated ascending aorta before the onset of a type A dissection(8), corroborating a need for more powerful aortic event predictors. This could be elongation of the ascending aorta as suggested and emphasized by the Maastricht group. It is generally believed that the aorta and large elastic arteries become tortuous with ageing. In this regard, the cross-sectional, propensity-matched study of non-cardiovascular patients was helpful in evaluating the geometric change during the ageing process dominated by lifelong exposure to pulsatile strain resulting in fracture and breakdown of elastin. Besides elongation and dilatation, this theory explains the age-related vascular stiffening as the reduction of elastin content impairs vessel compliance. Elastin content is highest in the aortic arch and proximal descending aorta. Furthermore, the mobile proximal aortic segments can move relatively free in the longitudinal direction as compared with the fixed distal parts. As circumferential strain values are comparable throughout the entire thoracic aorta, this provides a plausible explanation for an increasing diameter in the distal aorta but more elongation in the proximal aorta and arch. This observation is supported by independent finite element stress analysis with peak wall stress present both above the sinotubular junction, and distal to the left subclavian artery, thereby setting a local

stage for aortic dissection(9). Progressive ascending aortic growth in women, and the observation that both genders have similar absolute diameters at an older age, could provide the basis for the observation that aortic dissection is more predominant among men at younger age than women, while this difference between genders evens out with older age(10). Thus both the dynamic diameter and the length of the aorta play an important role in the pathophysiology of aortic dissection. Nevertheless, it should be emphasised that aortic dissection is triggered by multiple other factors. Previous guidelines recommended treatment based on hinge points in aortic diameter as a sole criterion, which however is insufficient. While the group in Maastricht effectively examined the influence of aortic elongation by geometric analysis as one new risk predictor, even the development of some global risk score with cut-off values is unlikely to cover all aspects of this disease entity. In addition to the classical comorbidities, haemodynamic and anatomical conditions, genetics, traumatic, iatrogenic and inflammatory factors certainly play an important role and should eventually be taken into consideration in the future.

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SUPPLEMENTARY DATA

Supplementary data 1: Baseline characteristics before propensity score matching.

	Control group (n = 40)	ATAAD group (n = 40)	p-value
Age (years)	62.0 [23-92]	63.5 [38-83]	0.39
Gender (male)	82 (39%)	25 (63%)	0.01
BSA (m²)	1.86 ± 0.22	1.97 ± 0.18	<0.001
Hypertension	69 (33%)	25 (63%)	<0.001
Diabetes	19 (9%)	1 (2%)	0.21
Medication			
Betablockers	41 (20%)	10 (25%)	0.52
ACE-inhibitors	39 (19%)	10 (25%)	0.39
Calciumblockers	23 (11%)	3 (8%)	0.78
Diuretics	35 (17%)	7 (18%)	1.00

Supplementary data 2: Distribution of propensity scores pre and post matching.

Evaluating the diagnostic accuracy of maximal aortic diameter, length and volume for prediction of aortic dissection

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ABSTRACT

OBJECTIVE

Management of thoracic aortic aneurysms (TAAs) comprises regular diameter follow-up until the indication criterion for prophylactic surgery is reached. However, this approach is unable to predict the majority of acute type A aortic dissections (ATAADs). The current study aims to evaluate the diagnostic accuracy of ascending aortic diameter, length and volume for occurrence of ATAAD.

METHODS

This two-center observational cohort study retrospectively screened 477 consecutive patients who presented with ATAAD between 2009 and 2018. Of those, 25 (5.2%) underwent computed tomography angiography (CTA) within two years before dissection onset. Aortic diameter, length and volume of these patients ('pre-ATAAD') were compared with those of TAA controls (n=75). Receiver operating curve (ROC) analysis was performed to evaluate the predictive accuracy of the three different measurements.

RESULTS

96% of pre-ATAAD patients did not meet the surgical diameter threshold of 55 mm before dissection onset. Maximal aortic diameters (45 [40-49] mm vs. 46 [44-49] mm, $p=0.075$) and volume (126 [95-157] cm³ vs. 124 [102-136] cm³, $p=0.909$) were comparable between pre-ATAAD patients and TAA controls. Conversely, ascending aortic length (84±9 mm vs. 90±16mm, $p=0.031$) was significantly larger in pre-ATAAD patients. All three parameters had an area under the curve of >0.800. At the 55 mm cut-off point, the maximal diameter yielded a positive predictive value (PPV) of 20%. While maintaining same specificity levels, measurements of aortic volume and length showed superior diagnostic accuracy (PPV 55% and 70%, respectively).

CONCLUSION

Measurements of aortic volume and length have superior diagnostic accuracy compared to the maximal diameter and could improve the timely identification of patients at risk for ATAAD.

KEYWORDS

Aortic dissection, aortic diameter, aortic elongation, CT, risk prediction

KEY POINTS

- Large registries have demonstrated that more than half of dissection patients present with diameters below the threshold for prophylactic surgery.
- Ascending aortic length is significantly increased in dissection patients compared to TAA controls. Measurements of aortic length and volume have superior diagnostic accuracy over diameters for prediction of dissection.
- Clinical implementation of aortic length and volume measurements might improve the selection of patients who benefit from preventive aneurysmectomy.

INTRODUCTION

Acute type A aortic dissection (ATAAD) is a medical emergency that carries high morbidity and mortality rates. Only half of patients survive until arrival at the hospital for emergency surgery, and another 20% of these die perioperatively due to severe disease complications (such as end-organ malperfusion)(1-3). To date, the maximal aortic diameter is the only recognized anatomic predictor for dissection and rupture. It has been shown that the probability for these to occur increases substantially when cross-sectional dimensions exceed 60 millimeters (mm)(4). Since the disruption risk inherent to smaller thoracic aortic aneurysms (TAAs) is low, it does not outweigh the risks of pre-emptive surgery. Therefore, current guidelines recommend referring patients for aneurysm extirpation when the maximal diameter grows beyond 55 mm(5-7). Despite their low risk, the relatively large number of patients with small TAAs cause more than 50% of dissections to develop in aortas below this size criterion – the so-called 'aortic size paradox'(7-9). Since lowering interventional thresholds would not necessarily imply a net mortality benefit (i.e., it would expose a large low-risk population to the considerable risk of surgery), recent studies have debated the clinical value of maximal diameter measurements and focused on the identification of new predictors in an attempt to enhance individualized risk assessment.

Arguably the most important limitation of maximal diameter measurements is the observation that these do not adequately represent the three-dimensional process of aortic growth. Elongation and cylindrical deformation (i.e., diameter growth proximally or distally from the widest portion of the aneurysm sac) are two scenarios of aortic remodeling that have shown to occur regardless of maximal diameter increase(10, 11). Therefore, measurements of aortic volume and length could provide additional information over diameters with regard to the detection of aneurysm progression. Whereas the predictive value of aortic volumetry has not yet been investigated, several studies have evaluated the potential role of excessive vessel lengthening in the pathophysiology of dissection(12-14). Although all of these studies reported that ATAAD patients had elongated ascending aortas when compared to healthy controls, these reports mainly included post-dissection measurements. This approach is debatable, since it has been shown that the aorta acutely dilates and elongates when it dissects(15). In the current retrospective cohort study, we have identified a group of patients who – for various indications – had undergone computed tomography angiography (CTA) within two years from ATAAD onset. Using this cohort, we were able to assess the geometry of the aorta shortly prior to dissection. By comparing findings with those of TAA controls, this study aimed to evaluate the diagnostic accuracy of ascending aortic diameter, length, and volume for the occurrence of acute type A aortic dissection.

MATERIALS AND METHODS

Study population

We retrospectively reviewed the clinical databases of the *Maastricht University Medical Center+* and *Heart Centre Freiburg University* between January 2009 and December 2018 for patients who were diagnosed with ATAAD and underwent CTA within two years before dissection onset. Patients with a history of cardiothoracic surgery, connective tissue disease (such as Marfan's syndrome, Loeys-Dietz, or Ehlers-Danlos) or bicuspid aortic valve (BAV) were excluded. The remaining patients were included to form the study population ('pre-ATAAD').

Consecutive patients who underwent CTA at the *Maastricht University Medical Center+* between January 2018 and December 2018 were included in the control groups. Exclusion criteria comprised (suspected) acute aortic syndrome, prior cardiothoracic or aortic surgery,

known BAV, and presence of any medical condition that might distort aortic shape (such as pulmonary malignancy or pneumothorax). The enrolled patients were subdivided into a group of apparently healthy controls (maximal ascending aortic diameter <40 mm), and a group of TAA patients (maximal diameter ≥40 mm). The local ethical committees approved the study protocol and waived the need for informed consent due to the observational character of the study.

Patient and public involvement

This research was done without patient involvement.

Image acquisition and analysis

All patients underwent contrast-enhanced CT on a second-generation (Maastricht and Freiburg) or third-generation (Maastricht) dual-source scanner (SOMATOM Definition Flash and SOMATOM Force, Siemens Healthineers, Forchheim, Germany, respectively). Pre-ATAAD and TAA patients typically underwent a dedicated aortic scan protocol that comprised a native CT of the entire aorta, a retrospective ECG-gated helical CT angiography (CTA) of the ascending aorta in caudocranial direction, and a non-ECG-triggered high-pitch scan (flash) from the aortic arch to the femoral bifurcation. Scans of the ascending aorta were acquired at slice thickness 0.6 mm using automated dose modulation (CARE kV, CareDose 4D™, Siemens Healthineers). They were reconstructed at an increment of 0.4 mm using raw-data based iterative reconstruction algorithms (Sinogram Affirmed Iterative Reconstruction [SAFIRE] or Advanced Modelled Iterative Reconstruction [ADMIRE], strength 3, dependent on scanner type). Comprehensive overviews of the various scan parameters per scanner are provided in Supplementary Tables 1 and 2. Scans of healthy controls were performed using oncological or vascular workflows, without ECG synchronization of the respective datasets. Monomeric, non-ionic, low-osmolar iodinated contrast medium (300mgI/ml; Iopromide; Bayer Healthcare, Berlin, Germany) was prewarmed to standardized 37°C before injection in the antecubital vein using catheter sizes between 18-22G. The injection parameters were monitored by a data acquisition system (Certegra™ Informatics Solution, Bayer Healthcare).

Images were analyzed by a single observer who was blinded for patient history (B.A., five years of experience in cardiovascular imaging), using a commercially available software package (Syngo.via™, Siemens Healthineers). Maximal diameters were measured orthogonal to the vessel centerline using the inner edge to inner edge technique (Figure 1A and 1D). Measurements of length and volume were performed on a 3D reconstruction of the thoracic aorta with automatically fitted centerline (Figure 1B-C and 1E-F). The ascending aorta was defined as the part between the sinotubular junction (STJ) and the origin of the brachiocephalic trunk. Segment length was measured as the centerline distance between the mentioned anatomic landmarks. The luminal volume was calculated using the adaptive region growing tool provided by the software. Clicking into the vessel initiated a region growing algorithm by segmenting connected voxels of a similar enhancement. Contours were corrected manually in the axial slices when required. Eventually, the volume of the segmentation was calculated automatically by multiplying reconstructed voxel size with the number of voxels included, under consideration of the reconstruction increment. Measurements were repeated in a random sample of 20 patients by the same observer and also carried out by a second observer (S.H., three years of experience) in order to test intra- and interobserver variability.

Figure 1. Methodology of the three different aortic measurements in a TAA patient and a pre-ATAAD patient. A-C demonstrate aortic measurements in a TAA patient. Panel A depicts a stretched view of the curved planar CT reconstruction with diameter measurement perpendicular to the centerline. The two right panels display a 3D CT model with measurements of ascending aortic length (B) and volume (C). D-F demonstrate similar measurements in a pre-ATAAD patient. Despite equal diameters, the pre-ATAAD patient exhibits a notably longer and larger ascending aorta. 3D: three-dimensional; CT: computed tomography; TAA: thoracic aortic aneurysm; ATAAD: acute type A aortic dissection.

Statistical analysis

Statistical analysis of the data was performed using commercially or freely available software (SPSS version 24, IBM, Armonk, New York, USA; or R Statistics, the R Foundation, Vienna, Austria). Continuous data are presented as mean ± standard deviation (SD) (or median and interquartile range [IQR] in the presence of skewedness) and were compared using the student t-test or Mann-Whitney U-test. Categorical data are expressed as frequencies and percentages and were compared using the Chi-square test. A p-value <0.05 was considered statistically significant.

Receiver operating characteristic (ROC) analysis was applied to measure the predictive accuracy of the three measurements, with the calculated area under the curve (AUC) representing the quality of discrimination. The specificity of the current surgical diameter cut-off (55 mm) was calculated with corresponding sensitivity and used as reference to determine the sensitivities of aortic length and volume at that specificity level. McNemar’s test was used to compare sensitivities between groups (DTComPair, R Statistics)(16, 17). In terms of diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) were reported along with 95% confidence intervals (CI).

Finally, intra- and interobserver agreement was analyzed using intraclass correlation coefficient (ICC) and normalized Bland-Altman analysis.

RESULTS

The demographic data of the different patient groups are presented in Table 1. Between January 2010 and December 2018, a total of 477 patients were diagnosed with ATAAD at the participating institutions. Of those, 25 (5.2%) had undergone CTA within two years before dissection onset. The median time interval between the pre-ATAAD scan and the actual dissection was 124 days [IQR 34-543 days].

In total, 258 healthy controls and 75 TAA patients were enrolled in the control groups. Scan indications for healthy controls ranged from evaluation of pulmonary nodules (45.3%) to suspicion of pulmonary embolism (45.0%), pneumonia (5.8%), and other (3.9%). All TAA patients underwent CT for periodical diameter surveillance.

Table 1. Baseline characteristics.

	Healthy controls (n=258)	Aortopathy		p-value*
		TAA controls (n=75)	Pre-ATAAD (n=25)	
Age (years)	64 [53-73]	69 [61-75]	69 [63-78]	0.668
Gender (male)	114 (44%)	50 (67%)	15 (60%)	0.457
Height (cm)	170 ± 9	174 ± 7	174 ± 7	0.767
Weight (kg)	73 [64-85]	80 [72-90]	78 [70-87]	0.347
BMI (kg/m²)	25.5 [22.3-28.8]	27.1 [24.5-29.6]	25.6 [23.4-27.7]	0.141
BSA (m²)	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.496
Hypertension	93 (36%)	56 (75%)	18 (72%)	0.710
Smoking	83 (32%)	19 (25%)	4 (16%)	0.530

Table 1. (continued)

	Healthy controls (n=258)	Aortopathy		p-value*
		TAA controls (n=75)	Pre-ATAAD (n=25)	
Dyslipidemia	42 (16%)	31 (41%)	8 (32%)	0.485
Diabetes	29 (11%)	3 (4%)	0	1.000

*p-values are given for comparison between TAA controls and pre-ATAAD patients.

Aortic dimensions and ROC-curve analysis

In the pre-ATAAD group, 24 of 25 subjects (96%) had maximal ascending aortic diameters below the interventional threshold of 55 mm. While diameters and volume were comparable, these patients had significantly longer ascending aortas than those with TAA but no dissection (90 ± 16 mm vs. 84 ± 9 mm, p=0.031) (Table 2).

Table 2. Aortic dimensions of the different patient groups.

	Healthy controls (n=258)	Aortopathy		p-value*
		TAA controls (n=75)	Pre-ATAAD (n=25)	
Diameter (mm)	33 [30-36]	46 [44-49]	45 [40-49]	0.075
Length (mm)	66 ± 9	84 ± 9	90 ± 16	0.031
Volume (cm³)	56 [45-67]	124 [102-136]	126 [95-157]	0.909

*p-values are given for comparison between TAA controls and pre-ATAAD patients.

All 358 patients were included in the ROC model (dissection n=25, control n=333). Within the entire clinical cohort, all three parameters had an AUC >0.800 for prediction of dissection (diameter: 0.810; length 0.842; volume 0.854, all p<0.001. See Figure 2A). The current surgical threshold of 55 mm showed to yield an excellent specificity of 98.8% (NPV: 93%, CI 90-96%). However, the corresponding sensitivity showed to be no more than 4% (PPV 20%, CI 0-55%). At same specificity levels (98.8%, Figure 2B), aortic volume (cut-off: 161 cm³, sensitivity 20%, p=0.045) and length (cut-off: 98 mm, sensitivity 28%, p=0.014) demonstrated five- and sevenfold higher sensitivity for ATAAD detection. Also, PPV of these parameters was markedly higher than that of the maximal diameter (PPV volume: 55%, CI 23-88% and PPV length: 70%, CI 23-88%), with similar NPV’s (volume 94%, length 95%). No statistical significance was reached when comparing the sensitivities of aortic length and volume (p=0.414). Combining the different measurements did not further improve diagnostic performance compared to measurements of aortic length alone.

Intra- and interobserver variability

Intra-observer agreement was excellent for all three parameters (ICC 0.94, 0.97, and 0.99 for aortic diameter, length, and volume, respectively). With ICCs of 0.95 (diameter), 0.94 (length) and 0.99 (volume), inter-observer agreement was also excellent. Bland-Altman plots are displayed in Figure 3.

DISCUSSION

Research into the natural risk of TAAs is constrained by multiple methodological issues, one of which is the observation that the dimensions of the aorta change when dissection occurs(15). In the current work, we have overcome this limitation by assessing the morphology of the aorta shortly before dissection onset. We found that i) 96% of ATAAD patients fail to meet criteria for prophylactic surgery prior to dissection, ii) aortic length is significantly larger in pre-ATAAD patients when compared to TAA controls, and iii) the sensitivities of aortic volume and length for prediction of dissection are five- and sevenfold higher than the sensitivity of the maximal diameter.

Guidelines for the preventative management of aortic disease depend solely on measurements of maximal cross-sectional dimensions and have long remained unchanged(5, 6). They have largely been based on early work from Davies et al., who longitudinally studied a cohort of TAA patients and found that the aortic diameter is strongly related to the risk of natural complications(4, 18). Even though the cut-off of 55 mm provides excellent specificity and precludes exposure to unnecessary intervention, it has been well recognized that the current surgical approach is unable to prevent the majority of dissections(8, 9, 19). Our findings confirm estimates by Ryłski et al., who modeled post-dissection aortas to pre-dissection dimensions and postulated that >90% of ATAAD patients would not have qualified for prophylactic surgery before dissection onset(20). As such, they emphasize the need for deciphering additional parameters that can improve patient selection for pre-emptive surgery.

Over the past decade, technological advances have facilitated the acquisition of high-resolution isotropic multi-slice spiral CT and magnetic resonance imaging (MRI) datasets. Whereas earlier techniques (such as ultrasound and spiral CT) only provided for two-dimensional (2D) images and measurements, modern acquisitions afford a detailed three-dimensional (3D) visualization of the human arterial system. This evolution has paved the way for more comprehensive radiological measurements, such as those of aortic length and volume shown here. Previous studies investigating vessel length have demonstrated that the healthy aorta gradually elongates with age and that the dissected aorta is notably longer than would have been expected based on age, gender, and body surface area (BSA)(12-14, 21-23). The current work adds to this knowledge by revealing that aortic length also serves as more discriminative ATAAD predictor than the maximal transverse diameter. Although the observed sensitivity of 28% may not seem earth shattering at

first glance, it means substantial and readily available improvement in the diseases' detection rate, with no trade-off in terms of specificity. Before the start of the study, we expected aortic volume to evolve into an even better indicator of future adverse events. However, our data has proven otherwise. Whereas the sensitivity of aortic volume was significantly higher than that of the maximal transverse diameter, we found no additional diagnostic value over measurements of aortic length. Yet, in line with previous studies, aortic volume did show excellent reproducibility, which could serve as important argument in favor of its use in clinical TAA follow-up(24). Aortic length and volume now require longitudinal and prospective validation as the next step towards their implementation into clinical practice guidelines.

It should be noted that current surgical indications are based on imaging data collected in the 1980s and 1990s, a time when measurements were performed mainly on axial images. Since then, and along with the transition to 3D imaging, the semiautomated centerline method has become routinely available. Multiple previous studies have reported that axial measurements significantly overestimate diameters when compared to centerline methods, especially in more tortuous aortic segments(25, 26). Based on these observations, it has been argued that current guidelines are not adapted to the use of centerline measurements, and that the surgical threshold should be shifted to smaller TAA sizes(27). Although we concur that this hypothesis deserves further attention, our data indicate that the diagnostic performance of the maximal diameter – even at lower cut-offs – remains lower than that of aortic volume and length (Figure 2B). As expected, lowering the threshold to 50 mm would increase diameter sensitivity (from 4% to 17%). Concurrently, however, the sensitivities of aortic volume (from 20% to 38%) and length (from 28% to 33%) would also increase.

Future directions

Prospective research into the pathophysiology of dissection is challenging due to the diseases' low incidence and the (life)long follow-up duration required for the condition to develop. The design of the current study has afforded an alternative way to evaluate the anatomy of the aorta prior to dissection onset. Our findings could lead to a paradigm shift in the preventative management of aortic disease, enabling the more timely identification of patients at risk. Emerging techniques like four-dimensional (4D) flow MRI and positron emission tomography (PET) permit imaging of the hemodynamic and inflammatory processes that potentially underlie aneurysm progression, and could further improve the detection rate of patients who are susceptible to dissection(28, 30).

Limitations

Some limitations of the current study should be addressed. First, a cross-sectional study design was used. Therefore, it is possible that any of the control patients will develop dissection on short terms. Future longitudinal studies are needed to evince a true causal relationship between the various anatomic measurements and the risk of unfavorable outcomes.

Second, the study population is relatively small and not representative of subjects with BAV or connective tissue disease. As the latter are known to suffer dissection at larger aortic diameters, our results are not generalizable to this patient population(9). Studies focusing specifically on genetically triggered aneurysms should investigate whether aortic volume and length measurements are of additional value in these patient entities.

CONCLUSIONS

The aortic diameter is incapable of predicting the vast majority of dissections. Measurements of aortic volume and length have superior diagnostic accuracy over maximal diameters and could improve the timely identification of patients at risk for ATAAD.

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Prediction of aortic dissection

EDITORIAL

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Aortic dissection is a low-incidence, high-impact and potentially catastrophic condition if not treated adequately and in time. Acute aortic dissection is diagnosed within 2 weeks of onset of symptoms, which is the high-mortality period. Patients surviving 2 weeks are considered to have subacute disease, and chronic aortic dissection is diagnosed after 8 weeks. The anatomical classification is based on the involvement of ascending aorta (type A according to Stanford) or not (type B)(1). Historical data for untreated type A aortic dissection show a mortality rate of 1%–2% per hour within the first 24 hours, resulting in a mortality rate of up to 50%–74% during the acute phase(2). Uncomplicated acute type B dissection is less frequently lethal, with survival rates for medically treated patients of 84% at 1 year. Within the risk factors, arterial hypertension is dominating. It affects arterial wall composition, causing intimal thickening, fibrosis, and calcification and extracellular fatty acid deposition. The extracellular matrix also undergoes accelerated degradation, apoptosis and elastolysis with hyalinisation of collagen. Other risk factors in the elderly are atherosclerosis, prior cardiac surgery and known aortic aneurysms. On the contrary, hereditary conditions of aortopathy (eg, Marfan syndrome and other genetic factors) are the main cause of dissection in younger patients. The pathophysiological denominator is a weakened aortic tunica media, which predisposes to dissection by splitting the cohesive layers of aortic wall. This weakening of the tunica media could be due to either a derangement or possibly a loss of structural elements in the media layer, including elastin, collagen, non-fibrous matrix and smooth muscle cells. The anatomical criterion based on aortic diameter, which is the only criterion in the latest guideline, is currently the best-evaluated predictor for aortic dissection and rupture with specific 'hinge points' (6 cm for the ascending aorta and 7 cm for the descending aorta)(3) However, the majority of patients dissect at an aortic diameter less than these hinge points, which was shown in the International Registry of Aortic Dissection (IRAD) registry, in which nearly two-thirds of type A dissection patients had an aortic diameter of <5.5 cm(4). Similarly, Rylski *et al* reported that of the 343 patients who had undergone CT angiography <2 years before and within 12 hours after aortic dissection onset, 334 (97%) patients had an ascending aorta diameter of <5.5 cm, and 315 (92%) patients had a diameter of <5 cm before dissection(5), which underlines the need for more powerful aortic event predictor tools.

An elegantly work about diameter, volume and length of the aorta in predissection phase was presented by the Maastricht group in the current issue of *Heart*. They compared in a two-centre matched cohort 25 patients suffering from acute type A aortic dissection (ATAAD) and undergoing CT within 2 years before dissection with 258 healthy subjects and 75 patients with thoracic aortic aneurysm using a propensity score matching strategy(6). More strongly accentuated than in IRAD registry, 96% did not meet the guideline-defined threshold of 5.5 cm in diameter. They could confirm a larger length and volume without any differences in diameter of ascending aorta in patients with ATAAD in the predissection phase as compared with propensity-matched controls with superior diagnostic accuracy. Similarly, the aortic length was significantly larger in patients with pre-ATAAD when compared with controls.

The same Maastricht group identified in a previous publication an age-dependending elongation of the aorta in healthy subjects and in patients with ATAAD. The length of the thoracic aorta increased by 59 and 66 mm in healthy men and women, respectively, between the ages of 20 and 80 years with a predominance on the ascending aorta (142%), the aortic arch (169%) and the proximal part of the descending aorta (247%)(7). A comparison of the ATAAD and control groups with adjustment to predissection dimensions revealed that elongation of the ascending aorta and diameter proved both to be independent predictors of dissection. Thus, the ascending aorta was longer and more dilated in patients with ATAAD compared with healthy controls, whereas longitudinal elongation in both the aortic arch and the descending aorta was not predictive(8). The aorta and the large elastic arteries become tortuous, and there is an elongation with increasing age. Similarly, there is vascular stiffening as the reduction of elastin content, which is highest in the aortic arch and the descending aorta,

Figure 1. Factors influencing the aortic dimensions and risk of aortic dissection in general.

impairs vessel compliance. Despite the fact that current guidelines try to define a user-friendly solution by restricting the prediction to diameter, this may not be sufficient. Dimensional anatomical parameters such as diameter, length and volume are certainly factors to be considered in the predictive analysis of aortic dissection. However, these parameters often represent the result of long-lasting influences of hypertension or connective tissue disorders, and a prediction tool based on anatomy only would leave many aspects unconsidered (Figure 1). Even the Aortic Dissection Detection risk score, which summarises baseline conditions with pain features, exam features and D-dimer values, is only an approximation of the multifactorial genesis of the disease. In addition to the classical cardiovascular risk factors, haemodynamic and anatomical conditions, genetics, traumatic, iatrogenic and inflammatory factors certainly play a role and should be taken into consideration, perhaps in a complex algorithm employing artificial intelligence brought to the bedside. For the time being and without access to such a tool yet, the need for an individual patient-specific management plan designed by a multidisciplinary aortic team is unchallenged.

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SUPPLEMENTARY DATA

Supplementary Table 1. Scan parameters for Siemens SOMATOM Flash.

Protocol	Native	Ascending aorta	Aorta (flash)
Mode	Spiral	Spiral	High pitch
Collimation (mm)	0.6	0.6	0.6
Acquisition (mm)	128*0.6	128*0.6	128*0.6
Tube voltage (kVp)	120	100	100
Dose modulation	on	on	on
mAs _{ref}	100	330	150
Rot.Time (s)	0.5	0.28	0.28
Pitch	0.9	0.17	2.65
Delay (s)	n.a.	Test bolus technique	Test bolus technique
Direction	Cranio-caudal	Caudo-cranial	Cranio-caudal
Reconstruction I			
Slice thickness(mm)	2	0.6	1.5
Increment (mm)	1.5	0.4	1.0
Kernel	I30f	I26f	I31f

kVp: peak kilovoltage; mAs: milliamperere-seconds.

Supplementary Table 2. Scan parameters for Siemens SOMATOM Force.

Protocol	Native	Ascending aorta	Aorta (flash)
Mode	Spiral	Spiral	High pitch
Collimation (mm)	0.6	0.6	0.6
Acquisition (mm)	192*0.6	192*0.6	192*0.6
Tube voltage (kVp)	120	100	80
Dose modulation	on	on	on
mAs _{ref}	80	330	174
Rot.Time (s)	0.5	0.25	0.25
Pitch	0.9	0.15	1.9
Delay (s)	n.a.	Test bolus technique	Test bolus technique
Direction	Cranio-caudal	Caudo-cranial	Cranio-caudal
Reconstruction I			
Slice thickness (mm)	2	0.6	1.5
Increment (mm)	1.5	0.4	1.0
Kernel	Br40	Bv40	Bv40

kVp: peak kilovoltage; mAs: milliamperere-seconds.

Supplementary Table 3. Pre-matching baseline characteristics.

	Controls (n=333)	Pre-ATAAD (n=25)
Age (years)	67 ± 11	69 ± 9
Gender (male)	50 (67%)	15 (63%)
BSA (m²)	1.9 ± 0.2	1.9 ± 0.1
Hypertension	56 (75%)	15 (63%)

ATAAD: acute type A aortic dissection; BSA: body surface area.

HEMODYNAMIC IMAGING

Part II

Clinical assessment of aortic valve stenosis: comparison between 4D flow MRI and transthoracic echocardiography

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ABSTRACT

BACKGROUND

The prevalence of valvular aortic stenosis (AS) increases as the population ages. Echocardiographic measurements of peak jet velocity (V_{peak}), mean pressure gradient (P_{mean}) and aortic valve area (AVA) determine AS severity and play a pivotal role in the stratification towards valvular replacement. A multimodality imaging approach might be needed in cases of uncertainty about the actual severity of the stenosis.

PURPOSE

To compare four-dimensional phase-contrast magnetic resonance (4D PC-MR), two-dimensional (2D) PC-MR and transthoracic echocardiography (TTE) for quantification of AS.

STUDY TYPE

Prospective.

POPULATION

20 patients with various degrees of AS (69.3 ± 5.0 years).

FIELD STRENGTH/SEQUENCES

4D PC-MR and 2D PC-MR at 3T.

ASSESSMENT

We compared V_{peak} , P_{mean} and AVA between TTE, 4D PC-MR and 2D PC-MR. Flow eccentricity was quantified by means of normalized flow displacement, and its influence on the accuracy of TTE measurements was investigated.

STATISTICAL TESTS

Pearson's correlation, Bland-Altman analysis, paired *t*-test, and intraclass correlation coefficient.

RESULTS

Four-dimensional PC-MR measured higher V_{peak} ($r = 0.95$, mean difference $+16.4 \pm 10.7\%$, $p < 0.001$) and P_{mean} ($r = 0.92$, mean difference $+14.9 \pm 16.0\%$, $p = 0.013$), but a less critical AVA ($r = 0.80$, mean difference $+19.9 \pm 20.6\%$, $p = 0.002$) than TTE. In contrast, unidirectional 2D PC-MR substantially underestimated AS severity when compared to TTE. Differences in V_{peak} between 4D PC-MR and TTE showed to be strongly correlated to the eccentricity of the flow jet ($r = 0.89$, $p < 0.001$). Use of 4D

PC-MR improved the concordance between V_{peak} and AVA (from 0.68 to 0.87), and between P_{mean} and AVA (from 0.68 to 0.86).

DATA CONCLUSION

4D PC-MR improves the concordance between the different AS parameters and could serve as additional imaging technique next to TTE. Future studies should address the potential value of 4D PC-MR in patients with discordant echocardiographic parameters.

KEYWORDS

Aortic stenosis, valvular disease, 4D flow MRI

KEY POINTS

- 4D flow MRI measures significantly higher flow velocities in aortic stenosis (AS) patients compared to transthoracic echocardiography (TTE).
- Difference between peak velocities as measured by 4D flow MRI and TTE is highly correlated to the eccentricity of the flow jet.
- 4D flow MRI increases concordance between the parameters that determine AS severity (peak velocity, mean transvalvular pressure gradient and aortic valve area).

INTRODUCTION

Calcific aortic stenosis (AS) is the most common valvular heart disease in developed countries, affecting up to 12.4% of elderly patients(1, 2). Since the Western population grows progressively older, AS will put an increasing burden on public health and health resources over the coming decades. Transthoracic echocardiography (TTE) is the key diagnostic tool for evaluation of stenosis severity, and main parameters recommended to be recorded include peak jet velocity (V_{peak}), mean transvalvular pressure gradient (P_{mean}) and aortic valve area (AVA)(3). However, certain pitfalls apply to the echocardiographic assessment of AS, which should be avoided in order to ascertain the accuracy of measurements(4). First, image quality is operator-dependent and can be hampered by poor acoustic windows. Second, Doppler measurements rely on a parallel alignment between the ultrasound beam and the direction of blood flow, and violation of this condition results in underestimation of flow velocities and pressure gradients(5). Third, AVA is calculated using the continuity equation, a formula that includes the cross-sectional area of the left ventricular outflow tract (LVOT). This area is typically computed from the LVOT diameter, implicating the outflow tract to have a circular shape. In fact, the LVOT is elliptical in the majority of patients, and this approach has been reported to result in a considerable underestimation of AVA(6, 7). In a subgroup of patients, in whom image quality is insufficient or there is discordance between the TTE-derived AS parameters, clinical-decision making may benefit from alternative non-invasive imaging techniques.

Phase-contrast magnetic resonance imaging (PC-MR) has evolved as a reliable tool for non-invasive flow and velocity measurements and has been validated in vitro and multiple patient groups(8-10). The technique is usually performed using a prospectively planned two-dimensional (2D) acquisition with a unidirectional through-plane velocity-encoding. However, this method is only capable of quantifying flow velocities in the direction oriented perpendicular to the imaging slice. Moreover, the exact location of peak jet velocity (the so-called vena contracta) cannot be visualized prior to planning of the acquisition plane, which further reduces the accuracy of measurements. For these reasons, 2D PC-MR has shown significant underestimation of flow rates and velocities when compared to TTE(11-13). Over recent years, three-directional three-dimensional PC-MR (better known as four-dimensional [4D] flow MR or 4D PC-MR) has emerged as a promising in-vivo flow imaging technique that enables visualization and quantification of complex flow patterns in the heart and large vessels(14-16). In contrast to unidirectional 2D PC-MR, 4D PC-MR provides for velocity-encoding in all three spatial directions. Furthermore, the entire acquired volume can be analyzed in search for the highest flow jet velocity. In healthy volunteers and patients with normally functioning valves, 4D PC-MR has shown improved flow quantification relative to echo(17, 18). We hypothesized that in AS patients, who often exhibit eccentric and dynamic flow jets, the technical features of 4D PC-MR could be even more advantageous(19). Hence, the purpose of the current study is to assess the performance of TTE and PC-MR in a cohort of AS patients, and to investigate the influence of flow eccentricity on the accuracy of measurements.

MATERIALS AND METHODS

Study population

Consecutive adult patients who visited our outpatient clinic for the echocardiographic follow-up of AS between June 2017 and December 2018 were invited for participation in this prospective single-center study. Exclusion criteria comprised prior aortic valve replacement, heart failure (NYHA class ≥ 3), renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m²), and

the regular exclusion criteria for MR (such as metallic implants and claustrophobia). Furthermore, patients with atrial fibrillation were excluded, since beat-to-beat flow variability caused by irregular heart rhythms might limit the accuracy of PC-MR measurements. Eventually, a total of 20 patients were included. Our local ethical review board approved the study protocol, and all participants provided written informed consent.

Transthoracic echocardiography

Echocardiograms were performed according to clinical guidelines using a Philips iE33 ultrasound system (Philips Medical Systems, Andover, MA, USA)(3, 20). Recordings were made from the subcostal, parasternal and apical windows with patients lying in supine or left lateral decubitus position. All images were obtained by experienced echocardiographers and reviewed by a single certified cardiologist with >15 years of experience in cardiac ultrasound (S.S.). Aortic V_{peak} was measured using continuous-wave Doppler ultrasound; the highest velocity recorded from any acoustic window was used for analyses. Transvalvular pressure gradients were calculated from velocity information through the modified Bernoulli equation ($P = 4 \cdot v^2$), with P_{mean} being the average gradient over the cardiac systole. AVA was computed using the continuity-equation as $AVA = Area_{LVOT} \cdot VTI_{LVOT} / VTI_{Aorta}$. In this equation, VTI_{LVOT} and VTI_{Aorta} are the velocity-time integrals of the LVOT and aorta as obtained by pulsed-wave Doppler and continuous-wave Doppler, respectively. The area of the LVOT was computed using the LVOT diameter as measured on a parasternal long-axis view: $Area_{LVOT} = \pi \cdot (Diameter_{LVOT}/2)^2$.

MR acquisition

All scans were performed on a 3T scanner (Ingenia CX, Philips Healthcare, the Netherlands) equipped with a 32-channel torso coil for signal reception. A steady-state free precession sequence was used to obtain ECG-gated cine images in 2- and 4-chamber long-axis views and in two orthogonal LVOT planes. Unidirectional 2D PC-MR was performed in end-expiratory breath-hold at the level of the LVOT and in two adjacent slices ranging from the aortic valve tips towards the sinotubular junction (Figure 1A). Typical PC-MR acquisition parameters are summarized in Table 1. Cine LVOT views were used to position imaging planes perpendicular to the aortic valve and aorta. Velocity-encoding (VENC) was individually adapted by repetition of acquisitions with decreasing VENC until the lowest value, at which no aliasing occurred, was reached.

Table 1. CMR acquisition parameters.

	2D PC-MR	4D PC-MR
FOV (mm x mm x mm)	350 x 300	350 x 280 x 75
Acquired voxel size (mm x mm)	2.5 x 2.5	2.5 x 2.5 x 2.5
Slice thickness (mm)	8.0	-
Reconstructed voxel size (mm)	1.22 x 1.22	1.46 x 1.46 x 2.5
Flip angle (°)	10	10
TE (ms)	2.4	2.3
TR (ms)	4.0	4.2
TFE factor	6	2
SENSE factor	2	2.5 (P) x 1.5 (S)

Table 1. (continued)

	2D PC-MR	4D PC-MR
VENC (cm/s)	210-600	210-600
Shot duration (ms)	48	33
(Reconstructed) cardiac phases	40	29-42*

*Depending on cardiac frequency. FOV: field-of-view; P: phase-encoding direction; S: slice direction; TE: echo time; TR: repetition time; VENC: velocity-encoding

Four-dimensional PC-MR acquisition was initiated immediately after manual administration of a low-dose (0.1 mmol/kg body weight) bolus of gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany). A 3D volume with full coverage of the thoracic aorta was acquired in a sagittal oblique orientation, using a retrospectively ECG-gated and respiratory navigated spoiled turbo-field echo sequence (Figure 1B). Velocity-encoding for the three spatial directions was set to same values as in 2D PC-MR. Gradient correction and local phase correction were performed from standard available scanner software. Acquisition lasted 17.2 ± 5.5 minutes, depending on heart and respiratory rate.

MR analysis

MR datasets were reviewed by a single observer (B.A., 5 years of experience in cardiac MR), who was blinded for echocardiographic findings. Two-dimensional PC-MR was analyzed semiautomatically (CAAS MR Flow 2.1, PieMedical Imaging B.V., Maastricht, The Netherlands).

Figure 1. Methodology for 2D and 4D PC-MR acquisition. (A) Through-plane 2D PC-MR was performed at the level of the LVOT and in two adjacent planes covering the aortic valve and aortic root. Magnitude and velocity images are provided for the imaging slice depicted in red. (B) In 4D PC-MR, a 3D volume covering the thoracic aorta was acquired. Velocity maps for the three spatial directions are shown bottom right. LVOT: left ventricular outflow tract; PC-MR: phase contrast magnetic resonance.

Regions of interest drawn by the software were checked for their adequacy across all time frames and manually corrected if deemed necessary. Flow rates and velocities were exported for each phase, and the aortic imaging slice that yielded highest V_{peak} was used for analyses. Planimetric LVOT area was obtained from magnitude images at peak systole. Velocity-time integrals were manually calculated by the observer as the area under the velocity-time curve and used for calculation of AVA using the continuity equation.

Four-dimensional PC-MR data were imported into a commercially available software package (CAAS 4D Flow 2.0, PieMedical Imaging B.V.), and additional phase offset correction and anti-aliasing was performed. Delimiter points were manually placed in the LVOT and descending aorta on a weighted speed image and marked the borders of the volume of interest (i.e., the thoracic aorta). This volume was then automatically segmented for the peak systolic phase. The adaptation tool provided by the software was used for manual correction of vessel lumen delineation in case of incorrectness of the automatic segmentation. After completion of the segmentation, analysis planes were placed just below the lowest insertion point of the aortic valve cusps (LVOT), and in the aortic region in which V_{peak} was identified. Calculations of pressure gradients and AVA were performed similarly as in 2D PC-MR. LVOT area was obtained by planimetry on magnitude images. Peak systolic flow displacement in the aortic plane was computed as the linear distance between the luminal center and the center of velocity, which represents the average position of pixels weighted by velocity information (see also Figure 4A)(21). Analysis of 4D PC-MR data of 10 randomly selected patients was repeated by the primary observer and also carried out by a second observer (Y.C., 4 years of experience) in order to assess intra- and interobserver variability.

Statistical analysis

Statistical analysis was performed using dedicated software (IBM SPSS Statistics, version 24, Armonk, NY, USA). Continuous data were tested for normality using the Shapiro-Wilk test. Baseline characteristics are presented as mean $\pm$ standard deviation or as frequency and percentages. Pearson's correlation and Bland-Altman analysis were performed to assess the agreement between the TTE- and PC-MR-derived AS parameters, while the paired samples *t*-test was used to determine whether there was a significant mean difference between both modalities. Intra- and interobserver variability for 4D PC-MR measurements were calculated using the intraclass correlation coefficient (ICC). A *p*-value <0.05 was considered significant.

RESULTS

Study population

Twenty patients were included and underwent consecutive TTE and MR. Mean time interval between both examinations was 17.2 ± 7.2 days. Pronounced respiratory motion artifacts were encountered in the 4D PC-MR dataset of one patient, who was therefore excluded from further analysis. Baseline characteristics are summarized in Table 2. Based on an echocardiographic AVA <1.0 cm², 5 patients were diagnosed with severe AS. The others suffered from moderate (AVA between 1.0 and 1.5 cm², *n* = 8) or mild (AVA >1.5 cm², *n* = 6) valvular stenosis. The aortic valve was bicuspid in 4 patients (1 severe and 3 moderate AS, all with raphes between the left- and right-coronary cusps). Of the 5 subjects with severe aortic stenosis, 4 underwent aortic valve replacement and experienced improvement of echocardiographic peak velocities (from mean 4.75 ± 0.43 m/s to 2.49 ± 0.25 m/s) and mean pressure gradients (from mean 50.8 ± 8.0 mmHg to 13.3 ± 2.5 mmHg).

Table 2. Baseline characteristics of the study population.

	N = 19	Range
Male	13 (68,4%)	
Age (years)	69.3 ± 5.0	57-77
Height (cm)	168.9 ± 7.3	150-181
Weight (kg)	75.7 ± 9.4	61-93
BMI (kg/m ²)	26.5 ± 2.4	21.1-29.8
BSA (m ²)	1.9 ± 0.14	1.6-2.1
Hypertension	16 (84.2%)	
Dyslipidemia	11 (57.9%)	
Diabetes	1 (5.3%)	
Smoker	3 (15.8%)	
eGFR	70.7 ± 14.9	44-90
NYHA classification		
I	15 (78.9%)	
II	4 (21.1%)	
Valve morphology		
Bicuspid	4 (21.1%)	
Tricuspid	15 (78.9%)	
TTE findings		
LVEF (%)	63.0 ± 5.5	50-70
LV mass (g)	162.3 ± 49.0	91-247
LVEDD (mm)	47.1 ± 5.1	39-59
LVESD (mm)	31.1 ± 4.7	24-41

BMI: body mass index; BSA: body surface area; eGFR: estimated glomerular filtration rate; LV: left ventricle; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; NYHA: New York Heart Association.

Peak jet velocity, mean pressure gradient and aortic valve area

Measurements of V_{peak} obtained by 2D PC-MR and 4D PC-MR were strongly correlated with those derived from TTE (Table 3, and Figures 2 and 3). However, there was a notable systematic difference between the three imaging techniques. Compared to TTE, 2D PC-MR underestimated V_{peak} by a mean difference of $-11.2 \pm 10.2\%$ ($p < 0.001$), whereas 4D PC-MR yielded a significantly higher peak jet velocity (mean difference from TTE: $+16.6 \pm 10.5\%$, $p < 0.001$). A similar pattern was found for P_{mean} : correlations between modalities were excellent, with pressure gradients from 4D PC-MR being significantly larger than those obtained by TTE or 2D PC-MR (4D PC-MR vs. TTE: $+13.8 \pm 16.3\%$, $p = 0.017$, and 2D PC-MR vs. TTE: $-30.2 \pm 17.6\%$, $p < 0.001$). Scatter diagrams revealed larger underestimation of peak velocities and pressure gradients by 2D PC-MR in more severe cases of AS, whereas 4D PC-MR and TTE maintained relatively good agreement (Figures 2 and 3).

Although higher V_{peak} and P_{mean} would suggest more critical stenosis, AVA was larger when calculated from 4D PC-MR (mean difference from TTE: $+19.5 \pm 20.1\%$, $p = 0.001$). Since the dimensionless index (i.e. the ratio between VTI_{LVOT} and VTI_{Aorta}) was comparable between techniques ($p = 0.76$), the higher AVA obtained by 4D PC-MR can be explained only by differences in LVOT area measurements. Indeed, planimetric LVOT area (4D PC-MR) was significantly larger than the same area that was computed from the echocardiographically obtained LVOT diameter ($4.7 \pm 0.57 \text{ cm}^2$ vs. $3.9 \pm 0.54 \text{ cm}^2$, $p < 0.001$).

Table 3. Mean and percentage differences between TTE and PC-MR.

	4D PC-MR vs. TTE				2D PC-MR vs. TTE			
	r	Δ (mean)	Δ (perc.)	p	r	Δ (mean)	Δ (perc.)	p
V_{peak} (m/s)	0.95	$+0.5 \pm 0.4$	$+16.6 \pm 10.5$	<0.001	0.95	-0.4 ± 0.4	-11.2 ± 10.2	<0.001
P_{mean} (mmHg)	0.92	$+4.3 \pm 7.2$	$+13.8 \pm 16.3$	0.017	0.92	-8.9 ± 7.7	-30.2 ± 17.6	<0.001
AVA (cm ²)	0.80	$+0.3 \pm 0.3$	$+19.5 \pm 20.1$	0.001	0.80	$+0.6 \pm 0.4$	$+38.2 \pm 25.4$	<0.001

AVA: aortic valve area; P_{mean} : mean transvalvular pressure gradient; PC-MR: phase contrast magnetic resonance; perc: percentage; V_{peak} : peak jet velocity.

Flow displacement

Flow displacement in the ascending aorta differed highly between individuals (range 0.02-0.15 for patients with tricuspid valves, range 0.07-0.15 for those with bicuspid valves). There was no significant relationship between the severity of AS and the eccentricity of the flow jet ($r = 0.23$ for the association between flow displacement and V_{peak} , $p = 0.35$). However, a strong correlation ($r = 0.89$, $p < 0.001$) was found between flow displacement and the extent to which V_{peak} differed between 4D PC-MR and TTE, indicating the influence of flow eccentricity on the accuracy of ultrasound measurements (Figure 4B).

Concordance between AS parameters

Regression analysis showed excellent correlation between TTE-derived V_{peak} and P_{mean} ($r = 0.97$, Figure 5A). In contrast, correlations between V_{peak} and AVA and between P_{mean} and AVA were only moderate ($r = 0.68$ for both). Use of 4D PC-MR markedly improved these correlations, to $r = 0.87$ and $r = 0.86$, respectively (Figure 5B).

Intra- and interobserver variability

Intra-observer agreement was excellent for 4D PC-MR measurements of V_{peak} (ICC 1.00), P_{mean} (ICC 0.99), and AVA (ICC 0.94). Also, interobserver agreement was excellent (ICC 0.97 for V_{peak} , ICC 0.96 for P_{mean} , and ICC 0.90 for AVA).

DISCUSSION

Transthoracic echocardiography is the imaging modality of first choice for the evaluation of AS, given its practicality, portability and cost-effectiveness. Furthermore, current thresholds for valve replacement are based on echocardiographic studies that investigated the association between various AS parameters and adverse outcomes(22-24). However, TTE should be performed with care, as its potential pitfalls may result in either under- or overestimation of stenosis severity(3, 4). In the current study, we investigated whether 4D PC-MR can overcome certain limitations that apply to TTE. Our main findings are: 1) 4D PC-MR measures higher V_{peak} and P_{mean} in AS patients when compared to TTE, 2) 2D PC-MR substantially underestimates AS severity when compared to TTE, 3) pronounced flow eccentricity is associated with greater differences in V_{peak} between TTE and 4D PC-MR, and 4) 4D PC-MR improves concordance between the parameters that define AS severity. To date, logistic constraints (such as long acquisition times and the need for advanced MR hardware and post-processing tools) have impeded the widespread use of 4D PC-MR. Nevertheless, it affords a uniquely detailed assessment of flow patterns in the heart and aorta. Validation studies have compared 4D PC-MR with echocardiography in healthy volunteers and in patients without valvular disease (i.e., subjects with laminar flow patterns), and found good agreement between

both modalities(17, 18). However, as previously reported by others, we found that systolic flow jets in AS patients are often eccentric(19, 25). Four-dimensional PC-MR is not hindered by flow eccentricity, since its multidirectional velocity-encoding provides for quantification of velocities regardless of the spatial orientation of the flow jet. In TTE, however, abnormal flow patterns confer risk for misalignment of the ultrasound beam with the AS jet. Therefore, it is conceivable that TTE underestimates V_{peak} and P_{mean} in AS patients, which is in line with the findings of the current study. The excellent correlation that was found between flow displacement and the extent to which TTE underestimated V_{peak} serves as internal validation for this hypothesis.

Of note, use of unidirectional 2D PC-MR led to substantial underestimation of velocities and pressure gradients, especially in patients with more critical valvular stenosis. Recently, Da Silva et al. have evaluated a 2D PC-MR sequence with three-directional velocity-encoding and demonstrated the importance of multidirectional flow imaging in AS patients(12). Their sequence, which they were able to acquire within one breath hold, showed improved correlations with TTE for most AS parameters. Rose et al. performed 4D PC-MR in a pediatric cohort of non-stenotic BAV patients and calculated the underestimation of peak velocities by unidirectional methods to

be 6.6%(26). Our study adds to this knowledge by showing that the benefits of 4D PC-MR are more pronounced in AS patients with higher peak velocities and in those with highly eccentric flows. Furthermore, and in contrast to 2D PC-MR, 4D PC-MR facilitates visualization of aortic flow patterns and estimation of secondary flow-related metrics (such as wall shear stress), which is of potential interest in the pathophysiology of valve-related aortopathy(15, 27, 28).

AVA is, in theory, the ideal parameter to reflect AS severity, albeit the most challenging one to assess. It has been well-described that AVA shows considerable variability depending on measurement method (anatomical vs. functional) and imaging modality(29). Two-dimensional echocardiography usually underestimates AVA in comparison to other imaging techniques, because it measures the anteroposterior (i.e., minor) axis of the LVOT for calculation of its cross-sectional area(6, 7). Our results confirm that the TTE-derived LVOT area is approximately 20% smaller than its planimetric equivalent from 4D PC-MR(30). Hence, AVA differs to the same extent. Since current thresholds for valve replacement are based on echocardiographic studies that showed $AVA \leq 1.0 \text{ cm}^2$ to be associated with increased mortality risk, the higher AVA from 4D PC-MR would require definition of new, modality-specific, cut-offs for AS grading. Nevertheless, the technique has potential to develop into a useful tool for the hemodynamic assessment of stenosis severity, as it is the first imaging modality that showed ability to improve correlations between different AS parameters(7). Whereas this might not be of added value for patients with symptomatic high-gradient AS (since these already qualify for valve intervention), it can be particularly useful for the assessment of patients with discordant echocardiographic grading patterns. Such patterns are observed in up to 35% of patients with severe AS and typically involve cases of low-gradient AS (i.e., presence of a small valve orifice [$AVA \leq 1.0 \text{ cm}^2$] accompanied by a relatively low transvalvular pressure gradient [$P_{\text{mean}} < 40 \text{ mmHg}$])(31, 32). Although, depending on flow status and LV ejection fraction, several subtypes of low-gradient AS have been acknowledged, the first step in their encountering should be to exclude any measurement errors from TTE. Future studies should investigate whether 4D PC-MR has the potential to distinguish between actual low-gradient severe AS and overestimated moderate AS, and if the technique can play a role in determining the need and timing of aortic valve replacement in this specific patient group.

Several limitations of the current study and the 4D PC-MR imaging technique should be addressed. First, there exists no gold standard for velocity measurements in AS patients against which our findings could be compared.

Second, in vitro studies have demonstrated that phase-contrast techniques tend to underestimate flow rates in stenotic flows, and that measurement errors increase with higher velocities and longer TE(33). Although 4D PC-MR revealed higher flow velocities than TTE in the current study, patients with severe AS were relatively underrepresented. Future studies that include a larger number of patients with highly accelerated flows are required to investigate the potential impact of the limited temporal resolution of 4D PC-MR on the accuracy of flow and velocity measurements in more detail.

Third, even though our results indicate that 4D PC-MR is a feasible imaging modality that can be performed using clinically available hardware and software platforms, shortening of scan duration is a prerequisite in order for the technique to find its way into clinical practice guidelines. Several technical advances (such as compressed SENSE, parallel imaging and novel reconstruction algorithms) hold promise to significantly reduce the long scan time of 4D PC-MR.

Finally, based on our results on improved concordance between V_{peak} , P_{mean} and AVA using 4D PC-MR, future studies should address the potential value of 4D PC-MR for the assessment of AS patients with discordant echocardiographic parameters.

In conclusion, 4D PC-MR can be performed with high intra- and interobserver accuracy in patients with AS. Pronounced flow eccentricity is associated with greater differences in V_{peak} between TTE and 4D PC-MR. Use of 4D PC-MR increases concordance between V_{peak} , P_{mean} and AVA. Based on these findings, future studies should address the potential value of 4D PC-MR for the assessment of patients with discordant echocardiographic AS grading.

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Characterization of ascending aortic flow in patients with degenerative aneurysms: a 4D flow magnetic resonance study

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Investigative Radiology - in press

Chapter

ABSTRACT

OBJECTIVES

Degenerative thoracic aortic aneurysm (TAA) patients are known to be at risk of life-threatening acute aortic events. Guidelines recommend pre-emptive surgery at diameters of $>55\text{mm}$, although many patients with small aneurysms show only mild growth rates and more than half of complications occur in aneurysms below this threshold. Thus, assessment of hemodynamics using 4D flow magnetic resonance has been of interest to obtain more insights in aneurysm development. Nonetheless, the role of aberrant flow patterns in TAA patients is not yet fully understood.

MATERIALS AND METHODS

A total of 25 TAA patients and 22 controls underwent time-resolved 3D phase contrast MR imaging with 3-directional velocity encoding (i.e., 4D flow MRI). Hemodynamic parameters such as vorticity, helicity and wall shear stress (WSS) were calculated from velocity data in three anatomical segments of the ascending aorta (root, proximal and distal). Regional WSS distribution was assessed for the full cardiac cycle.

RESULTS

Flow vorticity and helicity were significantly lower for TAA patients in all segments. The proximal ascending aorta showed a significant increase in peak WSS in the outer curvature in TAA patients, whereas WSS values at the inner curvature were significantly lower as compared to controls. Furthermore, positive WSS gradients from sinotubular junction to mid-ascending aorta were most prominent in the outer curvature, whereas from mid-ascending aorta to brachiocephalic trunk the outer curvature showed negative WSS gradients in the TAA group. Controls solely showed a positive gradient at the inner curvature for both segments.

CONCLUSION

Degenerative TAA patients show a decrease in flow vorticity and helicity which is likely to cause perturbations in physiological flow patterns. The subsequent differing distribution of WSS might be a contributor to vessel wall remodeling and aneurysm formation.

KEYWORDS

Aorta, aneurysm, 4D flow MRI, dissection

KEY POINTS

- Degenerative thoracic aortic aneurysm (TAA) leads to disturbed intra-aortic flow with decreased flow helicity and vorticity.
- Patients with TAA have asymmetrically distributed aortic wall shear stress (WSS), with elevated WSS values along the outer curvature.

INTRODUCTION

Thoracic aortic aneurysm (TAA) is defined as a local enlargement of the thoracic aorta to more than 150% of the expected diameter(1). Despite its asymptomatic character, TAA predisposes for occurrence of life-threatening aortic events (such as dissection or rupture). The risk of natural complications is correlated to the maximal aortic diameter and increases sharply at diameters $>60\text{ mm}$ (2, 3). Hence, current clinical guidelines recommend pre-emptive surgical extirpation of degenerative aneurysms $\geq 55\text{mm}$ (or smaller if concomitant risk factors are present)(4-6). However, more than half of type A dissections occur at diameters below the cut-offs for prophylactic intervention(7-9). Therefore, there is a need for additional predictors of TAA progression, dissection, and rupture(10).

Since dissection and rupture are commonly associated with hypertension there is a developing interest in the role of hemodynamics in the pathophysiology of aortic disease. Four-dimensional flow magnetic resonance imaging (4D flow MRI) is an emerging non-invasive imaging modality that provides comprehensive insight into aortic hemodynamics(11-13). The technique facilitates acquisition of time-resolved three-dimensional three-directionally encoded velocity data and allows for visualization and quantification of flow patterns and flow-derived hemodynamic markers(14). To date, abnormal hemodynamics (such as elevated wall shear stress [WSS], flow eccentricity, and flow vorticity) have been linked to different expressions of aortopathy in patients with Marfan's syndrome and bicuspid aortic valve (BAV)(15-18). Previous research has described that flow deviations predominantly occur in an aneurysmatic region and that these flow patterns normalize once the aortic diameter normalizes distal from the aneurysmatic area(19-21). However, flow patterns in patients with degenerative TAA have not quantitatively been characterized and the potential impact of hemodynamics on development and progression of degenerative aneurysms is not fully understood. The current prospective observational two-center study aims to characterize regional hemodynamics in the ascending aorta of patients with degenerative TAA and compare findings with those of healthy controls.

MATERIALS AND METHODS

Study population

Patients with degenerative TAA $\geq 40\text{ mm}$ who visited the outpatient clinic of the Maastricht and Leiden University Medical Centers were prospectively recruited. Exclusion criteria comprised prior aortic or cardiac surgery and the presence of connective tissue disorder, BAV or general contraindications for MR imaging. Patients with atrial fibrillation were excluded to ascertain the accuracy of MR flow measurements. A population of volunteers without aortic or valvular disease was included as control group. The study protocol was approved by the local medical ethical committee and all subjects provided written informed consent.

MR acquisition

Patients underwent MR examinations on 3T MR systems (Philips Ingenia, Philips Healthcare, Best, the Netherlands). The acquisition protocol included a 4D flow sequence with full volumetric coverage of the left ventricular outflow tract (LVOT) and thoracic aorta. Both medical centers used the same 4D flow sequence (Table 1). Data was acquired using retrospective ECG gating and navigator respiratory gating based on diaphragm excursion. Velocity encoding (VENC) was typically set at 150 cm/s .

Data analysis

Image analysis was performed by a single reader (M.R.) using commercially available software (CAAS MR Solutions 5.1, Pie Medical Imaging Maastricht, the Netherlands). First, the lumen of

the aorta was segmented from the magnitude images of the 4D flow dataset in peak systole. The segmented mesh was then copied over the entire cardiac cycle for analysis of additional heart phases. Cross-sectional planes were placed at four different locations: 1. aortic valve, 2. sinotubular junction (STJ), 3. mid ascending aorta, and 4. proximal to the origin of brachiocephalic trunk. The cross-sectional planes divided the aorta into three segments: aortic root (R), proximal ascending aorta (PAsc), and distal ascending aorta (DAsc) (Figure 1). The resulting three aortic segments were each divided into four anatomical regions (anterior and posterior inner curvature and anterior and posterior outer curvature). Wall shear stress (WSS) was defined as the tangential viscous force acting on the endothelial surface as a result of blood flow and calculated as previously described(22). Mean WSS values were calculated for each anatomic region per plane. Flow vorticity (ω) was defined as the vector that describes the flow rotation and calculated as follows:

$$\omega = \nabla \times v$$

, where v is the velocity vector and ∇ is Nabla, the differential operator. Nabla in combination with the cross product ($\times$) is called the rotation operator, or curl. Flow helicity (H) was defined as the dot-product of vorticity with the 3D flow vector and calculated as:

$$H = v \cdot \nabla \times v$$

Flow vorticity magnitude and helicity were both normalized for aortic volume per segment (mL) and corrected for stroke volume (mL).

Table 1: Four dimensional flow MR acquisition parameters.

	4D Phase Contrast MRI
FOV (mm × mm × mm)	350 × 280 × 75
Acquired voxel size (mm × mm × mm)	2.5 × 2.5 × 2.5
Reconstructed voxel size (mm × mm × mm)	1.46 × 1.46 × 2.5
Flip angle (°)	10
TE (ms)	2.3
TR (ms)	4.2
TFE factor	2
SENSE factor	2.5 (P) × 1.5 (S)
VENC (cm/s)	150-200
Shot duration (ms)	33
(Reconstructed) Cardiac phases	24-43

FOV: field of view; TE: Echo time; TR: repetition time; VENC: velocity encoding.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 25 (IBM, Armonk, USA). Normality distribution of the data was tested using the Shapiro-Wilk test. Continuous demographics are expressed as mean ± standard deviation (or as median and interquartile range in the presence of data skewness). Differences between groups were assessed using student's t-test (or Mann-Whitney U test, if deemed appropriate).

Figure 1: Aortic plane placement and division of segments. R: aortic root; PAsc: proximal ascending aorta; DAsc: distal ascending aorta.

Categorical variables are presented as frequencies and percentages and were evaluated using Chi-square test or Fisher's exact test. Correlations between parameters were tested using Spearman's R or Pearson's correlation coefficient. Gradients were analyzed using a Wilcoxon signed-rank test considering the presence of skewness. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 25 TAA patients and 22 controls were included. Patients with TAA were more likely to suffer from hypertension (48.0% vs. 4.3%, $p < 0.001$) and to use antihypertensive medication (Table 2). Additional demographics – such as age, gender, and body size – did not differ significantly between groups.

Aortic diameters were significantly larger in TAA patients at all levels of the ascending aorta (plane 2: 41.7 mm vs. 34.4 mm, $p<0.001$; plane 3: 42.7 mm vs. 32.5 mm, $p<0.001$; plane 4: 41.4mm vs. 31.5 mm, $p<0.001$).

Table 2: Baseline characteristics of the study population.

	Controls	TAA	p-value
N	22	25	-
Age (years)	63.5 [57.0 – 67.3]	64.5 [50.8 – 72.3]	0.790
Men	12 (54.5%)	15 (60.0%)	0.807
BMI (kg/m2)	25.5 [22.5 – 28.7]	26.4 [23.7 – 28.7]	0.565
BSA (m2)	1.90 (±0.26)	1.98 (±0.16)	0.281
Hypertension	1 (4.5%)	12 (48%)	0.001*
Hypercholesteraemia	2 (9.1%)	8 (32.0%)	0.079
Diabetes	2 (9.1%)	3 (12.0%)	1.000
Current smoker	4 (18.2%)	4 (16.0%)	1.000
Past smoker	7 (31.8%)	8 (32.0%)	0.989
Medication			
Beta blocker	1 (4.5%)	8 (32.0%)	0.025*
ACE-inhibitor	1 (4.5%)	12 (48.0%)	0.001*
Calcium antagonist	0 (0%)	5 (20.0%)	0.052
Nitrate	0 (0%)	0 (0%)	-
Statin	2 (9.1%)	8 (32.0%)	0.079

BMI: body mass index; BSA: body surface area. * = statistically significant.

Table 3: Maximal aortic diameters measured at three levels of the ascending aorta.

	Controls (n=22)	TAA (n=25)	P-value
Maximal diameter root (mm)	34.3 (±4.5)	41.7 (±6.0)	<0.001*
Maximal diameter Pas (mm)	32.5 (±4.1)	42.7 (±4.5)	<0.001*
Maximal diameter DAsc (mm)	31.5 (±4.2)	41.4 (±4.2)	<0.001*
Centerline length root (mm)	15.7 (±3.4)	17.2 (±3.6)	0.151
Centerline length PAsc (mm)	28.5 (±4.7)	33.3 (±9.3)	0.031*
Centerline length DAsc (mm)	30.3 (±5.2)	41.0 (±9.73)	<0.001*

Ascending aortic dimensions. Maximal aortic diameters (in mm) of the study population are measured at three levels of the ascending aorta. Centerline length (in mm) is measured in all three segments of the ascending aorta. PAsc = proximal ascending aorta, DAsc = distal ascending aorta. * = statistically significant.

Figure 2a. Flow vorticity normalized for aortic volume and stroke volume ($s^{-1}mL^{-2}$). Figure 2a shows the flow vorticity through the ascending aorta in controls (red) and TAA patients (grey). R: aortic root; PAsc: proximal ascending aorta; DAsc: distal ascending aorta. * $p<0.05$; # $p<0.01$.

Figure 2b. Absolute flow helicity normalized for aortic volume and stroke volume ($m\cdot s^{-2}\cdot mL^{-2}$). Figure 2b depicts the flow helicity through the ascending aorta in controls (red) and TAA patients (grey). R: aortic root; PAsc: proximal ascending aorta; DAsc: distal ascending aorta. * $p<0.05$; # $p<0.01$.

Peak normalized vorticity was significantly lower in the aortic root of TAA patients ($64.4 s^{-1}mL^{-2}$ vs. $90.0 s^{-1}mL^{-2}$, $p=0.001$), as well as in the proximal and distal ascending aorta ($52.6 s^{-1}mL^{-2}$ vs. $74.1 s^{-1}mL^{-2}$, $p=0.013$, and $30.6 s^{-1}mL^{-2}$ vs. $49.5 s^{-1}mL^{-2}$, $p=0.005$, respectively) (Figure 2a). Peak absolute normalized helicity was significantly lower in TAA patients at the level of the aortic root ($5.5 m\cdot s^{-2}\cdot mL^{-2}$ vs. $7.3 m\cdot s^{-2}\cdot mL^{-2}$, $p=0.001$), proximal ascending aorta ($6.3 m\cdot s^{-2}\cdot mL^{-2}$ vs. $8.9 m\cdot s^{-2}\cdot mL^{-2}$, $p=0.013$) and distal ascending aorta ($3.0 m\cdot s^{-2}\cdot mL^{-2}$ vs. $5.8 m\cdot s^{-2}\cdot mL^{-2}$, $p=0.003$) (Figure 2b). Besides total values being significantly lower, partial derivatives show distinct differences, whereas areas of high vorticity in controls are mostly located at the inner curvature, whilst TAA patients show a less uniform distribution throughout the lumen (Figures 3 and 4).

Figure 3. Separate components of rotation in vorticity calculation. Images depict values of a central vertical plane of a single representative subject per group. Red and blue are positive and negative values, respectively.

Dynamics of WSS over the cardiac cycle for different planes and different regions of the ascending aorta are depicted in Figure 4. In general as compared to controls, peak WSS in TAA patients was lower at the sinuses of Valsalva, while it was higher at the outer curvature and lower at the inner curvature at the proximal ascending aorta and returning to lower values at the distal ascending aorta. Peak WSS was significantly lower at the level of the sinuses of Valsalva in TAA patients at the posterior part of the inner curvature (729 mPa vs. 955 mPa, $p=0.026$), the anterior part of the inner curvature (652 mPa vs. 874 mPa, $p=0.036$) and the posterior part of the outer curvature (769 mPa vs. 979 mPa, $p=0.049$). Peak WSS was significantly lower at the anterior part of the inner curvature of the proximal ascending aorta in TAA patients (734 mPa vs. 864 mPa, $p=0.026$), whereas it turned out to be significantly higher at the anterior part of the outer curvature (1285 mPa vs. 963 mPa, $p=0.007$). The distal ascending aorta showed significantly lower peak WSS values in TAA patients at the anterior area of the inner curvature (773 mPa vs. 986 mPa, $p=0.006$), the posterior area of the inner curvature (936 mPa vs. 1306 mPa, $p<0.001$) and the posterior area of the outer curvature (707 mPa vs. 947 mPa, $p=0.001$). Peak WSS did not differ significantly at other regions.

Of note, positive peak WSS gradients were observed between the STJ and PAsc in TAA patients at the outer curvature posterior (769 mPa to 1119 mPa, $p=0.007$), at the outer curvature

Figure 4. Visualization of ascending aortic flow velocities and flow directions in the systolic heart phase with most pronounced flow perturbations of a TAA patient and a healthy control. Blue and red indicate low and high velocity, respectively. Full videos of flow patterns in these subjects are available as Supplemental Digital Content (See videos Supplemental Digital Content 1 and 2, showing ascending aortic flow patterns).

anterior (839 mPa to 1285 mPa, $p<0.001$) and at the inner curvature posterior (729 mPa to 938 mPa, $p=0.004$), whereas controls only showed a significant positive gradient at the inner curvature posterior from STJ to PAsc (955 mPa to 1138 mPa, $p=0.027$). From PAsc to DAsc a negative gradient is seen in TAA patients at the outer curvature posterior and anterior (1119 mPa to 707 mPa, $p<0.001$ and 1285 mPa to 964 mPa, $p=0.002$, respectively). Controls showed a positive gradient between PAsc and DAsc for the inner curvature posterior and anterior (1138 mPa to 1306 mPa, $p=0.003$ and 864 mPa to 992 mPa, $p=0.008$, respectively) (Figure 5).

DISCUSSION

In the current study, we assessed hemodynamic parameters in the ascending aortas of patients with degenerative TAA and compared them to those in healthy controls. We found that TAA patients i) have decreased normalized aortic flow vorticity and helicity, ii) show more asymmetrically distributed peak WSS values with elevated WSS at the outer curvature and decreased WSS at the inner curvature, and iii) show a positive WSS gradient from the sinotubular junction to the proximal ascending aorta.

Aberrant flow patterns

Physiological vorticity and helicity play a role in maintaining stable flow through the aorta (19, 23). According to Poiseuille's law of flow in a U-bend shape, such as the thoracic aorta, centripetal forces in the proximal part cause a shift of the parabolic peak velocity from the center of aorta to the inner curvature, where distally in the U-bend, centrifugal forces dominate and cause a shift towards the outer curvature. The secondary flow patterns that occur as a consequence, consisting of two counter rotating in-plane vortices, are needed to maintain stable flow and mass transportation. In the current study, these secondary flow patterns were clearly seen in controls when taking a look at the rotation components of the flow vorticity, whereas the pattern in TAA patients was found to be different (Figures 3 and 4). These secondary flow patterns in the healthy aorta have been demonstrated to compensate

for the adverse effects of the aortic curvature on blood flow, hence sparing the ascending aorta and arch from low-density lipoprotein (LDL) deposition and atherogenesis(24). The normal aortic ageing process involves luminal dilatation and elongation, which occur in association with decreased flow helicity and vorticity(23, 25, 26). Changes in blood flow have been of increasing interest in patients with aortic disease. Recent 4D flow MR studies reported pronounced helical and vortical flow patterns in patients with TAA, connective tissue disease and BAV(17, 19, 27). However, most of these studies used qualitative observations using stream- or path-line analysis, which are prone for bias and difficult to analyse regarding the secondary in-plane flow patterns. Only one previous study quantified flow vorticity in the ascending aorta in patients with BAV, showing increased vorticity as compared to healthy controls(28). Yet, given that a substantial part of the included BAV population had dysfunctional valves with concomitant high peak flow velocities, this result could be foreseen when looking at the formula to calculate vorticity. Compared to healthy controls and as opposed to BAV, we found a decrease in flow vorticity and helicity in degenerative ascending aortic aneurysms. We hypothesize that the transformations of aortic dimensions with increasing age lead to substantial perturbations in the in-plane vorticity, with abnormal flow patterns as a consequence. Moreover, subsequently to the need of vorticity and helicity to stabilize flow, declining vorticity and helicity increases the risk of flow abnormalities such as flow separation. Flow separation might occur with diminishing secondary in-plane vortices and are a possible cause of large 'slow' vortices in TAA patients. It is proposed that this could lead to unequal distribution of WSS, with more risk of LDL transportation along the side of the vessel wall that experiences low WSS(24).

Wall Shear Stress

Wall shear stress is an important parameter when describing the mechano-transduction of flow stresses on the vessel wall. Both, low and high WSS play a role in the pathophysiology of aortic disease. Results from in vitro studies indicate that elevated WSS contributes to aortic dilatation, while low WSS is associated with atherosclerotic plaque formation(29, 30). High WSS and positive WSS gradients have been shown to result in adapted gene expression in endothelial cells which initiates endothelial proliferation, extracellular matrix degradation and aneurysm formation (30). Mahedevia et al. used 4D flow MRI and found a relationship between different BAV fusion patterns and the location of peak ascending aortic WSS, which might be part of the link between BAV and the associated aortopathy(17). Moreover, a high ratio of circumferential to total WSS has been described as a cause of poststenotic aortic dilatation (i.e., aneurysm formation distal to a stenotic aortic valve)(31).

Contrary to studies that have observed an association between elevated WSS and vessel dilatation, there is evidence that rupture of aneurysms occurs at regions of low WSS. It is hypothesized that low WSS and thrombus deposition predominates at regions of flow recirculation, which results in adventitial degeneration and subsequent aneurysm rupture(32). One previous 4D flow MR study concluded that TAA patients exhibit significantly lower WSS in all aortic segments and regions during peak systole(19). Our results do not support this conclusion. First, we found that WSS is asymmetrically distributed around the vessel wall. Although the averaged WSS per segment may be lower in TAA, we have demonstrated that peak WSS in the outer aortic curvature was significantly higher as compared to controls. Second, due to aberrant flow patterns, awareness for looking beyond peak systole rises, since these flow patterns occur more towards end-systole(33). A discrepancy between peak systole and peak WSS might be a plausible cause for deviating results as compared to the earlier study(19). Along with the positive WSS gradient, this elevated peak WSS could promote aortic dilation in this region.

Mechano-sensing of wall shear stress and other mechanical stresses in the arterial wall is of great importance(34). The exact influence of aberrant flow and deviated WSS on mechano-transduction deserves further evaluation, considering a previously described association of aortic stiffness with aortic disease progression(35). An interesting goal for future studies would thus be to evaluate MR methods that combine flow analysis and markers of vessel wall stiffness such as pulse wave velocity and MR elastography(36-38).

Study limitations

Some limitations of the current study need to be addressed. First, the accuracy of WSS estimations by 4D flow MR is limited by the technique's inherent spatial and temporal resolution. Consequently, WSS estimations are consistently lower than those derived from model-based computational fluid dynamics (CFD) simulations (which have arbitrary high spatial and temporal resolution)(39). However, the MR acquisition protocol was similar for all study subjects, which allows for reliable WSS comparison between patient groups.

Second, we created a static 3D geometry during peak systole and used this to calculate WSS, vorticity and helicity over the cardiac cycle. This approach neglects potential cyclic movement and distensibility of the ascending aorta. However, segmentation was performed on velocity data, making it infeasible to create accurate geometric models in phases with low flow velocities (especially diastole).

We found a decrease of flow vorticity and helicity and an unequal distribution of WSS with higher peak WSS in TAA patients. The decrease of helicity and vorticity are a possible cause of aberrant flow in degenerative thoracic aortic aneurysms, which is likely to induce the unequal distribution of wall shear stress. These variations in peak wall shear stress and wall shear stress gradients are potential contributors to vessel wall remodeling and thus could promote further aortic dilation.

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Summary
General discussion
Future outlook

Chapter

The preventive management of ascending thoracic aortic aneurysm (TAA) comprises stringent control of risk factors and periodic imaging for assessment of aortic valve function and aneurysm size(1-3). Using state-of-the-art acquisition and post-processing techniques, we have evaluated the timing and clinical value of aortic diameter measurements for prediction of acute aortic syndromes (AAS). Furthermore, we aimed to identify novel imaging markers that improve the identification of patients at risk. The current chapter discusses the presented studies in light of their clinical and scientific relevance and provides an outlook for future research.

PART I – ANATOMIC IMAGING

Aneurysm surveillance intervals

The indication for pre-emptive surgical extirpation of TAA relies on a maximal aortic diameter ≥ 55 mm. This cut-off is based on studies conducted between 1985 and 1996, which revealed sharp ‘hinge points’ in the size at which AAS occur(4-6). Despite the indispensable role of imaging in TAA management, no standardized timing intervals for diameter surveillance have been defined. Consequently, follow-up frequencies vary between patients and are primarily determined by the insights and preferences of the treating physician. In **Chapter 3**, we calculated yearly expansion rates of non-syndromic TAA and used these to propose diameter-specific intervals for imaging

follow-up. Contrary to the prevailing view that all aneurysms gradually enlarge(7) we found that nearly half of all TAA remain stable over time. Moreover, we showed that (semi-)annual imaging – which is recommended by some current guidelines(2, 8) – carries no therapeutic consequences for patients with small aneurysms (diameter < 50 mm). The proposed imaging protocols prescribe triennial imaging of TAA that are > 5 mm away from the predetermined surgical threshold and showed to be as accurate as yearly imaging with regard to the timing of intervention (Figure 1).

The study presented in **Chapter 3** has several strengths compared to existing literature that reports on the natural evolution of TAA. Previous studies included heterogeneous populations (including patients with connective tissue disease and chronic dissections)(4, 9-11), while others did not distinguish between aneurysms at different anatomic locations of the aorta(10, 12). In a recent systematic review, the presence of Marfan syndrome and a distal aneurysm location (i.e., in the descending or thoracoabdominal aorta) were identified as the main factors predisposing to rapid TAA growth(13). Since we used different imaging modalities to evaluate aortic diameters, one should consider the limitations that relate to the potential measurement bias between these techniques(14). Moreover, imaging intervals were inconsistent, for which it was unable to assess exact yearly growth. The latter is not irrelevant since American guidelines also recommend prophylactic surgery in patients with TAA expansion > 5 mm/year(2). Future (randomized) studies using standardized follow-up intervals are needed to prospectively validate the safety and cost-effectiveness of less frequent imaging strategies.

The aortic diameter – a poor man’s surrogate

Chapter 2 discusses the clinical value of aortic diameter measurements. On the one hand, current surgical thresholds have near 100% specificity for prediction of dissection. Thus, they accurately select those with highest relative risk and preclude unnecessary surgical intervention. On the other hand, it has become increasingly clear that most dissections occur in aortas with diameters below interventional cut-offs(15, 16). The International Registry of Acute Aortic Dissection (IRAD) reported that 59% of enrolled patients (n=591) had diameters < 55 mm at the time of presentation(17), which is comparable to the findings in our database (**Chapter 5**). The explanation for this paradoxical observation lies in the right-skewed distribution of aneurysm sizes, with 97.6% of TAA patients having aortic diameters between 40 and 50 mm(18). One suggestion to increase the sensitivity of diameter measurements is to lower surgical cut-offs, favoring prophylactic intervention at smaller ascending aortic sizes(19). Three arguments substantiate this claim:

- Current surgical thresholds are based on post-dissection imaging studies and neglect the sudden increase in aortic size at the moment of dissection onset. Recent data has shown that post-dissection diameters are approximately 30% larger than pre-dissection dimensions(20-22). This finding indicates that dissection develops at smaller aortic sizes than previously thought.
- Current cut-offs are based on older imaging techniques. Along with the advent of three-dimensional (3D) imaging, centerline diameter measurements found their way into clinical practice(23). Compared to axial measurements, these have improved intra- and interobserver agreement(24). However, multiple studies reported that centerline diameters are consistently smaller than those obtained by traditional measurement methods(23-26). Therefore, surgical cut-offs require adaptation to the use of state-of-the-art imaging methods.
- Outcomes of TAA patients have improved as a result of optimization of surgical techniques and centralization of aortic care into specialized centers(27). Over the last decades, the perioperative mortality rate for elective procedures has declined from 4.3% to 1.3%-2.3%(28, 29). Moreover, stent grafting of the ascending aorta is emerging as a safe therapeutic option in those with favorable anatomy and may further improve surgical outcomes(30). For these reasons, the balance between the risks and benefits of surgery deserves re-evaluation(31).

In **Chapter 6**, we used pre-dissection computed tomography (CT) to study the geometry of the aorta at the moment of impending dissection, and confirmed that 96% of observed dissections occurred at diameters <55 mm(22). As expected, the sensitivity of the maximal diameter for prediction of dissection would increase (from 4% to 17%) when the surgical cut-off is shifted to ≥ 50 mm, while specificity remains high (95.5%). Ongoing studies will further evaluate the optimal surgical indication criterion and could lead to guideline changes in the near future.

In addition to the considerations above, this thesis shows that other anatomic markers can improve prediction of AAS. In **Chapters 5** and **6**, we focused on elongation of the ascending aorta and found that aortic length more accurately predicts dissection as compared to the maximal diameter. This finding was validated in a recent longitudinal study by a group from Yale(32), whose previous work formed the basis of many recommendations within current guidelines. However, in their study, Elefteriades et al. referred to aortic length as the 'neglected dimension'. We do not entirely agree with this statement, since the assessment of longitudinal aortic dimensions requires high-resolution electrocardiographically (ECG)-gated isotropic datasets and advanced post-processing software packages (Figure 2). Therefore, rather than neglected, we think that it was not until recently that measurements of aortic length became feasible. Now that 3D imaging has become common in daily practice, it is time to maximally exploit its possibilities and embrace the novel predictors that these techniques afford.

Figure 2. Non ECG-gated CT angiography of a patient with a chronic type A dissection, performed on a single-slice CT-scanner with a rotation time of 1.0 s, slice thickness of 5 mm and a reconstruction increment of 4 mm. The transversal slice **(A)** shows clear dissection membranes in both the ascending and descending thoracic aorta, and a calcification in the dissection membrane of the descending aorta (arrow). The lack of cardiac gating causes pronounced stair-step artifacts in the sagittal oblique multiplanar reconstruction **(B)** with complete dissemination of the dissection membrane in the ascending aorta and aortic arch.

Aortic elongation and volumetry

'Aortic unfolding' is a term commonly used in chest X-ray reports and is generally thought to represent age-associated aortic dilatation. However, the aortic diameter increases by only 3% per decade, which seems out of proportion to the degree of unfolding observed in X-ray studies(33-35). In **Chapter 4**, we described the age-related evolution of longitudinal aortic dimensions and showed that the thoracic aorta elongates by 7% (ascending aorta), 12% (arch) and 25% (proximal descending aorta) per decade of life. Also, we found that the aortic apex gradually shifts away from the branch vessels to a more distal position. Therefore, it is likely that aortic unfolding depicts the process of aortic lengthening rather than dilatation.

There are several reasons to assume that aortic elongation plays a role in the pathogenesis of dissection. First, biomechanical studies have shown that the forces acting on the aortic wall

increase when a vessel becomes more tortuous(36). Second, the intimal entry tear runs in the circumferential direction in 84% of dissection cases(37), suggesting stretch in the longitudinal direction. In **Chapter 5**, we modeled the ascending aortas of dissection patients to pre-dissection dimensions and showed that these were significantly longer than those of propensity-matched healthy controls. The previously mentioned Yale study confirmed our results by investigating ascending aortic length (AAL) in a prospective cohort of TAA patients. They showed that AAL ≥ 13 cm was associated with a five-fold higher risk of adverse events compared to AAL <9 cm(32). The authors also assessed the accuracy of the 'aortic height index' (AHI), which they defined as the sum of the aortic diameter and length normalized for patient height. The AHI showed to be a more powerful predictor for dissection and rupture than any other anatomic parameter (diameter, normalized diameter, AAL, normalized AAL) alone. This index is close to our idea that aortic volume should be added to the measurement parameters derived from aortic CT or MR. As presented in **Chapter 6**, we found that aortic volumetry holds added value over measurements of aortic diameters alone, and that it increases the positive predictive value (PPV) for dissection from 20% to 55%. The concept of normalizing aortic volume measurements to patient body size is interesting and deserves further attention.

PART II – HEMODYNAMIC IMAGING

In Part I of this thesis we have demonstrated that aortic length and volume superiorly predict dissection as compared to the maximal diameter. Nevertheless, even in the best possible scenario, the sensitivity of anatomic measurements did not outreach 28%. Since aortic disease is a biomechanical process that commonly occurs in association with hypertension, hemodynamic imaging may further improve the selection of those at risk for AAS(38-40).

4D flow MR imaging

Flow imaging with phase-contrast magnetic resonance (PC-MR) is conventionally performed in two dimensions (2D). The technique is based on the feature of hydrogen atoms to accumulate an MR phase shift proportional to the speed at which they move along a magnetic gradient field. Two-dimensional PC-MR acquires unidirectionally-encoded velocity data that is directed either through or parallel to a prescribed imaging plane ('through-plane' or 'in-plane', respectively). It is routinely used for the evaluation of a broad spectrum of cardiovascular conditions, including valvular regurgitation and shunts. Over the past decade, technical advances have facilitated the development of 4D PC-MR (or 4D flow MR). This technique captures three-directionally encoded velocity data in a 3D volume with time (i.e., synchronization to the cardiac cycle) as the fourth dimension(41-43). 4D flow MR offers several advantages as compared to 2D PC-MR. First, three-directional velocity-encoding has shown improved flow and velocity quantification as compared to unidirectionally-encoded methods(44-51). Second, 4D flow MR allows post-hoc analysis and reduces operator-dependency(52). Third, the technique offers the ability to evaluate novel intravascular hemodynamic markers such as flow helicity and wall shear stress (WSS). However, these advantages come at the cost of prolonged scan times and susceptibility to motion artifacts (due to the inability to perform acquisition during breath-holding). In our institution, the acquisition of a respiratory-compensated 4D flow MR dataset takes between 15-20 minutes depending on heart rate and respiratory gating.

Flow patterns from 4D flow MR datasets can be analyzed using stream- or pathline visualization. Streamlines follow velocity vectors of each acquired voxel at an instantaneous time point. Pathlines display the temporal evolution of flow over the entire cardiac cycle. The color-coding of stream- and pathlines represents flow velocity and allows identification of regions with flow acceleration (such as in aortic stenosis and coarctation).

4d flow MR for assessment of aortic valve disease

Transthoracic echocardiography (TTE) is the clinical gold standard for assessment of aortic stenosis (AS). **Chapter 7** investigates the diagnostic accuracy of 4D flow MR for AS classification by comparing measurements against 2D flow MR and TTE. Using streamline visualization, we found that post-stenotic systolic flow in the ascending aorta is mostly eccentric. Under this condition, and in contrast to 2D PC-MR, 4D flow MR benefits from its three-directional velocity-encoding. Moreover, streamline analysis allows optimized positioning of analysis planes in the region of highest flow velocity. Compared to TTE, 4D flow MR increased the congruity between the parameters used for AS grading. This finding is of interest since discordant echocardiographic AS grading patterns (which are observed in 28.7% of AS patients) pose a challenge to clinicians in determining AS severity(53-55). Future studies that specifically focus on discordant AS are needed to assess the potential added value of 4D flow MR in this patient group.

As a future outlook, additional to basic flow metrics, recent studies have presented 4D flow MR-derived energy measurements that reflect aortic stenosis severity. In echocardiography, the modified Bernoulli equation ($\Delta P=4v^2$) is used to calculate pressure gradients from Doppler-derived velocity measurements. However, this formula assumes laminar flow and neglects important boundary conditions (such as the flow velocity in the left ventricular outflow tract [LVOT] and LVOT shape)(56). MR-derived turbulent kinetic energy (TKE) is defined as energy loss caused by flow turbulence and has been proposed as a marker that better reflects the increased workload placed on the left ventricle. Recent 4D flow MR-studies found that TKE highly depends on aortic valve morphology and function, and is significantly elevated in patients with AS(57). Although its clinical significance and relation with prognosis have yet to be established, there is growing evidence that flow energetics can characterize aortic valve disease complementary to traditional flow measurements(58, 59).

4d flow MR in thoracic aortic aneurysm

Normal aortic flow is laminar and follows a right-handed helical outflow pattern through the aortic arch. Age-related aortic stiffening causes a change in helix direction and increases flow velocities and WSS(60-62). To date, most 4D flow MR studies in the setting of aneurysmal disease have been performed in patients with bicuspid aortic valve (BAV). Since medial degeneration is also present above normally functioning bicuspid valves, it has long been thought that the aortopathy in BAV patients results from a systemic connective tissue disorder(63, 64). However, 4D flow MR studies have revealed that aortic flow patterns are highly affected by valvular abnormalities, causing pronounced helical flow patterns and elevated regions of WSS along the outer aortic curvature(65-68). Of note, this region is typically the site of the asymmetric dilatation observed in BAV and has shown to be especially prone to histologic medial degeneration(69, 70).

It is estimated that 0.5% of the population has been diagnosed with TAA(71). Although most previous 4D flow MR studies pointed their attention to Marfan syndrome or BAV, these are the underlying causes of only 21.5% of TAA(72). The remainder (i.e., 69.800 cases in the Netherlands(73)) are labeled as degenerative. In **Chapter 8**, we have evaluated flow patterns in patients with degenerative TAA and non-stenotic tricuspid valves. In our population, we found decreased flow helicity and vorticity as compared to healthy controls. Also, we observed large systolic vortex rings in the distal ascending aorta, which can be explained by the central (laminar) flow jet encountering a sudden increase in aortic diameter. This is completely different from flow patterns in BAV. In BAV, the outflow through the bicuspid valve is intrinsically eccentric and causes impingement of a high-velocity flow jet on the aortic vessel wall. Therefore, and in contrast to BAV, we postulate that the aberrant flow patterns in degenerative TAA are the result of aortic dilatation rather than its primary cause. Nevertheless, both flow mechanisms result in

supraphysiologic WSS at the outer curvature of the ascending aorta, aggravating endothelial proliferation, extracellular matrix degradation, and smooth muscle cell apoptosis(38, 42, 74).

There is great future potential of 4D flow MR in the sense that it adds a functional dimension to the classical anatomical display. However, some limitations need to be overcome for the technique to find its place in clinical practice. First, advanced acceleration methods are required to achieve shorter scan times. Second, image acquisition remains challenging and currently limits implementation to hospitals with state-of-the-art MR platforms and devoted physicists. Third, as always in imaging, it is mandatory to prove a causation between 4D flow MR and outcome. As yet, only one study has longitudinally assessed the correlation between flow imaging markers and TAA expansion. In a small study population (median follow-up duration: 4 years), this study found flow eccentricity ($r=0.65$) and maximal WSS ($r=0.5$) to be significantly associated with aneurysm growth(75). Another study collected tissue samples from patients undergoing elective aortic replacement and found pronounced medial degeneration in regions with elevated WSS(76). In summary, further research that improves 4D flow MR acquisition and proves its clinical relevance is needed.

Future outlook

For decades, the maximal aortic diameter has been the key parameter to monitor TAA. This thesis describes the limitations of 'straightforward' aortic size measurements and demonstrates the need for more advanced imaging parameters to guide clinical decision-making. Several ongoing studies aim to further improve the diagnostic accuracy of aortic imaging. The aortic valve is the door to the aorta, and should not be forgotten when assessing TAA risk. Our efforts to implement 4D flow MR at the Maastricht University Medical Center+ have led to our participation in the RADAR-study ('earlier Recognition of Aortic Dissection and Aneurysm Rupture', CVON 2017/08 RADAR). This multicenter project aims to develop an integrated MR approach to improve the predictive value of both anatomic and hemodynamic imaging markers. Initiatives like these, and those of others who have made impressive progress in the fields of genetics and biomarkers, will jointly bring us closer towards the overarching objective: to reduce the incidence and mortality of aortic disease. Let us walk further towards this ultimate goal, and move beyond diameters.

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10

Chapter

GLOSSARY OF TERMS

Acute aortic syndrome (AAS)

A spectrum of aortic conditions that have similar presentations but distinct demographic and pathophysiological characteristics. Major AAS entities include aortic dissection, intramural hematoma, penetrating ulcer and unstable aortic aneurysm.

Aortic aneurysm

A permanent focal dilatation of the aorta having a $\geq 50\%$ increase in diameter as compared to the expected diameter (based on age, gender, and body size).

Aortic dissection

A disastrous condition in which the inner lining of the aortic vessel wall is torn, allowing blood to enter into the wall and create a false lumen.

Aortic elongation

The process in which the aorta lengthens and eventually becomes more tortuous.

Aortic size paradox

The paradoxical observation that most acute aortic syndromes occur in patients with aortic diameters below surgical interventional criteria.

Aortic valve stenosis

Congenital, degenerative or rheumatic narrowing of the aortic valve, causing a transvalvular pressure gradient. Hemodynamically important aortic valve stenosis will lead to heart failure and mortality if left untreated.

Bicuspid aortic valve (BAV)

The most common congenital form of valvular heart disease (prevalence: 0.5-2%), which is characterized by presence of two unequal-sized aortic valve leaflets (instead of three normal leaflets.)

Thoracic aortic aneurysm (TAA)

An aortic aneurysm located within the thoracic cavity. Thoracic aortic aneurysm (TAA) encompasses a wide range of locations (aortic root, ascending aorta, aortic arch, descending thoracic aorta) and etiologies. For the purpose of this thesis TAA indicates an aneurysm of the aortic root or ascending aorta.

Wall shear stress

The frictional force exerted on the vessel wall by the blood flow, and which depends on blood viscosity and flow profile.

SCIENTIFIC AND SOCIETAL IMPACT

‘Impact [*noun*: im-pakt]: the change in the world which results from research’.

Diseases of the aorta, the largest artery of the human body, occur relatively infrequent as compared to other forms of heart and vessel disease. However, the aorta serves a vital function in the human body, rendering any aortic disease to be life-threatening. The death rate of aortic diseases in the Netherlands exceeds 150.000 annually. Two-thirds of all acute aortic syndromes (AAS) occur in patients that are less than 65 years old. Timely recognition of patients at risk is potentially life-saving and, thus, has great socio-economic impact. This thesis focuses on the role of imaging for prediction of AAS, ranging from timing of imaging follow-up to the application of novel anatomic and hemodynamic imaging markers. One of the most important conclusions from our work is that these novel markers can superiorly predict AAS as compared to simply measuring the maximal aortic diameter. Ever since publication, our findings have been validated by other research groups, raising hope that they can improve patient care in the near future. The Dutch Heart Foundation has acknowledged the high potential of advanced imaging by providing funds for the RADAR-study (‘earlier Recognition of Aortic Dissection and Aneurysm Rupture’). In this multi-institutional CVON (Cardiovasculair Onderzoek Nederland)-project, we combine forces with researchers from Leiden University Medical Center (LUMC) and Delft University of Technology (TU Delft) to develop an integrated magnetic resonance (MR) imaging platform that can further improve identification of patients at increased risk. Although the development and clinical evaluation of new imaging methods will take many years, the results from projects like the RADAR-study might revolutionize the future preventive management of aortic disease.

Although advanced imaging techniques enhance the ability to predict and monitor disease, they are a major contributor to health care expenditure. Therefore, they should be used in a cost-effective and expedient way. The results presented in this thesis reveal that a substantial part of currently performed annual routine imaging does not lead to changes in patient management, resulting in an important source of waste. The (cost-)efficacy of aortic imaging is one of the prioritized researched questions in the 2019 knowledge agenda of the Dutch Society of Cardiology (Nederlandse Vereniging voor Cardiologie, NVVC) and will receive further attention in coming years.

The results presented in this thesis are relevant to all patients with aortic disease. Aortic disease can be a worrisome diagnosis, and new follow-up strategies may impact quality of life, stress and anxiety levels. On the other hand, development of more sensitive imaging methods may also be reassuring. Obtaining information about these aspects is crucial for successful implementation of new surveillance approaches. For a better focus on patients’ view, research funders increasingly stimulate involvement of patients with experience of the condition in health care research. In our ongoing projects, we appreciate the valuable input from the ‘Contactgroep Marfan Nederland’, which is the national interest group of patients with Marfan syndrome. Their knowledge and experience has proven complementary to that of our research group and will enhance dissemination of research results in the future.

NEDERLANDSE SAMENVATTING

De grote lichaamsslagader (ook wel aorta) transporteert zuurstofrijk bloed van het hart naar organen, spieren en weefsels. Gezien haar belangrijke functie is een aandoening van de aorta potentieel levensbedreigend. In Nederland zijn naar schatting 200.000 patiënten met een verwijding (aneurysma) van de aorta. Bij ongeveer 87.500 bevindt betreft dit het gedeelte van het bloedvat in de borstholte. Patiënten met een aneurysma hebben een verhoogd risico op het ontwikkelen van een acuut aorta syndroom (AAS; zoals een scheur in de vaatwand). Een complete scheur van de aorta in de borstholte is vaak fataal. Bij een scheur in de binnenste laag van de vaatwand (een zogenaamde dissectie) is een spoedoperatie nodig om het aangedane deel te vervangen. Desondanks heeft ook een dissectie een hoog mortaliteitsrisico (circa 70%). Om het optreden van ruptuur of dissectie te voorkomen wordt een preventieve chirurgische aorta-vervanging verricht bij patiënten met een aorta-diameter ≥ 55 mm. Patiënten met een bijkomende klep- of bindweefselziekte hebben een verhoogd risico op AAS, bij hen is de grenswaarde voor operatie daarom ≥ 50 mm. In dit proefschrift is de voorspellende waarde van diameter-metingen voor het optreden van AAS onderzocht. Tevens is gezocht naar nieuwe anatomische en hemodynamische metingen die het optreden van AAS nauwkeuriger kunnen voorspellen.

In **Hoofdstuk 1** wordt het onderwerp van dit proefschrift geïntroduceerd en worden de doelen van het onderzoek beschreven. **Hoofdstuk 2** is een beschouwing van bestaande wetenschappelijke literatuur, waarin de voorspellende waarde van diameter-metingen nader besproken wordt. In eerdere onderzoeken wordt gesteld dat 97% van alle AAS-patiënten een aortadiameter heeft die kleiner is dan de afkapwaarde voor profylactische chirurgie. Dus, zelfs als deze patiënten adequaat werden opgevolgd, zouden ze niet in aanmerking zijn gekomen voor preventief chirurgisch ingrijpen. Hoofdstuk 2 beschrijft ook de potentieel toegevoegde waarde van nieuwe, veelbelovende beeldvormende technieken (zoals 4D flow MRI en PET-CT) waarmee het in de toekomst wellicht mogelijk wordt om patiënten met verhoogd risico op AAS in een vroeger stadium te herkennen.

Het is tot op heden onduidelijk hoe vaak de aorta-diameter moet worden gemeten bij patiënten met een thoracaal aneurysma van de aorta (TAA). In **Hoofdstuk 3** is dit onderzocht. De belangrijkste conclusies van dit hoofdstuk zijn dat de aorta niet zo snel groeit (gemiddeld slechts 1 mm per 5 jaar), en dat driejaarlijkse follow-up derhalve volstaat voor patiënten met een TAA < 50 mm. Pas indien de diameter tussen 50 en 55 mm is, is jaarlijkse opvolging nodig om tijdige verwijzing voor preventief chirurgisch ingrijpen te garanderen.

Hoofdstukken 4, 5 en 6 bekijken de diagnostische waarde van metingen van aortalengte en -volume. In **hoofdstuk 4** is beschreven hoe de aortalengte met de leeftijd verandert en welke invloeden hierin een rol spelen. Gedurende het leven wordt de aorta ongeveer 25% langer. Hoge bloeddruk versnelt dit verouderingsproces. Op basis van de aortalengte kan 28% van alle dissecties vroegtijdig worden herkend. Deze parameter is daarmee een stuk gevoeliger dan de aortadiameter (4%). De verwachting was dat metingen van aortavolume (zijnde een afspiegeling van zowel diameter als lengte) nog gevoeliger zouden zijn, maar dit bleek niet het geval (sensitiviteit: 20%). Aangezien er geavanceerde beeldvormende (verwerkings-)technieken nodig zijn om de lengte van de aorta te kunnen meten, was dit tot voor kort nog geen klinische routine. Met huidige CT- en MRI-technieken kunnen deze metingen wel routinematig verkregen worden. Op basis van onze bevindingen, en die van andere onderzoekers die soortgelijke resultaten hebben gepubliceerd, is de verwachting dat de aortalengte in de toekomst een belangrijkere rol gaat spelen in de beeldvormende follow-up van TAA-patiënten.

Hoewel de aortalengte in vergelijking met de diameter meer AAS tijdig herkent, is de voorspellende waarde nog niet optimaal. Bijna alle AAS-patiënten hebben hypertensie. Derhalve ontstaat er de laatste jaren steeds meer interesse in beeldvormende technieken die in staat zijn om de hemodynamiek in de aorta af te beelden. Eén van de technieken die het verst is ontwikkeld,

is een 4-dimensionale MRI-scan (zogenaamde 4D flow MRI). Hiermee kunnen anatomische en hemodynamische metingen worden gecombineerd, en kunnen afwijkende bloedstroomprofielen (en de gevolgen hiervan op de vaatwand) in kaart worden gebracht. In **Hoofdstuk 7** hebben we de nauwkeurigheid van deze techniek onderzocht bij patiënten met aortaklepstenose, door de gemeten bloedstroomsnelheden te vergelijken met die van Doppler echo-onderzoek. Uit dit onderzoek blijkt dat de metingen die met 4D flow MRI worden gedaan betrouwbaar zijn, ook bij patiënten met hoge flow-snelheden. In **Hoofdstuk 8** hebben we vervolgens bekeken hoe de bloedstroom bij aneurysma-patiënten verschilt van die van gezonde vrijwilligers. In dit hoofdstuk is met name gekeken naar de wandschuifspanning (de kracht van de wrijving van de bloedstroom langs de vaatwand). Bij gezonde vrijwilligers blijkt deze wall shear stress gelijk verdeeld over de omtrek van de vaatwand. Echter, bij aneurysma-patiënten is deze krachtsverdeling asymmetrisch, met een hoge piek op de wand van de buitenste curvatuur van de aorta. De hypothese is dat deze verhoogde schuifspanning er in de loop van de tijd voor zorgt dat de aorta verder verwijdt (zoals een rivierbedding uitdijt onder invloed van het stromende water). Door patiënten in de komende jaren op te volgen hopen we dit causaal verband in de toekomst te kunnen bevestigen.

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Lieve pap, jij was mijn allereerste proefpersoon voor de 4D flow MRI. De scan verliep toen nog niet zo soepel, met als gevolg dat je twee uur en een kwartier in de scanner hebt gelegen. Er zijn volgens mij ook maar weinig ouders die zichzelf contrastvloeistof laten toedienen voor het promotieonderzoek van hun zoon (dat vond ik overigens wel even spannend...). Het is gelukkig niet voor niks geweest. Heel erg bedankt voor de steun en alle momenten waarop je/jullie in de afgelopen jaren zijn bijgesprongen. Ik vind het erg knap hoe je je nu staande houdt na het overlijden van mama, ondanks dat ik weet dat dat niet altijd meevalt. Weet dat we er graag voor je zijn als het nodig is.

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Allerliefste Marian, eigenlijk is dit voor een belangrijk deel ook jouw proefschrift. We zijn nu meer dan 11 jaar samen en je hebt me altijd gesteund in alles wat ik deed. Je kwam terug vanuit Den Haag voor mijn opleiding, zodat we in Maastricht samen ons leventje konden gaan opbouwen. Ondanks dat jij ook last moet hebben gehad van de stress die mijn onderzoek me soms bezorgde, heb je me altijd aangemoedigd in de keuzes die ik maakte. We hebben de afgelopen jaren hard gewerkt om alle ballen in de lucht te houden, en ondanks dat het soms pittig was is dat heel aardig gelukt. Nu mijn promotie (bijna) is afgerond en de kindjes ouder worden, krijgen we langzaam ook weer wat meer tijd voor ons tweetjes. En daar heb ik ontzettend veel zin in. Ik hou van je!

Er zal tijdens mijn verdediging helaas een stoeltje leeg blijven op de eerste rij van de Mindersbroedersberg. Lieve mama, jouw ziek zijn en overlijden bracht veel verdriet gedurende mijn onderzoeks-jaren. Toch was de laatste tijd samen, waarin we elkaar veel hebben gezien, enorm fijn en waardevol. Ik had je graag nog een keer trots gemaakt. We missen je.

ABOUT THE AUTHOR

Bouke Piet Adriaans was born on December 28th 1986 in Eindhoven, the Netherlands. In 2004, he graduated from secondary school at the Van Maerlant Lyceum in Eindhoven and moved to Maastricht to study Molecular Life Sciences and Health Sciences (Maastricht University, the Netherlands). He followed his medical training at the same institution from 2006 onwards. In the final year of medical school, he participated in a research internship at the department of cardiology under supervision of Dr. S. Schalla. He graduated in 2013 and subsequently started his clinical training in cardiology at the Maastricht University Medical Center+ (supervision: Prof. dr. H.J.G.M. Crijns). In 2016, he was offered a position as PhD-candidate in cardiovascular imaging at the department of radiology and nuclear medicine (supervision: Prof. dr. J.E. Wildberger, Prof. dr. H.J.G.M. Crijns and Dr. S. Schalla). His main research topic was imaging of the aortic valve and thoracic aorta, with focus on prediction of acute aortic syndromes. The results of this research are presented in this thesis. He has resumed his clinical training in 2020 at the VieCuri Medical Center (Venlo, the Netherlands), while holding a part-time research position at the Cardiovascular Research Institute Maastricht (CARIM). He expects to finish his registration as cardiologist mid-2024.

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