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On Pathophysiology and Treatment of Aortic Disease

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Abstract

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Pathophysiological processes underlying abdominal aortic aneurysm (AAA) formation and aortic dissections (AD) are largely unknown. Molecular imaging of the inflammatory component may improve our understanding of AAA and AD pathophysiology. The aims of this thesis were to evaluate the feasibility of positron emission tomography/magnetic resonance imaging (PET/MRI) to study in vivo pathophysiological changes of these aortic pathologies, and to study the outcomes after complex contemporary endovascular treatment thereof.In Paper I, we evaluated the feasibility of 18-F-fluorodeoxyglucose (FDG) PET/MRI to identify markers for inflammation in asymptomatic medium-large AAA. We identified FDG uptake and gadolinium enhancement (GE) in the aneurysmal wall, however FDG uptake corresponded rarely with mural inflammatory changes on MRI. In Paper II, we investigated whether inflammatory activity by means of FDG-PET/MRI can be detected in small to medium sized AAA, confirming the presence of inflammatory markers in the majority of patients. In Paper III, FDG-PET/MRI was used to characterize the inflammation and its transformation from acute to chronic phase in acute Stanford type B dissections. Highly increased FDG-activity was present in the dissected descending aorta in the acute phase, which markedly decreased over the course of a few months. MRI inflammatory changes were present in 60% of patients.In Paper IV, we evaluated the outcome and aortic remodelling after thoracic endovascular aortic repair (TEVAR) for chronic dissections. High rate of false lumen thrombosis occurred for dissections localized to the thoracic aorta covered by the stent-graft, but was more uncommon for extensive dissections distally. Aortic remodelling and sac shrinkage occurred in the thoracic aorta, but not distally. Reintervention rates were substantial (one third of cases). Paper V evaluated outcome of complex endovascular repair of post-dissection aneurysms of the arch and thoraco-abdominal aorta. Results were comparable to other recent reports using this new approach, however occurrence of retrograde Stanford type A dissection following arch fenestrated repair warrants caution.In conclusion, FDG-PET/MRI is a promising technique for studying inflammation in AAAs and ADs in vivo. For chronic aortic dissections, endovascular treatment results in good short-term outcome, but in the long-term re-interventions were common and adequate follow-up is thus of importance

Keywords: Abdominal aortic aneurysm, aortic dissection, fenestrated branched stent grafts, PET, molecular imaging, inflammation

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Kuzniar, M., Tegler G., Wanhainen A., Ahlström H., Mani K., Hansen T. (2020) Feasibility of Assessing Inflammation in Asymptomatic Aortic Aneurysms with Integrated 18F-Fluorodeoxyglucose Positron Emission Tomography/Magnetic Resonance Imaging. *Eur J Endovasc Surg*, 59:464-471

II Kuzniar, M., Tegler G., Wanhainen A., Hansen T., Mani K. Assessing Inflammation in Small to Medium sized Asymptomatic Abdominal Aortic Aneurysms with Integrated 18F-Fluorodeoxyglucose Positron Emission Tomography/Magnetic Resonance Imaging, Manuscript

III Kuzniar, M., Tegler G., Wanhainen A., Hansen T., Mani K. Longitudinal assessment of inflammatory activity in type B aortic dissection with integrated FDG-PET/MR imaging, Manuscript

IV Hellgren T., Kuzniar M., Wanhainen A., Steuer J., Mani K. (2021) Clinical and morphological outcome of endovascular repair for chronic type B aortic dissection. *Ann Vasc Surg*, 72:390-399

V Kuzniar M., Wanhainen A., Tegler G., Mani K. (2021) Endovascular treatment of chronic aortic dissection with fenestrated and branched stent grafts. *J Vasc Surg*, 73:1573-1582

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Contents

Abbreviations

AAA	Abdominal aortic aneurysm
AD	Aortic dissection
ATBAD	Acute type B aortic dissection
B-EVAR	Branched endovascular aortic repair
CD4+	Cluster differentiated 4 +
CE	Contrast enhancement
CT	Computer tomography
DBIIIA	DeBakey type IIIA aortic dissection
DBIIIB	DeBakey type IIIB aortic dissection
DWI	Diffusion weighted image
ECM	Extracellular matrix
ESVS	European society of vascular surgery
EVAR	Endo vascular aortic repair
F-EVAR	Fenestrated endovascular aortic repair
GE	Gadolinium enhancement
^{18}F-FDG	18-F-fluorodeoxyglucose
F/B-EVAR	Fenestrated and branched endovascular aortic repair
ILT	Intraluminal thrombus
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
LGE	Late gadolinium enhancement
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PD-TAAA	Post-dissection thoraco abdominal aortic aneurysm
RTAD	Retrograde type A dissection
TAA	Thoraco-abdominal aorta
TAAA	Thoraco-abdominal aortic aneurysm
TBR	Target to background ratio
TBAD	Type B aortic dissection
TEVAR	Thoracic endo vascular aortic repair
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor-α
TIMP	Tissue inhibitors of metalloproteinase
VEGF	Vascular endothelial growth factor
vSMC	Vascular smooth muscle cells

Introduction

Abdominal aortic aneurysm

Epidemiology and definitions

The word "Aneurysm" derives from the Greek word ἀνεύρυσμα, meaning widening or dilatation of an artery. In 1975 MacGregor suggested defining abdominal aortic aneurysm (AAA) as infrarenal aortic diameter being greater than 30 mm, which is still the most widespread definition used to this day.[1] However, the normal infrarenal aortic diameter varies with gender, age, bodyweight[2] as well as imaging modality.[3] To compensate for these variations, an alternative definition has been adopted that the infrarenal diameter should be 1.5 times larger than the expected normal diameter. [1, 4] Contemporary screening studies have shown that the prevalence in 65year old men is 2.2% in Sweden, and 3.3% among men 65-74 years in Denmark.[5, 6] The prevalence in women is fourfold lower with AAA prevalence rates in women over 60 years being 0.7%.[7, 8]

The natural course of most abdominal aortic aneurysms (AAA) is to gradually expand and in some cases eventually rupture. In 1955, Crane introduced the aneurysm diameter measurement as a potential tool to predict aneurysm rupture and to select patients for prophylactic repair.[9] To this day the AAA diameter remains the most widely used marker of disease progression and rupture risk.[3] Currently ESVS 2019 guidelines for management of AAA in men are: aneurysms <55 mm should be managed conservatively and aneurysms >55 mm should be considered for elective repair.[1] Randomized trials have disproven the potential benefits of earlier intervention, for either endovascular or open repair, in aneurysm sizes <55 mm.[10] Women, however, have a four times higher rupture risk of small AAA and so repair in women may be considered for aneurysms at lower threshold diameter of >50 mm.[1, 11]

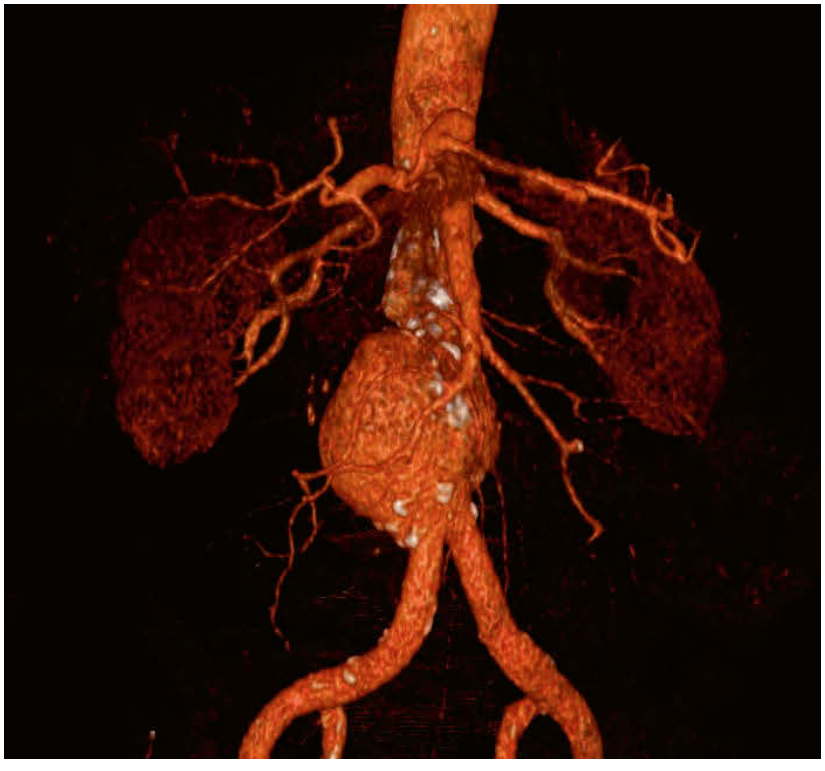

Figure 1 3D image illustrating infrarenal abdominal aortic aneurysm (AAA) 57 mm in diameter

Aetiology and pathophysiology

AAAs were traditionally considered to be a consequence of atherosclerotic disease, indeed they share a similar risk factor profile with atherosclerosis (such as smoking, high cholesterol, old age, male gender, and hypertension). But the histological characteristics differ, with extracellular matrix degradation and chronic inflammation being mainly AAA specific characteristics. On molecular level, protease inhibitors such as tissue inhibitors of metalloproteinase (TIMPs) and plasminogen activator inhibitor-1 are less expressed in AAAs than in atherosclerotic disease.[12, 13] A recent study identified thousands of differentially expressed genes in AAAs and atherosclerosis compared to controls (840, 1,014 and 1765 differentially expressed genes in small, large aneurysms and atherosclerosis, respectively).[14] Furthermore, not all patients with atherosclerosis develop AAA. Current understanding is that AAA is a complicated multifaceted process with an unknown aetiology, separated but possibly related to atherosclerosis. Generally, on histology, aneurysm expansion is characterized by degradation of extracellular matrix (ECM), increased turnover of collagen in the aortic wall, neovascularization, medial and adventitial inflammation, and smooth muscle cell apoptosis[15]

ECM degradation mechanisms are decreased concentration of elastin in the aneurysmal wall. [16, 17] As the pathogenetic process progresses, the elastin degradation is coupled with the decrease in collagen content, which is thought to be the ultimate cause of rupture.[18, 19] Elastin and collagen are degraded mostly by matrix metalloproteinases (MMPs), which are proteolytic enzymes. MMPS are found to be overexpressed in the AAA wall.[20] There are 23 types of human MMPs and numerous have been reported as important in AAAs: MMP-1,-2,-3,-8,-9,-10,-12, and -13.[21] In particular MMP-2 and MMP-9 appear to work in concert and play an important role in AAA formation.[22] In AAAs the protein amount, as well as the proteolytic activity, of both MMP-2 and MMP-9 are several folds higher than in normal or atherosclerotic aortic tissue.[23, 24] MMP-9 activity has also been associated with rupture as very high MMP-9 levels have been detected at sites of AAA rupture, causing focal aortic wall weakening, suggesting local "hot spots" of MMP hyperactivity. [13] In another study, MMP-9 serum levels were 6 fold increased in ruptured AAA compared to non-ruptured AAA.[25] In addition, MMPs regulate the ECM by releasing cryptic fragments and exposing neoepitopes. [26]

The matrix-degrading properties of MMPs are balanced by the presence of inhibitors, such as TIMPs. AAA elevated expression of MMPs is counterbalanced by increased TIMPs production but the balance between MMPs and TIMPs seems to be in favor of MMPs. [13] Allaire et al. demonstrated that local inhibition of MMPs activity by TIMP-1 had the potential to inhibit aneurysm rupture.[27]

Vascular smooth muscle cells (vSMCs), found predominantly in aortic medial layer, have important functions in AAA formation such as ECM regeneration and degradation, contractility, proliferation, apoptosis. Interestingly, vSMCs are plastic and have the capability to switch phenotype from contractile to synthetic. In pathology such as AAA, vSCMs switch to a synthetic phenotype under the induction of transforming growth factor beta (TGF-β): the cells have lower levels of contractile proteins but higher levels of molecules providing a macrophage-like synthetic phenotype with increased proteolytic enzyme production contributing to further degradation of the aneurysm wall.[28-30] *In vitro*, Bogunovic *et al.* could show a loss of contractility in vSMCs derived from sporadic AAA patients biopsies.[31] Furthermore, in AAA, the vSMCs are depleted through apoptosis causing a reduction in ECM regeneration capacity[32, 33].[32, 33]

Genetic and epigenetic components are also important in AAA formation. Some mutations impair the vSCM contractile apparatus, TGF-β signaling pathway, as well as the ECM. To study *in vitro* how these genetic alterations affect the vSMCs functionality and their interaction with ECM, Yeung *et al.* generated vSCMs by trans-differentiation from human dermal fibroblasts using TGF-β.[30, 34] Thus, Burger *et al.* showed that genes encoding for the contractile function (ACTA2, MYH11), the TGF-β signaling (SMAD3) and the ECM elastic laminae (FBN1) impaired migration velocity and contractility

(ACTA2), and trans-differentiation efficacy (SMAD3 and FBN1).[34] There is also strong evidence that constitutional genetic factors are involved in AAA formation. A large Swedish twin study by Wahlgren *et al.* showed that monozygotic twin has a 24% probability of having an aneurysm if the other twin also has aneurysmal disease, but this probability diminishes to 4.8% in cases of dizygotic twins.[35]

The inflammatory cells migrate into the AAA wall from peripheral blood. A pro-inflammatory state is induced where T-lymphocytes and macrophages are the most prominent cells.[36] They release pro-inflammatory cytokines (monocyte chemoattractant protein-1, interleukin-1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α), etc) that further activate MMPs and contribute to affect vSMC functions.[13, 28] The majority of lymphocytes present in AAAs are CD4+ T cells which produce a specific proinflammatory cytokine interleukin-17, an established mediator of experimental AAA formation.[37]

Neovascularization is another characteristic of AAAs which facilitates and increases the influx of these inflammatory cells into the AAA wall.[38] Aneurysmal formation is accompanied by the expression of vascular endothelial growth factor (VEGF) that mediates neo-vascularization.[39] Hypoxia is hypothesized by some as being a possible driver for this angiogenetic process. Intraluminal thrombus (ILT) may act as a barrier for oxygen transport, leading to hypoxia of the aneurysmal wall, which in turn leads to neovascularization, permitting oxygen influx to the hypoxic regions, and compensatory increase of inflammatory cells with subsequent release of proteolytic enzymes. [13, 40] The extent of angiogenesis correlate with level of inflammation in the AAA wall.[41]

Several investigators have also studied inflammatory biomarkers in peripheral blood of patients with AAA where elevated plasma concentration of macrophages induced the production of cytokines such as IL-1β, IL-6, TNF-α, and interferon gamma.[42] Furthermore, high sensitive CRP has been found elevated in the blood of patients with large aneurysms.[43]

Several microorganisms have been hypothesized to trigger AAA development, including Borrelia burgdorferi and Mycoplasma pneumoniae.[44]

Aortic dissections

Epidemiology, definitions and Thoracic Endovascular Aortic Repair (TEVAR)

Reports suggest that aortic dissection, described first in 1761 by Morgagni, is relatively common acute aortic event that ranges from 3.5-12 cases per 100 000 inhabitants per year.[45-49] An aortic dissection is a result of an acute severe injury to the most inner layer of the aortic wall, the intima, allowing blood to propagate within the diseased medial layer, dividing the aortic wall into a true and false lumen. The site of intimal tear is often associated with inflammatory activity and underlying degeneration of the medial wall layer.[50] Typical clinical symptoms are acute onset of sharp, often migrating, back or chest pain, but other diverse clinical manifestations (stroke, syncope, extremity, or coronary ischemia) are not uncommon, which may result in as many as 60% of patients not being recognized clinically and only first identified at autopsy.[51] Furthermore, up to 7% may even be clinically silent.[51] Risk factors are medical conditions that either increase mechanical shear stress or degeneration of the aortic wall , including hypertension, present in up to 80% of patients, old age, bicuspid aortic valve, aortitis, aortic aneurysm, and connective tissue disease (such as Marfan syndrome and Loeys-Dietz syndrome)[52, 53]. Females patients are generally older at presentation and have higher mortality and worse surgical outcome compared to men.[52]

The most commonly used classifications for aortic dissections are the DeBakey system, proposed first in 1965, and the Stanford classification, proposed in 1970.[54, 55] The DeBakey system take into consideration the origin of the primary entry tear as well as the extent of involvement of the disease:

Type I: Entry tear originates in ascending aorta with the dissection extending distally to the aortic arch involving descending aorta
Type II: Entry tear originates in and the dissection is localized only in ascending aorta
Type IIIA: Entry tear originates in and limited to descending aorta
Type IIIB: Entry tear originates in descending aorta with the dissection extending distally to the diaphragm also involving the abdominal aorta.

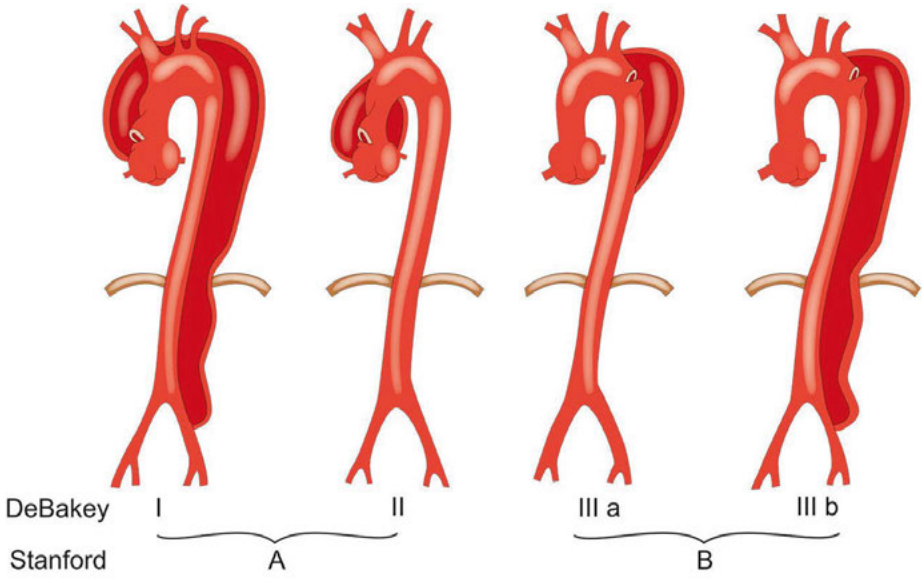

Figure 2 DeBakey and Stanford classification of aortic dissections

(Courtesy of Mats-Ola Eriksson)

Stanford classification has two subgroups, based on the involvement of the disease, type A involves the ascending aorta whilst type B does not involve the ascending aorta. Lombardi et al. proposed in 2020 a new aortic dissection classification, that is better adapted to the increasing modern endovascular treatment, as it involves entry tears in the aortic arch, and in more detail describes the direction (antegrade, retrograde) and extent of the dissection.[56]

Stanford type A dissections require immediate open surgical repair due to greatly increased risk for aortic rupture and cardiac tamponade. Medical therapy, with anti-hypertensive agents (primarily beta blockers), is recommended as the first line treatment for un-complicated type B dissections whereas complicated type B dissections are recommended to undergo surgical repair, primarily with Thoracic Endovascular Aortic Repair (TEVAR). Early complications requiring endovascular repair may include aortic rupture, mal-perfusion of organs, refractory arterial hypertension, refractory pain and rapid false lumen expansion. Approximately 75% of all acute type B dissections (TBAD) are deemed as uncomplicated at presentation and are thus primarily treated with best medical therapy.[57] Serial imaging is needed to monitor potential complications and to identify patients that might require surgical repair during follow-up. Contrast-enhanced computer tomography (CT) is often the modality of choice in the acute setting due to its rapid acquisition time and excellent availability, with specificity and sensitivity approaching 100%.[53] Magnetic resonance imaging (MRI) has similar diagnostic capability and does not require ionizing radiation, and might be more appropriate as follow-up imaging

of young patients with increased radiation burden from repeated scanning. Multiple studies have shown favourable two years survival with medical therapy alone for uncomplicated TBAD, ranging from 80-90% [57-59] However, the principal late complication of aortic dissection, aneurysmal degeneration of the outer wall of the false lumen, usually develops beyond 2 years, with 20-40% of patients experiencing aneurysmal rupture or progression requiring surgical intervention. [57, 58, 60].

TEVAR was first introduced in Ukraine by Volodos et al in 1987 to treat a post-traumatic injury of the thoracic aorta, and has revolutionized the management of thoracic aortic diseases.[53, 61] In setting of aortic dissections, the primary aim of TEVAR is to cover the entry tear in order to reduce flow and achieve thrombosis of the false lumen, to reduce aneurysm sac diameter and risk of rupture, and to induce aortic-remodelling defined as endo-graft stimulated true lumen diameter expansion and false lumen regression. Achieving aortic remodelling is important as it has been associated with better survival.[62] In acute complicated type B dissections, TEVAR has proven to be a valuable alternative to open surgery, with studies showing promising outcomes.[63] Additionally, in subacute uncomplicated type B dissections, the effect of TEVAR in addition to best medical therapy was studied in a randomized trial, showing that TEVAR resulted in reduction in maximal aortic diameter and reduced aorta related mortality at 5 years. [64] However, in chronic complicated type B dissections the role of TEVAR is still debated, and given the decreased plasticity of the dissection membrane in this chronic setting, the ability of the stent-graft to induce false lumen thrombosis and promote aortic remodelling is uncertain.[65]

Figure 3 Thoracic Endovascular Aortic Repair (TEVAR) for chronic dissection with fenestration for left carotid artery. False lumen is patent distal to stent graft.

Aetiology and pathophysiology

The pathophysiological process before and after the onset of aortic dissection is not fully understood. Elastin is an important connective tissue component of the aortic wall, enabling the aorta to stretch and contract during cardiac cycle. Histopathological studies, from autopsy specimens from patients with aortic dissections, show extensive inflammatory cell infiltration and medial aortic wall degeneration, in particular cystic medial necrosis and elastin fragmentation.[66] Normal ageing of the aorta is also associated with increased elastin dysfunction. Cross-links between elastic fibers are vanishing with age, creating space between elastic fibers which is instead filled with proteoglycans, resulting in stiffening of the aorta.[67] Apart from age, other medical conditions that further aggravate the medial degeneration of the aorta and elevate the risk for aortic dissection include hypertension, connective tissue disease, aortic aneurysm, and bicuspid aortic valve. Hypertension, one of the main risk factors, is present in up to 80% in patients with AD, and is proven to reduce blood flow in vasa vasorum causing ischemia in the outer third of the aortic wall, which is often the propagation site of the dissection.[68] This hypoxia in the aortic wall is believed to be the trigger of the evidenced extensive infiltration of inflammatory cells, mostly macrophages, into the medial layer of aortic wall.[69] Macrophages in turn, release pro-inflammatory interleukins, promote

VEGF promoted neovascularization, and produce MMPs, in particular MMP-1-9 and-12, which accelerate the degradation of the extracellular matrix, potentially leading to AD.[50]

Post-dissection aneurysms and fenestrated/branched endovascular aortic repair (F/B-EVAR)

Some 20-50% of patients will develop late complications, most commonly aneurysmal degeneration of the aortic wall, following acute aortic dissection.[58, 70, 71] Patients with chronic type B dissections experience distal aortic growth or aneurysm formation in 73% when on medical therapy and 63% after TEVAR.[57] These reports imply that aneurysm development in a chronic dissection setting should be considered more as rule than an exception. Some investigators have calculated the rupture risk of these post dissection aneurysms to be to be as high as 30% per year, if the aortic diameter exceeds 60 mm.[72] European Society guidelines recommend that 60 mm should be the threshold for repair, but that patient with aortic diameter 56–59 mm can also be considered for repair.[53] Post-dissection aneurysms have traditionally been treated with open or hybrid surgery of the arch or thoracoabdominal aorta. However, this is a major undertaking and requires sternotomy and circulatory arrest with extracorporeal circulation for arch repair, or thoraco-laparotomy and left heart bypass for thoraco-abdominal repair. In efforts to reduce the surgical trauma to the patient and improve mortality and morbidity, that still remain high after open repair or hybrid repair, total endovascular approach, with fenestrated and branched endovascular aortic repair (F/B-EVAR), has been evolving as a possible option.[73-75] Early favourable outcomes have been reported, however, constricted to small series and limited to a few numbers of high volume centres.[75, 76]

There are additional technical challenges involved when treating dissecting aneurysms with fenestrated/branched endo-grafts: narrow true lumen creating problems in graft design and implantation, with limited space for catheter manipulation and expansion of branches; distal sealing zones may include dissected visceral aortic branches and/or iliac arteries creating difficulty in achieving complete aneurysm seal; aortic branches may not originate from the same lumen impeding the cannulation of target vessels.[77] Considering that fenestrated and branched endovascular repair in setting of chronic dissection is a relatively new approach, bearing in mind the aforementioned technical challenges, it is important to evaluate the outcomes and safety of such treatment.

Endoleakage following F/B-EVAR

Endoleaks remain an inherent challenge with the endovascular technique and are responsible for most of the reinterventions following fenestrated and branched endovascular aortic repair regarding both atherosclerotic aneurysms and post dissection aneurysms. Please see figure 2 below for classification of endoleaks after F/B-EVAR as proposed by Oderich et al. [78]

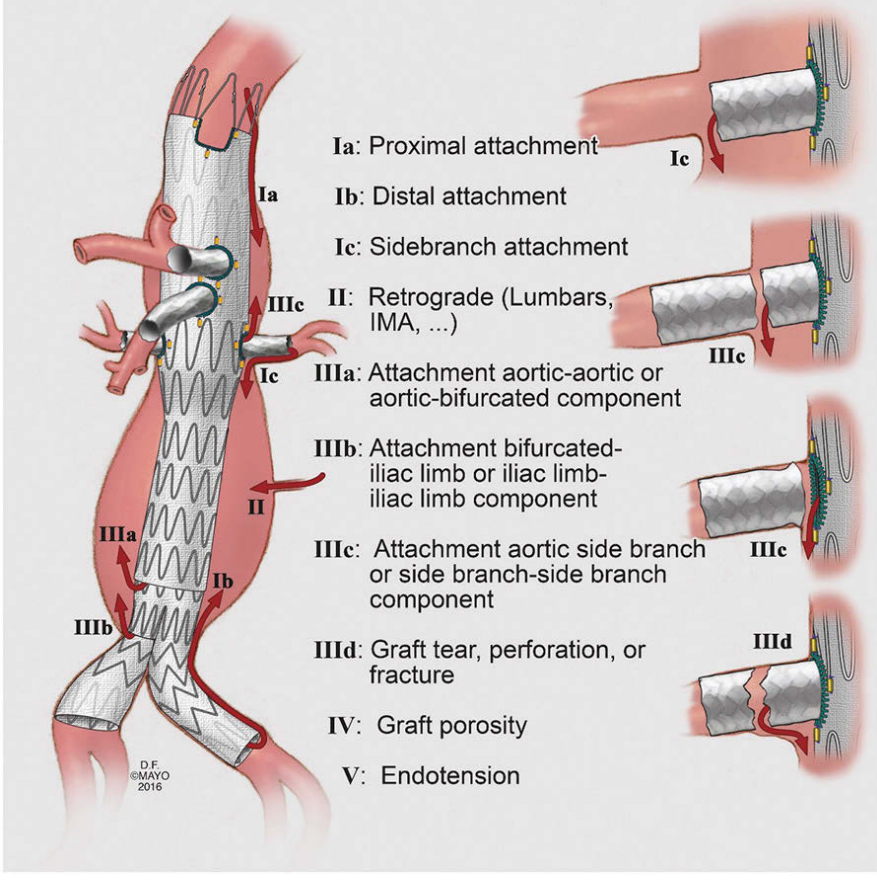

Figure 4 Target vessel endoleak classification following fenestrated endovascular repair as proposed by Oderich et al. (Reproduced by permission of Journal Vascular Surgery, and Mayo Foundation for Medical Education and Research)

Molecular imaging

PET – Positron Emission Tomography

PET is a molecular imaging technique that detects photons, which are emitted by an organ after administration of a tracer linked to a positron emitting radioactive isotope. When this isotope decays, it emits a positron that subsequently collides with an electron, and annihilates into two photons striking opposing detectors which are composed of photomultiplier tubes. [79] The interaction between photons and crystals turns into an electronic signal.

This PET signal can be fused, with either a computer tomography (CT) or magnetic resonance imaging (MRI), for anatomical and diagnostic accuracy.

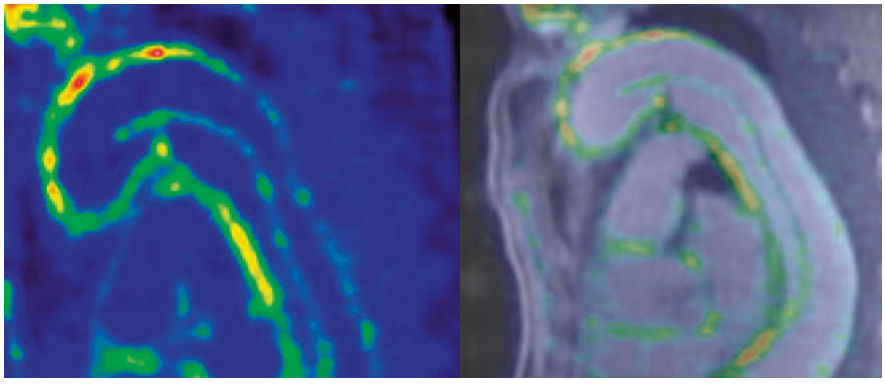

Figure 5 PET image (left panel) fused with contrast enhanced MRI (right panel) in acute type B aortic dissection showing increased PET signal in the arch and dissected descending aorta

^{18}[F]-FDG - 18-F-fluorodeoxyglucose

Pacák et al first prepared ^{18}F-FDG in late 1960s, and it was investigated as a tumour seeking tracer in the early 1980s.[80, 81]

Today the majority of PET imaging in clinical medicine and research is performed using 18-F-fluorodeoxyglucose (FDG), which reflects glucose uptake and metabolism resulting from increased cellular activity.

FDG is a glucose analogue, transported into cells using glucose transporters (GLUT). Once inside the cells, FDG is phosphorylated to FDG-6-phosphate and cannot be metabolized further in the glycolytic pathway, and so it is trapped and accumulates intracellularly.

Elevated rates of glycolysis and increased glucose transport reflecting the increased metabolic demand for glucose, are recognized features in many types of tumor cells explaining the enhanced FDG uptake in cancer. However, increased FDG uptake is not only limited to neoplastic lesions. The same principles of increased glucose transport and metabolism also apply to

inflammatory cells.[82] The increased FDG uptake by inflammatory cells has been confirmed by experimental studies, for instance Zhao et al established a strong correlation between arterial FDG uptake and macrophage content.[83] In clinical medicine 18F-FDG PET is currently used to detect inflammation in vascular disease such as arteritis[84], inflammatory and mycotic AAA[85-87], as well as with instable atherosclerotic plaque[88]. F-FDG PET can reliably detect inflammatory activity in atherosclerosis[89] and reports show correlation between aortic FDG uptake and degree of inflammation on histology[90].

Standard uptake values (SUV) are used to determine the FDG activity in PET imaging, and are derived according to the formula: SUV = [measured radioactivity concentration(kBq/ml)]/[decay corrected injection dose (kBq)/patient's weight (g)] , thus taking into account decay time, administered dose and body weight. To correct for remaining FDG in blood, the target-to-background ratio (TBR) can also be calculated by dividing the SUV value by left over blood-pool SUV.

It is difficult to evaluate arterial FDG uptake, some investigators use only visual assessment of the arterial wall for presence of FDG hotspot areas, others rely on SUV thresholds, whilst some assess target to background ratios (TBR) values.[89, 91] It is challenging to define specific SUV thresholds indicating inflammation in the arterial wall, as there is no accepted standard for arterial inflammation[92].

MRI – magnetic resonance imaging

Magnetic resonance imaging (MRI) is particularly suited for molecular imaging purposes as it provides superior morphological information and uses inherent parameters that reflect the cellular structure and activity of the tissues being imaged.

MRI is based on the basic principle of nuclear magnetic resonance described in the 1940. This principle is based on the interaction between the atomic nuclei, radiofrequency energy (RF) and a magnetic field. Hydrogen nuclei has a positively charged proton rotating around its axis which in turn induces a magnetic field making the protons behave like a small bar magnet, with a north and south pole. Fortunately, for imaging purposes, we have a lot of hydrogen atoms in our body: water 60% and fat 30%. When placed under a strong magnet, such as MRI, all the proton axes line up with the magnetic field creating a net magnetic vector pointing with the MRI magnetic field. When a radiofrequency pulse (RF) is added (same frequency as the precession of hydrogen protons calculated by the Larmor equation), it causes the protons to resonate and the magnetic field is deflected to transverse orientation (90 degrees to the MRI magnetic field). When the RF signal is switched off the protons “relax” to their previous state. Two kinds of relaxations occur: spin-lattice relaxation (T1) is the regrowth of the longitudinal magnetization and

spin-spin relaxation (T2) is the loss of transverse magnetization. These relaxation times are tissue dependent (different for water and fat), thus generating tissue specific signals which are detected by the receiver coils in the MRI scanner. By varying the RF sequences parameters, using echo time (TE) and repetition time (TR), images can be produced that accentuate the differences more in either T1 or T2. In T1 weighted image (T1w) the signal is predominantly decided by the T1 properties of tissues, for instance long T1 times (water) appear darker and short T1 times (fat) appear brighter. In T2 weighted images (T2w) the signal depends predominantly on T2 properties, long T2 times (water) appear bright and short T2 times (fat) appear dark.

Contrast enhanced (CE) MRI, for instance with Gadolinium which is the most frequent used contrast agent in clinical use, can enhance signal intensity by shortening T1 relaxation time. This is particularly useful when identifying the arterial wall. In arterial inflammation the accumulation of gadolinium agents is believed to be caused by increased wash-in, leakage of gadolinium from neo-vessels and increased endothelial permeability, and increased extracellular space (increased distribution volume).[93] Gadolinium is known to accumulate in inflammatory tissues several minutes after its venous injection and can visualize neovascularization and inflammatory cells within vulnerable plaques[94, 95]. In vasculitis disease morphological changes such as vessel wall oedema, gadolinium enhancement and/or wall thickening are typical imaging findings on (CE)-MRI of active disease in Takayasu´s arteritis and giant cell arthritis[96-98] These aortic mural changes decrease under corticosteroid treatment[99].

MRI can also be used for in vivo detection of oedema in tissues. Increased water content in tissues leads to longer T2 relaxation time resulting in strong signal intensity of oedematous tissue on T2 weighted images. This technique has been used to assess oedema in myocardium, coronary and carotid arteries and in vasculitis.[97, 100, 101]

Diffusion weighted imaging (DWI) is another functional parameter used in MRI that detects the movement (diffusion) and accumulation of water molecules in tissues. Water molecules diffuse freely in extracellular space but their movement or diffusion is restricted when inside the cell. For instance, in malignancies or ischemic brain tissue, water molecules accumulate intracellularly (K-Na^+ cell-membrane pump shuts down causing Na^+ to accumulate in the cell which leads to osmoses of water molecules) after which diffusion is limited, thus producing an intense signal on DWI-MR images, indicative of oedema.

PET/MRI vs PET/CT

The concept of integrated PET/MRI introduces several advantages as compared with PET/CT including superior morphological characteristics due to MR, a good spatial match between the PET and MR images and increased discrimination of the FDG uptake in the aortic wall from uptake in a thrombus or peri-aortic tissue such as lymph nodes.[102] The aortic wall is not clearly defined on CT but can be visualized and assessed for thickness on MRI.

In addition, functional parameters from diffusion weighted imaging (DWI) and contrast enhanced MR (as described above), both relevant as biomarkers for inflammation, can be acquired.

PET/MRI is equipped with new generation PET digital detectors with improved spatial resolution and has more advanced reconstruction algorithms.

In addition, MRI could avoid the ionizing radiation of CT and yield lower patient radiation exposure with PET/MRI than with PET/CT. This is particularly important in pediatric patients and patients of young age requiring repeated scanning. On the other hand, PET/MRI has longer acquisition times, limited field of view, and costs more.

Figure 6 Integrated positron emission tomography (PET) magnetic resonance imaging (MRI) scanner installed in Uppsala University Hospital in 2014

Rationale behind molecular imaging of AAAs and ADs

Molecular imaging of AAA and AD offers a possibility to assess the pathologic processes occurring in the aortic wall during aneurysm formation. As previously mentioned, there are still gaps in our knowledge regarding what triggers aortic wall degradation, and why some patients progress to symptomatic or ruptured aneurysms while others don't. It has been established that even small aneurysms (<55mm) rupture[103, 104] and so there are concerns about making the AAA diameter alone the marker in risk stratification. Furthermore, some large aneurysms may grow to a substantial size without rupture[105]. Introduction of screening programs, along with the use of abdominal imaging for other problems, have led to an increase in identification of patients with small AAA. Currently, all patients with screening detected AAA undergo regular ultrasound surveillance which is decided based on the aneurysm size; there is no medical intervention at hand to decrease the risk of aneurysm growth to offer these individuals. Despite close follow-up imaging of medically treated aortic dissection survivals to detect complications, the death rate remains high, approximately 40% at 10 years.[70] There is a clear need for better individual risk stratification, in order to tailor follow-up, reduce the number of unnecessary repairs and to decrease the number of unanticipated ruptures. Functional imaging could provide in vivo data on aortic pathologies, potentially differentiating aneurysms or dissections with pathological properties that indicate more aggressive disease. Furthermore, functional imaging could potentially be used to monitor the response to medical interventions aiming to modify aneurysm growth.

Aims of the thesis

The overall aim of this thesis was to study pathophysiology of asymptomatic AAA by means of molecular imaging as well as to evaluate outcomes after endovascular treatment of chronic aortic dissections.

1. To evaluate the feasibility of PET/MRI to identify markers of inflammation in medium to large asymptomatic AAAs.

2. To evaluate the ability of PET/MRI to identify markers of inflammation in small to medium sized AAAs.

3. To longitudinally evaluate inflammatory activity in acute type B dissections (ATBAD) with PET/MRI.

4. To evaluate long-term remodelling, survival and reintervention outcomes after TEVAR for chronic type B dissections (CBAD).

5. To evaluate early and mid- term outcomes after total endovascular repair of post dissection aortic aneurysms.

Patients and methods

Paper I, II and III

Patients

For Paper I and II, patients with asymptomatic AAA were identified from the routine AAA surveillance database at Uppsala University Hospital and were prospectively invited to participate. Patients with medium to large aneurysms (AAA>45mm) on duplex ultrasound and a mean aneurysm growth rate of >2mm/year were included in Paper I and patients with small to medium sized AAAs (<45mm)) were included in Paper II.

In Paper III, patients with acute type B dissections referred to Uppsala University Hospital between 2017 and 2021 were longitudinally included. At the time of inclusion, patients in Paper III were considered to have uncomplicated dissections primarily intended for medical management.
Exclusion criterias were diabetes (insulin dependent), renal impairment (glomerular filtration rate <45ml/min), claustrophobia, and mechanical or electronic implants (pacemaker) not compatible with MRI.

Methods

In Paper I and II patients underwent a single PET/MRI examination, however, in Paper III patients underwent PET/MRI examination in different phases of the dissection, within 2 weeks of index event (acute phase), 2-4 months (subacute phase), 9-12 months (early chronic phase) and 21-24 months (late chronic phase).

Quantification of FDG uptake was performed by drawing Region of interest (ROI) around the aortic wall on all trans-axial slice images. Maximum and mean standardized uptake values (SUV) of aortic wall were calculated for each axial slice and the values were then added and divided by the total amount of axial slices thus obtaining the averaged SUV maximum and SUV mean for the entire aortic wall. To correct for remaining circulating FDG in blood, target to background ratio (TBR) was calculated by dividing the SUV values by averaged venous blood SUV (obtained from averaged SUV from 6 ROIs in inferior vena cava). See figure 6 for an example of ROI placement around the aneurysm wall.

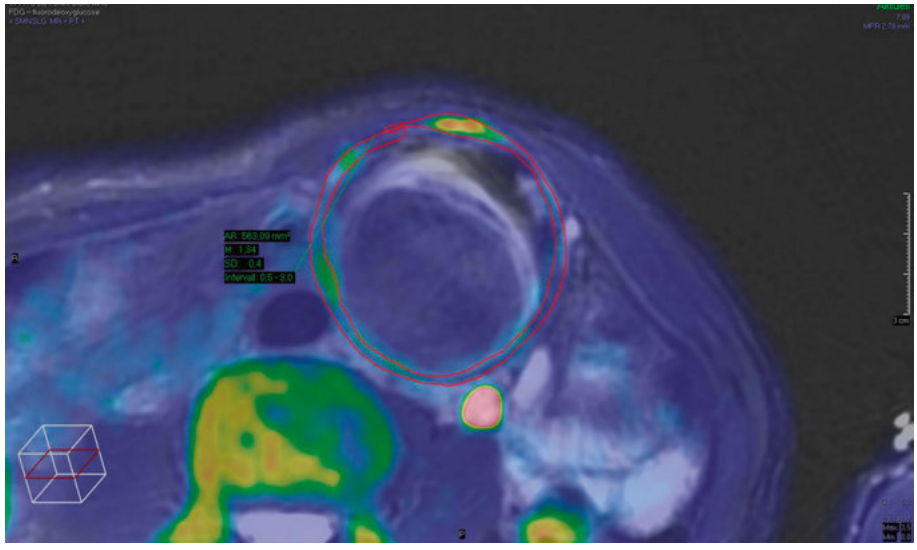

Figure 7 Region of interest (ROI) drawn around aneurysmal wall on volume matched T2 weighted MRI and PET image when calculating standard uptake values (SUV)

In Paper I and II, evaluation of FDG uptake, according to methodology described above, was performed in aneurysmal aorta and in the non-aneurysmal adjacent segments; aortic neck and supra-renal aorta. In Paper III, evaluation of FDG uptake was performed at each time point, and in three segments of aorta; ascending aorta, aortic arch, and dissected descending aorta.

Metabolic activity in each aortic segments was analyzed and compared to each other and in Paper III, between each time point, to evaluate the transformation of inflammation overtime in acute type B dissections.

In Paper I and II regions of increased focal FDG uptake ("hot spots") in the aneurysm wall were counted for each patient and quantified. For Paper I correlations between MRI and PET signal were investigated: at the position of each FDG hotspot, MRI images were examined for presence of corresponding focal inflammatory aneurysmal wall changes (contrast enhancement, wall thickening and oedema). Contrast enhanced (CE) MRI images (6 min post contrast trans-axial T1w images) were visually investigated for overall presence of gadolinium enhancement in the aneurysm wall (Paper I and II) and in the dissected descending aorta (Paper III) as suggested marker of inflammatory activity. For Paper I, we analyzed the relationship between PET/MRI inflammatory markers, intra-luminal thrombus and recent AAA growth and in Paper III we investigated the relationship between PET/MRI findings and false lumen status and clinical outcome.

PET/MRI protocol used in Paper I, II and III

Patients were examined with a Signa PET MR (GE, Healthcare,Waukeesha,WI, USA) unit equipped with digital PET detectors. 18-F FDG was used as PET tracer, 6 MBq/kg body weight, administered intravenous 3 hours before PET acquisition of a single bed position with a transaxial field of view (FOV) of 40 cm during 25 minutes. Patients fasted over-night and had a normal glucose blood level. The PET data were reconstructed with VUE Point FX-S using 28 subsets, four iterations, 192x192 pixel matrix, and a 3 mm sharpness filter. The vendor two-point Dixon approach was used for attenuation correction. MRI sequences were acquired as follows:

- Transversal T2 weighted (w) fatsat (FS) propeller with respiratory triggering (slice thickness 6 mm, field of view (FOV) 38 cm)
- Transversal diffusion weighted images (DWI) with b-value 0, 50, 200, 500 and 800.
- Transversal LAVA-Flex breath hold with water and fat (scan duration 18s, matrix 224x200, FOV 40cm)
- Contrast enhanced sequence LAVA FS pre-contrast and 1, 3 and 6 min after gadolinium contrast agent intravenous injection. (scan duration 18 s, matrix 256 x180, FOV 40 cm, slice thickness 4 mm). Gadolinium contrast agent (Dotarem) was given with a dose of 0.2ml/kg and a flow rate of 2 ml/s.

Paper IV and V

Patients

All patients treated for chronic aortic dissections (Stanford type B or residual dissection after type A repair >14 days from index event), including reoperations, from 1999-2019 from a single-centre, Uppsala University Hospital. Patients treated with thoracic endovascular aortic repair (TEVAR) were included in Paper IV and patients that underwent either fenestrated/branched endovascular aortic repair (F/B-EVAR) of the arch, or of thoracoabdominal aorta (TAA), or a combination of F/B-EVAR in both arch and thoracoabdominal aorta, were included in Paper V. Patients were identified through prospective local hospital registries and Swedish National Vascular Registry (Swedvasc).

Indications for surgical treatment at the study centre were aneurysmal degeneration, aortic rupture, treatment-refractory pain, and mal perfusion of visceral organs and/or limb. Patients treated with thoraco-abdominal hybrid

procedures (open surgical visceral artery debranching followed by TEVAR) were excluded.

Methods

All-cause mortality at 30 days and Kaplan-Meier survival estimates up to 3 years (Paper V) and up to 5 years (Paper IV) were calculated. To determine long-term survival in Paper IV, the personal identification number (PIN) of each patient was cross-matched with the Swedish national population registry to ensure completeness which ascertains 100% survival follow-up. Based on PIN cross-matching, data were obtained from the cause of death registry for all patients deceased before 2015. Aorta- related death was defined as any death secondary to aortic rupture, dissection or postoperative complications to TEVAR. In Paper V, technical success was defined as successful introduction and deployment of the main graft, successful incorporation of target vessels to main graft, absence of type I or III endoleaks (unless planned staged procedure) or graft obstruction, and absence of conversion to open repair or death within 24 hours of surgery.[106]

Other outcomes included peri-operative procedural data, major complications, reinterventions, and aneurysmal sac behaviour (maximum aortic diameter and false lumen patency). Additionally, assessment of long- term aortic remodelling (Paper IV), and analyses of late endoleaks and branch patency (Paper V) were performed. In Paper IV, aortic remodelling was analysed from morphological data from pre- and postoperative CT angiography studies at five fixed levels along the aorta: 2 cm distal to the left subclavian artery, bifurcation of the pulmonary trunk, coeliac trunk, right renal artery and infrarenal aorta. In Paper V, morphological data on aneurysm sac behaviour, false lumen patency, endoleaks and branch patency was analysed from last available postoperative CT angiography images.

Re-interventions outcomes are reported as Kaplan Meier estimates of from freedom of reintervention up to 3 years (Paper V) and 5 years (Paper IV) with analyses of the underlying cause as well as type of re-intervention performed.

Statistics

Continuous data for paper I, II, III, IV and V were assessed for normality with histograms and presented with mean ± standard deviation in case of normal distribution or median with range in case of non-normally distributed data. Comparisons between continuous variables was performed with Mann-Whitney test for non-normally distributed data, and Student's unpaired t-test for normally distributed data. Comparisons between categorical variables was performed with chi square test or Fischer exact test. The statistical software SPSS (versions 21, 23 and 26) were used for analyses, and $P<0.05$ was considered significant.

For paper I and II unpaired t-test was used to compare the mean and maximum TBR for each aortic segment. In Paper I correlations were carried out using Spearman.

For Paper III Mann U Whitney was used to compare TBR for each aortic segment and time point.

For paper IV, 30-day survival was calculated as ratio, while long-term survival and freedom from reintervention were estimated with Kaplan-Meier and compared using log-rank test.

For paper V, survival and freedom-from-intervention were assessed with Kaplan-Meier curves and compared using log-rank test.

Ethical considerations

Papers I, II and III were performed with the approval of the Regional Ethics Committee of Uppsala (Dnr 2016/201) and the regional radiation committee. All patients gave written consent prior to study participation. Paper IV and V were retrospective analyses approved by review board in Uppsala (Dnr 2017/027).

Results

Paper I

In this study of PET/MRI imaging of asymptomatic medium to large size AAA we included 15 patients with a median AAA size 54 mm (range 52-62 mm) and with a median expansion rate/year of 3 mm (range 1-13 mm) The most recent annual expansion rates were for ten patients <4 mm, for four patients between >6 mm and <9 mm, and for one patient 13 mm. No subject had imaging characteristics nor symptoms of inflammatory AAA. Overall mean SUVmax in the aneurysmal wall (2.5 SD=0.5) was significantly higher compared to blood pool activity (1.0 SD=0.2); $p<0.001$). A total of 36 FDG hot spots were identified in the aneurysmal walls in 13/15 (87%) subjects.

Mean and maximum TBR was higher in the suprarenal aorta and non-aneurysmal aortic neck compared to adjacent aneurysmal aorta (maximum TBR: suprarenal aorta 3.1 SD=0.6; aortic neck 2.7 SD = 0.5; and aneurysmal aorta 2.5 SD=0.5, $p<0.001$). Mean TBR and maximum TBR for each aortic segment are shown in Figure 8.

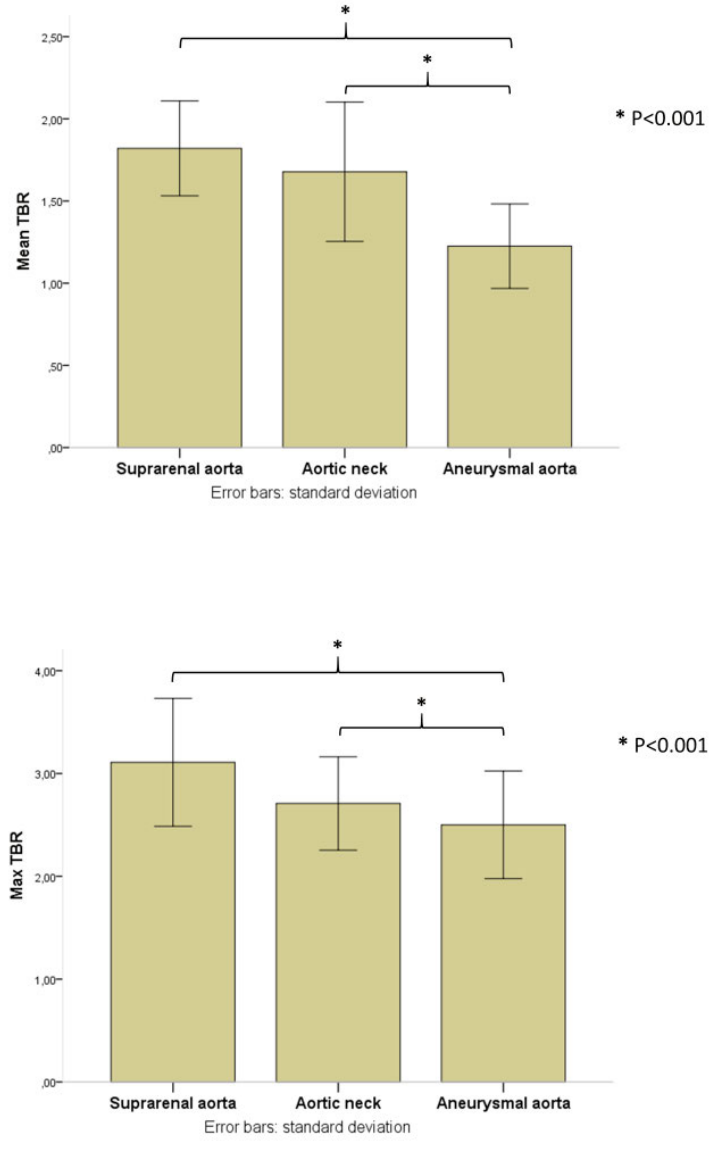

Figure 8 Mean and maximum target background ratio (TBR) of fluoro-deoxyglucose uptake for each aortic segment

MRI displayed corresponding focal mural morphological changes in 9/36 hot spots (25%) and in three out of 13 subjects (23%) with focal FDG uptake. In one of the three subjects where FDG hot spots corresponded to MR structural abnormalities, a rapid aneurysm growth of 13 mm during the recent year of follow up was observed. See figure 9.

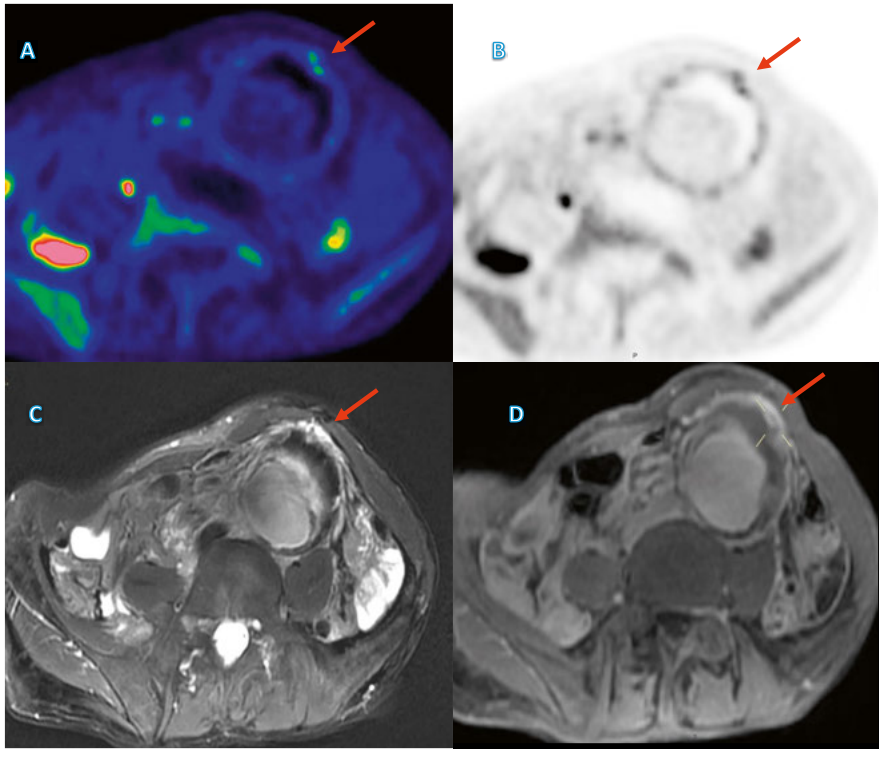

Figure 9 Patient with 63 mm abdominal aortic aneurysm and rapid aneurysm sac expansion (13 mm/year). A+B) Positron emission tomography magnetic resonance imaging (PET MRI) shows focal FDG uptake (arrow) in aneurysm wall C) MRI T2 weighted images shows increased signal indicative of oedema D) Contrast enhanced MRI shows contrast enhancement at the site of FDG hot spot

LGE in the aneurysm wall was identified in eight of 15 patients (53%) and all patients with LGE also had thickening (>2 mm) of the aneurysm wall. PET/MRI characteristics are presented in table 1.

Table 1 Positron emission tomography magnetic resonance imaging (PET MRI) characteristics in 15 patients with medium to large AAAs.

Case (No)	AAA size (mm)	AAA growth (mm)	FDG hotspots (No)	LGE in AAA	Mean SUVmax in FDG hot spots (range)	Focal morphological aneurysmal wall changes in site of FDG hot spot (No)		
						LGE	WT	Oedema
1	52	1	3	No	3.7 (2.9-4.7)	2	2	2
2	52	1	1	No	3.5	No	No	No
3	62	1	1	No	3.5	No	No	No
4	52	1	0	Yes	-	-	-	-
5	51	2	1	No	2.8	No	No	No
6	52	2	2	No	4 (4.3-3.6)	No	No	No
7	54	2	3	No	3.1 (2.8-3.4)	No	No	No
8	54	3	4	Yes	3.4(2.6-4.5)	3	3	3
9	52	3	0	Yes	-	-	-	-
10	54	3	5	No	3.8 (3.4-4.1)	No	No	No
11	57	7	2	Yes	3 (2.7-3.4)	No	No	No
12	65	7	2	Yes	2.1 (2.1-2.2)	No	No	No
13	65	8	3	Yes	3.6 (3.5-3.8)	No	No	No
14	47	8	4	Yes	2.8 (2.5-3.2)	No	No	No
15	63	13	5	Yes	3 (2.7-3.3)	4	4	4

FDG=18F-fluorodeoxyglucose; WT=wall thickness; SUV=standardised uptake value; LGE=late gadolinium enhancement; AAA= abdominal aortic aneurysm

Maximum wall thickness was greater in aneurysm wall segments with maximum intraluminal thrombus (median 4.3 mm (range 2.1 - 7.9 mm)) compared to wall segments with minimum or no intraluminal thrombus (median 2.2 mm (range 1.6 - 2.8 mm), $p< 0.001$)). The median annual aneurysm expansion rate was higher in aneurysms with aneurysmal wall LGE than those without (7 mm vs 2 mm, $p=0.03$). There was a positive correlation between the number of FDG hot spots and recent AAA growth ($r=0.62$, $p=0.013$). However, there was no correlation between maximum SUV in FDG hot spot, or maximum TBR in aneurysm wall, and recent AAA growth.

Paper II

The study included eight men and two females with median age of 77 (range 66-80) and a median aortic diameter of 43 mm (35-48). Visual analyses showed that focal FDG-uptake in aneurysmal wall was present in 90% of

patients with a total of 15 regions of focal uptake. CE-MRI revealed that gadolinium enhancement (GE) as a possible marker of angiogenetic inflammation was present in the aneurysm wall in 50% of patients. See Figure 10.

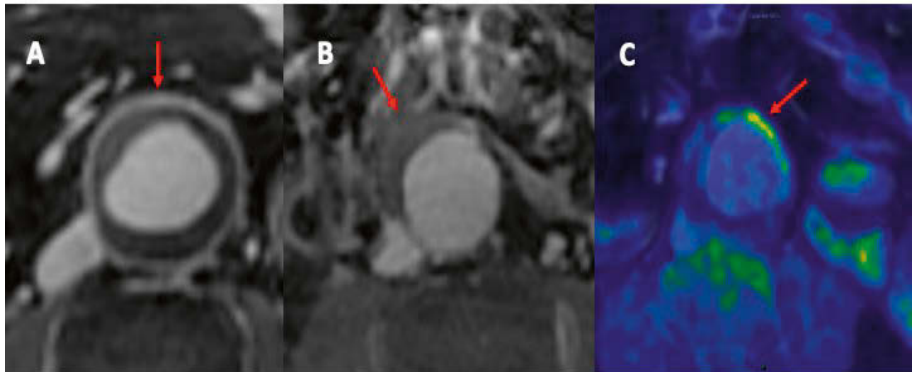

Figure 10 A) Gadolinium enhancement (arrow) in 42 mm abdominal aortic aneurysm (AAA) on T1 weighted magnetic resonance image (MRI). B) No presence of gadolinium enhancement (arrow) in a 36 mm AAA on T1 weighted MRI C) Focal uptake of 18F-Fluorodeoxyglucose (arrow) in 45 mm AAA

In contrast, quantitative analyses showed similar findings as in Paper I, namely that TBR maximum and mean was slightly lower in the aneurysmal aorta compared to the seemingly healthy supra-renal aortic segment (2.3 SD=0.39 vs 2.8 SD=0.45, $P<0.01$ and 1.1 SD=0.25 vs 1.7 SD=0.21, $P< 0.01$ respectively). See table 2 for PET/MRI characteristics for the ten study patients.

Table 2 Positron emission tomography (PET) magnetic resonance imaging (MRI) characteristics of the 10 study patients with small to medium sized abdominal aortic aneurysms (AAAs)

Patient No	AAA size	Mean TBR	Max TBR	FDG Hotspots, No	Average SUVmax in Hotspots (range)	Gadolinium Enhancement
1	48	0.99	2.4	2	3.5(3.0-3.9)	No
2	47	1.1	2.5	4	3.6 (3.1-3.9)	Yes
3	45	0.82	2.1	2	3.4(2.9-3.4)	Yes
4	44	0.8	2.1	1	3.0	No
5	43	0.82	1.5	0	0	Yes
6	42	1.2	2.4	2	2.8(2.7-2.9)	Yes
7	42	1.38	2.4	1	2.8	No
8	38	1.22	2.4	1	2.6	Yes
9	38	1.33	2.9	1	3.7	No
10	36	1.39	2.7	1	3.1	No

SUV=standard uptake value; FDG=18F-fluorodeoxyglucose

Paper III

Visually, increased FDG uptake was detected in dissected descending aorta, in the acute phase of the dissection in all patients, decreasing markedly to subacute and early chronic phase. In the acute phase, 60% of patients had also visually increased FDG activity seen in ascending aorta and the aortic arch which declined in subacute phase. MRI markers of inflammation such as gadolinium enhancement (GE) and increased T2 signal, indicative of edema, were increased in 60% of patients in the acute phase of the dissection and did not disappear over time, except in one patient that interestingly had complete lumen thrombosis of the false lumen.

Quantitative evaluation with whole vessel SUV TBR measurements showed that in acute phase, the dissected descending aortas TBR was significantly increased compared to the ascending aorta and the aortic arch (descending aorta: 5.8 SD 1.3; aortic arch: 4.2 SD 0.6; ascending aorta: 3.3 SD 0.8, $P<0.01$), decreasing significantly to subacute phase (3.5 SD=0.6, $p<0.01$) and decreasing moderately further to early chronic phase (2.9 SD 0.4, $p=0.04$, $p<0.01$) to then be stable in late chronic phase (3.1 SD 0.4, $p=0.9$) .

Not only the dissected descending aorta but also the non-dissected ascending aorta and the aortic arch TBR decreased from acute phase (ascending aorta: 3.3 SD 0.8, arch: 4.2 SD 0.6) to subacute phase (ascending aorta: 2.8 SD 0.6, $p<0.02$, arch: 2.7 SD=0.4, $p<0.01$). See table 3 and Figure 11 for maximum TBR analyses and longitudinal development for each aortic segment.

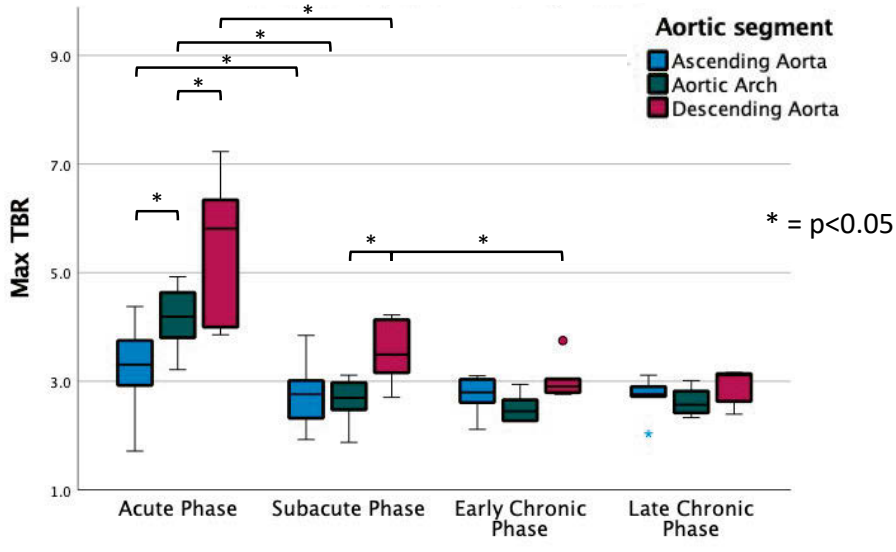

Figure 11 Maximal Target To Background ratio (TBR) analyses and longitudinal development for each aortic segment

Correlations between PET/MRI findings and clinical outcome showed that there was a trend to higher FDG uptake in acute phase in patients that required surgical repair vs patients that remained on medical therapy during follow up (6.8 vs 5.4, p=0.33). Furthermore, MRI inflammatory changes more frequent in patients that required surgical repair vs patients that remained on medical treatment (100% vs 33%, p=0.048) See Figure 12 and table 3 for longitudinal PET/MRI imaging characteristics.

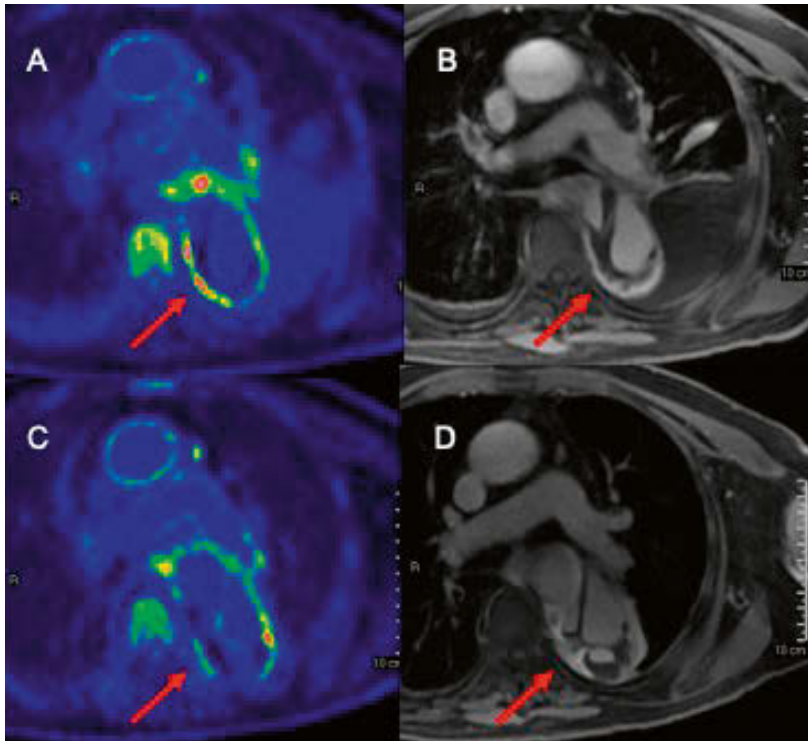

Figure 12 Positron emission tomography magnetic resonance imaging (PET MRI) characteristics in a patient with acute type B aortic dissection in different phases of an acute type B dissection; A+B) acute phase <14 days showing FDG uptake (upper left arrow) and gadolinium enhancement (upper right arrow); C+D) subacute phase 3-4 months decreasing FDG uptake (lower left arrow) and gadolinium enhancement (lower right arow)

Table 3 Positron emission tomography magnetic resonance imaging longitudinal characteristics for the 10 study patients

Case	Maximal TBR for each time point				MRI inflammatory markers for each time point			
	<2 weeks	3-4 months	9-12 months	21-24 months	<2 weeks	3-4 months	9-12 months	21-24 months
No	TBR	TBR	TBR	TBR	GE/T2	GE/T2	GE/T2	GE/T2
1	3.9	3.3	2.8	3.1	Neg/Neg	Neg/Neg	Neg/Neg	Neg/Neg
2	3.9	2.0	2.9	3.3	Pos/Pos	Pos/Pos	Pos/Pos	Pos/Pos
3	5.3	3.6	3.1	3.1	Neg/Neg	Neg/Neg	Neg/Neg	Neg/Neg
4	6.3	4.2	3.8	3.2	Pos/Pos	Pos/Pos	*/Pos	*/Pos
5	6.3	4.2	(TEVAR)	(TEVAR)	Pos/Pos	Pos/Pos	(TEVAR)	(TEVAR)
6	6.2	4.1	2.8	2.6	Pos/Pos	Neg/Neg	Neg/Neg	Neg/Neg
7	7.2	(TEVAR)	(TEVAR)	(TEVAR)	Pos/Pos	(TEVAR)	(TEVAR)	(TEVAR)
8	7.2	(OR)	(OR)	(OR)	Pos/Pos	(OR)	(OR)	(OR)
9	4.0	3.2	2.9	2.9	Neg/Neg	Neg/Neg	Neg/Neg	Neg/Neg
10	5.4	3.1	2.7	2.7	Neg/Neg	Neg/Neg	Neg/Neg	Neg/Neg

*=Gadolinium could not be administered due to increased Creatinine levels on follow-up; TBR= Target to Background Ratio; OR=Open Repair; TEVAR= Thoracic Endovascular Aortic Repair; GE=Gadolinium Enhancement; T2=signal enhancement on T2 weighted images; MRI=Magnetic Resonance Imaging

Paper IV

The study included 50 patients undergoing TEVAR for subacute or chronic dissection pathologies (40 elective, 10 urgent, mean age 62,4 years). There were 10 patients (20%) with deBakey type IIIA dissections (DBIIIA) and 40 patients (80%) with deBakey type IIIB dissections. Majority (n=45) underwent standard TEVAR procedures, but five procedures were performed with fenestrated or branched TEVAR (F/B-TEVAR); two arch aneurysms repaired with branched TEVAR, two TAA aneurysm repaired with branched TEVAR, and one distal descending aneurysm repaired with visceral fenestrated TEVAR. The indication for TEVAR was: post-dissection aneurysm in forty cases (80%); aortic rupture in one case (2%); hypoperfusion of viscera or limbs in four cases (8%); treatment-refractory pain in two cases (4%); and a combination of the aforementioned indications in 3 cases (6%). The mean length of the aorta covered was 22.1 cm (SD 7.0).

The 30-day mortality was 4% (n=2). One patient died due to heart failure following an uneventful standard TEVAR procedure. The second patient died suddenly on the 28th postoperative day following a visceral branched TEVAR procedure, cause of death was not substantiated. Two strokes occurred (4%), both following standard TEVAR procedures. No patients suffered paraplegia or renal failure.

Mean clinical follow-up was 76 months (SD 46) and median radiological follow-up was 46 months (IQR 67).

The estimated survival (Kaplan Meier) at 1-,3-, and 5 years was 94.0% (95% CI [83; 98]), 91.7% (95% CI [79; 97]) and 76.5% (95% CI [61; 87]). No late deaths occurred among patients treated with fenestrated or branched-TEVARs, but 19 late deaths occurred among the patients treated with standard TEVAR. In 13 cases the information on cause of death could be retrieved and six of these were aorta related. Three patients died from aortic rupture due to progression of the aortic dissection after 2 months, 4.3 years and 6.7 years respectively. Two patients died from post dissection aneurysms: one patient after 4.9 years due to multiorgan failure following thoracoabdominal hybrid repair, and one patient after 3.7 years from rupture distal to the thoracic stent-graft before a planned reintervention. Finally, one death is recorded as intact thoracic aortic aneurysm, but no further information could be retrieved since the patient resided in another county. Please see Figure 13 for estimates of long-term survival.

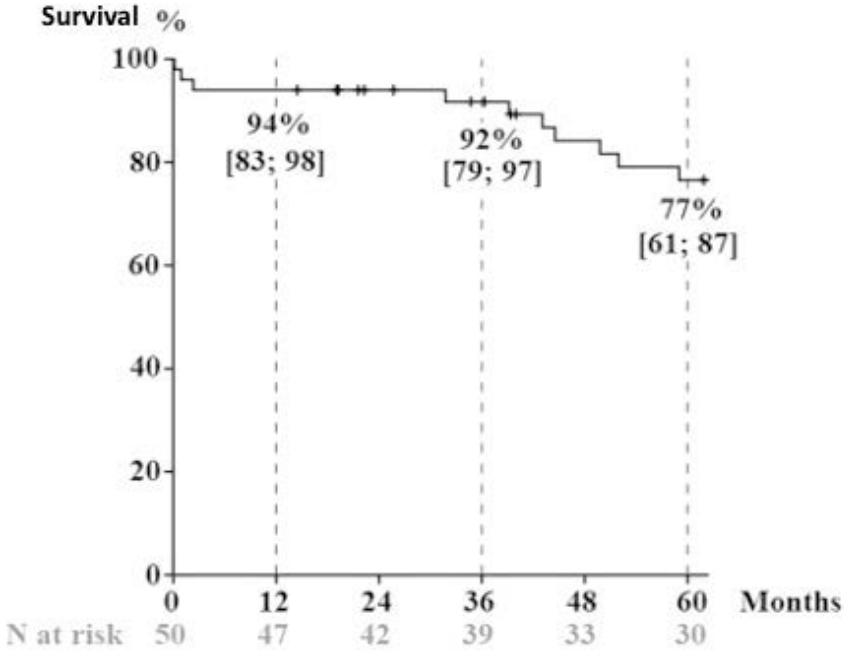

Figure 13 Long-term survival after TEVAR for chronic type B aortic dissection. 95% CI presented within brackets. Standard error <10% for all survival estimates.

Freedom-of-reintervention at 5 years was for entire cohort 68.6% (95% CI [53; 80], TEVAR for DBIIIA: 60.0% and TEVAR for DBIIIB: 71.2%. In total, 26 reinterventions were performed on 18 patients with majority of reinterventions (20/26) for aortic dilatation distally or proximally to the stentgraft. See Table 4

Table 4 Reinterventions after endovascular repair for chronic type B dissec-

	Standard TEVAR (n=45)	Fenestrated or branched TEVAR (n=5)
Stent graft extension		
Distal	17	0
Proximal	2	1
Stent graft in coeliac trunk to cover re-entry	1	0
Visceral bypass with distal stent graft extension	1	0
Plug bronchial arteries[a]	1	0
Embolization lumbar artery[a]	2	0
Balloon-dilatation of aorta and deployment of suprarenal stent[b]	1	0

[a]Performed due to persistent flow in the false lumen parallel to the stent graft
[b]Performed due to compressed true lumen distal to stent graft and visceral hypoperfusion

Complete false lumen thrombosis was seen in 90.0% of DBIIIA and 30.8% of DBIIIB dissections on last follow-up CT (p=0.001). Considering the entire cohort, the mean maximal aortic diameter decreased from 58.7 mm preoperatively to 51.9 mm on last CT (p=0.003).

In the thoracic aorta, TEVAR resulted in a significant increase in true lumen over time with +10.0 mm (95% CI [6.4; 13.6]) (p<0.001) and a significant decrease in false lumen with -11.9 mm (95% CI [-15.2; -8.5]) (p<0.001). See figure 14.

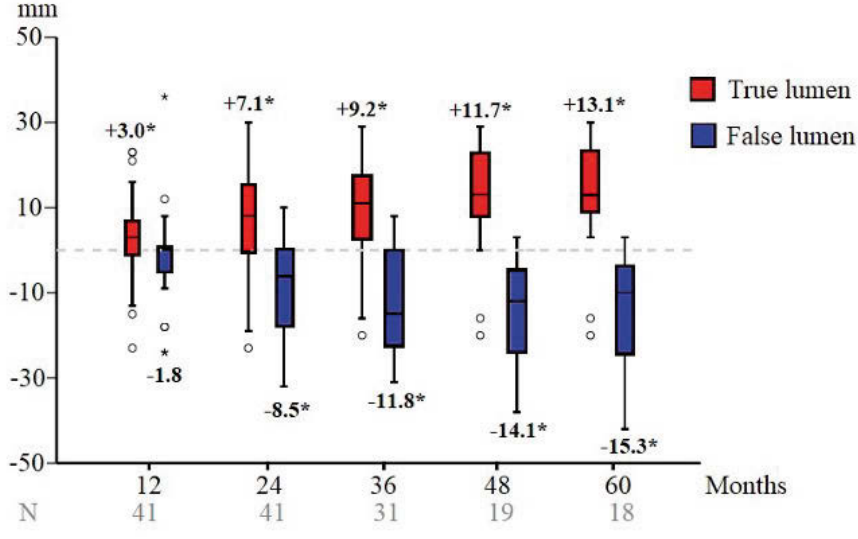

Figure 14 Change of true and false lumen diameter of the thoracic aorta after TEVAR for chronic type B aortic dissection. Mean change in millimeter is displayed above or below the respective box. *=p≤0.05.

In the infrarenal aorta (only DBIIIB included), the changes are minimal, with an increase of both the true and false lumen with +3.1 mm (p=0.001) and +1.0 mm (p=0.464) respectively. See Figure 15.

Interestingly five of the six late aorta-related deaths had complete false lumen thrombosis, three had false lumen shrinkage on thoracic level and one had false lumen shrinkage at the infrarenal level.

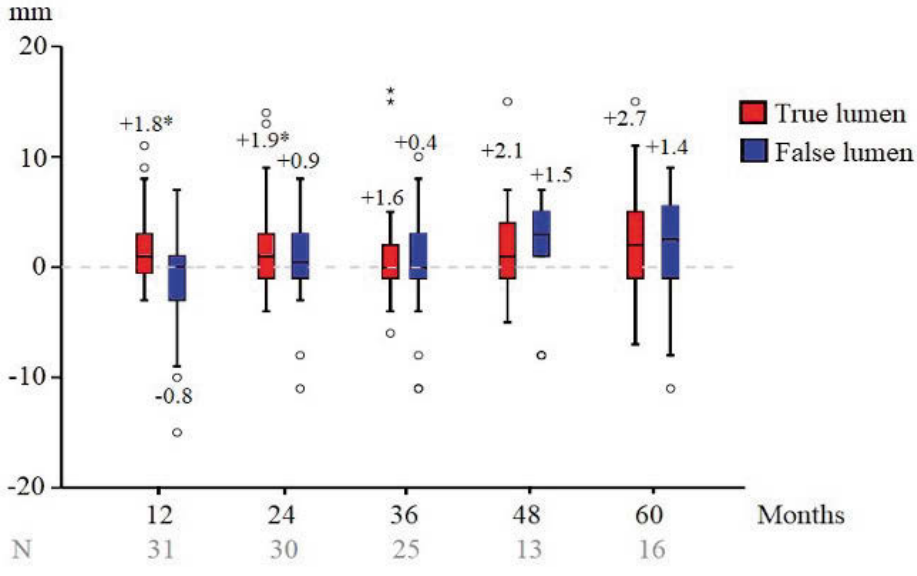

Figure 15 Change of true and false lumen diameter of the infrarenal aorta after TEVAR for chronic DeBakey type IIIB aortic dissection. Mean change in millimeter is displayed above or below the respective box. *=p≤0.05.

Paper V

A total of 27 F/B-EVAR procedures were performed on 26 patients with post dissection aneurysms; 12 aneurysms involving the arch and 14 aneurysms involving the thoracoabdominal aorta. 7 patients (27%) had confirmed connective tissue disease all of which had undergone previous aortic repair providing a “secure” proximal landing zone in a surgical graft. Adjunctive procedures were carried out in 16 patients (68%), most commonly left subclavian (n=12) and hypogastric (n=8) deviations. In total 72 arteries were targeted: 22 arteries in aortic arch and 50 arteries in visceral aorta.

Technical success was achieved in 24/27 (89%) procedures. Failures were one retrograde type A dissection requiring open conversion (arch group); one persistent type Ic endoleak (arch group) due to a residual dissection flap extending deep in the right carotid artery, and one persistent type III endoleak in the patient with TAA rupture.

Overall, 30- and 90-day mortality was 4% (n=1) and 11% (n=3), respectively. One patient died suddenly 12 days post discharge after an uneventful arch F-EVAR from an autopsy confirmed retrograde type A dissection with cardiac tamponade. This patient originally had a type B dissection with native ascending aorta and descending aortic aneurysm with proximal extension to the left subclavian, requiring treatment with arch F-EVAR for adequate landing zone.

Second was the above-mentioned patient from the arch group with persistent type Ic endoleak from a residual dissection in the right carotid artery, resulting in a sudden death on 45 post-operative day due to descending aortic rupture confirmed at autopsy. Third patient died on post-operative day 87 following visceral F-EVAR repair. This death was also procedural related and a result of multiorgan failure following colonic ischemia and abdominal compartment syndrome.

Temporary spinal cord ischemia (SCI) occurred in 3 patients (11%) with onset on second postoperative day and despite prophylactic spinal drainage being performed in all cases. Standard management protocol with increasing spinal drainage and blood pressure resulted in full recovery at discharge. Three strokes (11%) occurred, however only one of these were permanent following an arch F-EVAR repair. This patient suffered a 1 cm large infarction in pons brain area and recovered partially, to full mobility but with sensory deficit in the left extremities at discharge.

Five patients (19%) required early (in-hospital) intervention: one conversion with sternotomy and ascending repair due to retrograde type 1 dissection (above mentioned); one access site complication; one patient with ruptured TAA emergently repaired with 4-F-EVAR that subsequently required multiple reinterventions following with relining of bridging stents and TEVAR due to endoleaks II, IIIa and IIIc; and coiling of renal artery bleeding in two patients following TAA repair (including the patient that succumbed to multiorgan failure). See table 5 for summary of short-term results.

Table **5** Short-term results of the 27 fenestrated and branched procedures

Variable	**Arch Aneurysm**	**TAA Aneurysm**
Mortality 30 days	1(7)	0
Mortality 90 days	2(15)	1(7)*
Spinal cord ischemia	2(14)	1(7)
Permanent	0	0
Transient	2(14)	1(7)
Stroke	2(14)	1(7)
Permanent	1(7)	0
Transient	1(7)	1(7)
Myocardial Infarction	0	0
Renal failure (dialyses)	0	1(7)*
ACS (requiring laparotomy)	0	1(7)*
ICU stay	1(0-20)	1(0-56)
Hospital stay	7(4-32)	8(4-87)
Reinterventions (in hospital)	2(15)	3(21)

* Same patient suffering multiple complications
TAA = thoraco abdominal
ICU = Intesnive care unit

During follow-up (23 months (range 0.5-118)) only one death occurred which was not procedural related (traumatic subdural hematoma).

The estimated combined survival at 3 years was 84.2% ± 7.2%. Survival estimates were stratified for arch repairs, at 75.0% ± 12.5%, and for TAAs, at 92.9% ± 6.9%, log-rank P=0.22 in Figure 16.

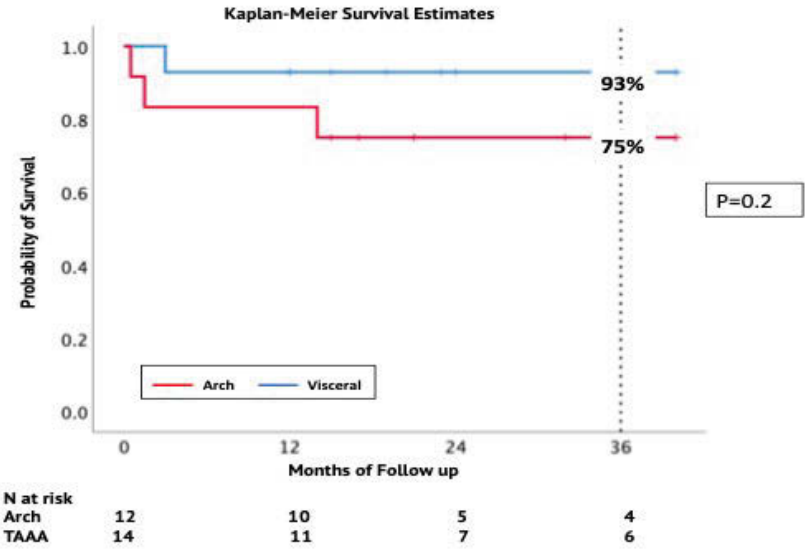

Figure 16 Kaplan Meier survival estimates for patients undergoing branched and fenestrated procedure in the aortic arch and visceral aorta.

Twelve patients (44%) presented endoleaks: Four type Ib endoleaks in the arch group, most as a result of residual dissection distal to the stentgraft; type Ic (n=3) and IIIc (n=2) endoleaks in the TAA group from visceral branches; and seven type 2 endoleaks in the entire cohort.

Late re-interventions occurred solely in the TAA group with 52% of patients undergoing reinterventions at 36 months. Apart from one case of proximal disease progression, all reinterventions were performed for endoleaks. Please see table 3 for details on all re-interventions and outcomes.

Table 6 Late reinterventions and outcomes during follow-up in patients (N =14) treated with fenestrated and branched endovascular aortic repair (F/B-EVAR) of thoracoabdominal aorta (TAA). No late re-interventions in patients treated in the arch segment.

Cause for reintervention	**No.**	**Type of procedure**	**Follow up imaging after reintervention**
Endoleaks			
Type IC	3	Distal extension CA,SMA	No endoleaks
		Distal extension CA	No endoleaks
		Distal extension CA,SMA RRA	Type II LRA (not stented)
Type II	3	Coiling lumbar artery	Type II lumbar artery
		Coiling lumbar artery (second intervention)	Type II lumbar artery
		Open ligation LRA (second intervention)	No endoleak
Type IIIC	1	Prox extension CA,SMA	Type II IMA
Type IIIC+II combined	1	Prox extension RRA coiling lumbar	Type II lumbar artery
Proximal progression of dissection	1	TEVAR descending aorta	No endoleaks

CA=Celiac Artery; SMA=Superior Mesenteric Artery; RRA=Right Renal Artery; LRA=Left Renal Artery; TEVAR=Thoracic Endovascular Aortic Repair

Freedom-of-reintervention at 3 years was for entire cohort 71% ± 10.1%, arch: 100% and TAA: 48% ± 15.1%, log-rank 0.01. See figure 17

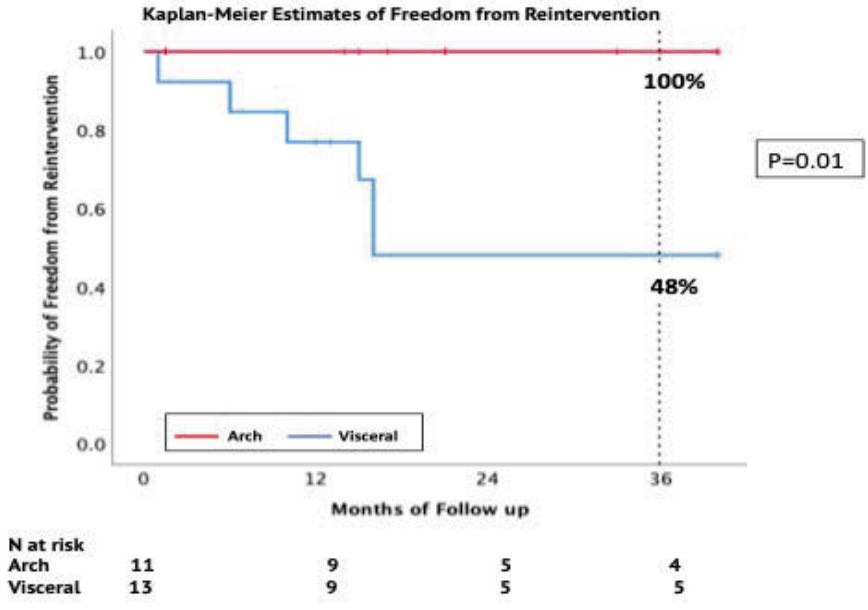

Figure 17 Kaplan Meier estimates of freedom from reintervention during follow up after branched and fenestrated procedure in the aortic arch and visceral aorta among patients surviving 30 days.

General discussion

Molecular imaging of asymptomatic AAAs

In paper I, we explored the potential of combining both functional (PET) and structural imaging (MRI), in the form of fully integrated PET/MRI, to investigate the prevalence of increased FDG uptake and MRI findings of inflammatory mural changes in medium to large asymptomatic AAAs with a recent history of growth. Furthermore, we investigated the relationship between MRI signs of inflammation and FDG uptake in the aortic wall.

FDG hot spots were identified in the aneurysmal wall in the vast majority of subjects (87%). The prevalence of focal FDG uptake in our study was relatively high compared to other reports on large aneurysms. Sakahalisan *et al.* was the first to report increased visible FDG uptake in 39% of the patients[85]. Courtois *et al.* performed PET-CT imaging on 18 patients with symptomatic and asymptomatic AAAs[107]. Among these patients eight patients showed visual FDG uptake (44%) while ten patients showed no FDG uptake. Specimens taken during surgery showed that FDG site was characterized by proliferative leukocytes and increased MMP expression. Another investigation of 12 AAA by the same research group found visible FDG uptake in six patients (50%)[108]. In 2014 Nchimi *et al.* performed 68 FDG-PET examinations on 53 patients with aneurysms in infrarenal (n=47) and thoracic aorta (n=6)[109]. Twenty-five examinations (38%) showed ≥ 1 aneurysm wall area of increased FDG uptake which was associated to increased wall stress as evaluated by finite element simulation. However, several groups, including our own, have previously not been able to detect any visible aneurysm wall-specific FDG uptake in patients with asymptomatic AAAs.[110, 111] In 2012 Palombo *et al.* in a case-controls study investigated 40 male patients with large asymptomatic AAA and failed to detect visual focal FDG uptake in any patient. The authors concluded that FDG hot spot is an extremely rare finding in patients with AAA close to surgical indication[91].

FDG uptake is hard to interpret as also other non-inflammatory cells can take up FDG (for example smooth muscle cells, endothelial cells) which is probably why studies using merely FDG-PET on AAAs suggest poor predictive value for aneurysm growth. With PET/MRI we use multiple imaging techniques to study different aspects of the inflammatory process as LGE is a marker for angiogenesis (linked to inflammation) and FDG is a marker for increased metabolic activity, mostly seen in inflammatory cells. [41, 92, 94]

Comparing and studying these markers can help us better understand the inflammatory activity in large AAAs. For instance, the presence of both LGE and FDG might be an indication of a higher inflammatory index and therefore increased risk for disease progression. In Paper I using these techniques, we identified LGE as a promising biomarker for disease activity, with a 4-fold higher recent annual AAA growth in the LGE positive group. However, we found little overlap between FDG and LGE in large aneurysms, present in only three of 13 patients (23%) with focal FDG uptake. Interestingly one patient with positive overlap also had a rapid aneurysm growth 13mm/y.

Our understanding of late-stage AAA pathology is helped by histological samples taken during surgery, however, pathophysiological mechanisms in early stages of AAA disease are less understood and cumbersome to study. Preclinical studies on rats are unable to fully recapitulate human AAA disease, but suggest that macrophage aortic wall destruction and angio-genesis also play an important role in progression of small AAAs.[94, 112] As mentioned above, FDG uptake has been observed mostly in symptomatic, fast expanding and large AAAs, colocalizing focal PET signal with macrophage infiltration and increased MMP levels, which are increased in plasma in patients with AAA rupture.[24, 85, 90, 107] In contrast, in small asymptomatic AAAs, PET signal is a rare finding.[91, 111] This low FDG uptake could be related to limitation of PET to detect inflammation in early stages of aneurysm disease or that inflammation indeed is absent in vivo.

The key question underlying Paper II, was whether PET/MRI had the potential to detect inflammatory changes in small aneurysms in vivo. Results from Paper II show that the majority of patients presented with focal FDG uptake and gadolinium enhancement (GE) in the aneurysmal wall. The true pathological nature underlying this focal FDG activity in small AAAs can only be extrapolated from above mentioned FDG-PET studies on large AAAs where histological validation of the PET signal was able to be obtained during surgery, showing increased inflammation and proteolytic activity.[108, 113] Pathophysiological basis behind presence of gadolinium enhancement (GE), which we identified in half of the patients, remains uncertain. However, GE is considered to reflect endothelial permeability, angio-genesis and arterial wall inflammation, which are features also frequently implicated in growth and rupture of AAAs, suggesting that GE of the aneurysm wall warrants further investigation as a potential surrogate marker of increased disease activity in AAAs.[13, 93, 94, 114, 115]

The relatively high prevalence of visible focal FDG uptake in Paper I and II could partly be explained by the PET protocol used in our study. The purpose of the selected PET protocol was to be able visualize small focal FDG uptakes in the aortic wall. To achieve this, we used a long-time period (3h) between injection and scanning to decrease background noise. Also, a long scanning time was used. The increased amounts of counts in the raw data made it

possible to apply PET reconstruction algorithms with 4 instead of more conventional 2 iterations and a post sharpening filter of 3 mm instead of more conventional 5 mm. All this together with the increased sensitivity of the digital detectors in the PET/MR and the use of Time of flight could theoretically have increased the possibility to detect small focal uptakes that with more conventional scanning protocol and previous generations of PET detectors would be blurred and not viewed as focal uptakes.

In addition, in Paper I, we included aneurysms with relatively fast expansion rate at baseline (>2 mm annually adjusted). AAAs have intervals with different expansion rates, with presumably higher metabolic activity during episodes of more rapid expansion and significant correlation between annual adjusted AAA growth >2 mm and clinical events has previously been reported.[116]

Although we found a high prevalence of visible focal FDG uptake in AAA wall, the quantitative analyses from Paper I and II shows that FDG uptake in the aneurysmal aorta was lower as compared with the adjacent non-aneurysmal aortic segment, which is in line with previous observations. [91, 117, 118]This is most likely the result of a gradual reduction in cell density in the wall of large aneurysms. It is documented that the progressive increase in aneurysmal diameter is coupled by a reduction in cell density in the AAA wall.[110] FDG tracer directly correlates with overall cell density as demonstrated by Marini et al.[110] Thus, a reduction in cell density in large AAAs causes a reduction in cells able to retain FDG. In addition, several reports have suggested an inverse relationship between FDG uptake and future AAA growth.[117, 118]

Molecular imaging of aortic dissections

In Paper III, PET/MRI was used to study the inflammatory activity in the aortic wall over time in patients with acute type B aortic dissections (ATBAD) resulted in several findings. First, descending aorta had the highest FDG-uptake in the acute phase of the dissection (within 14 days after onset). Reeps et al showed that FDG-uptake was increased in acute aortic dissections (3-13 days) as compared with chronic stable dissections[119] which is confirmed by our finding in Paper III. Differentiation between acute and chronic dissections may be an important clinical issue, especially considering that up to 7% with ATBAD are asymptomatic, and so far, neither CT nor the unspecific plasma biomarkers, for instance d-dimers and fibrinogen, can reliably determine the exact age of aortic dissection. [51, 120] Secondly, the non-dissected ascending aorta and aortic arch also showed increased FDG activity in acute phase, normalizing at 3 months. This elevated arterial wall inflammation in the non-dissected adjacent aortic segments could be caused by the underlying conditions preceding dissection or by the acute event itself. Case studies have reported increasing FDG aortic wall uptake days prior to onset of aortic

dissection, and hypertension, the major risk factor for dissection, is associated with increased plasma levels of pro-inflammatory markers (such as VEGF, IL-6 and MMPs), also found in dissected aortic walls in necropsy studies.[69, 121-123] Escalation of anti-hypertensive therapy in the post dissection phase, reduces mechanical aortic wall stress and hypoxia, and thereby aortic wall inflammation, and might reflect the gradual decline in aortic wall FDG activity seen in our results.

The temporal FDG uptake patterns in paper III show that the inflammation of the descending aorta decreased dramatically from acute phase (<14 days) to early chronic phase (9-12 months) with the greatest magnitude of decrease within 3 months, indicating a dynamic hyperinflammatory state of the aortic wall during this time period. These natural patterns of decline of arterial wall TBR, should be considered when evaluation the impact of drugs on arterial wall inflammation in setting of uncomplicated acute aortic dissection, and might also have relevance with regards to timing of pre-emptive TEVAR.[124] On one hand, performing TEVAR during acute dissection phase, and with pathologically increased arterial FDG uptake and systemic hyper-inflammatory state, has been shown to be less safe, but on the other hand, aortic remodeling after TEVAR decreases with the chronicity of the dissection.[125-128] Strictly based on inflammatory patterns in Paper III, showing that most of the inflammatory response has settled within 3-4 months, could indicate that performing TEVAR around this time-point might be safer. This hypothesis is supported by the INSTEAD trial, demonstrating that performing pre-emptive TEVAR for uncomplicated type B dissections in subacute or early chronic phase (most patients treated 10-12 weeks, range 2-52 weeks) was safe resulting in improved aorta-related mortality compared to those receiving best medical treatment (BMT) alone, while also inducing aortic remodeling in 79% at 5 years.[64]

As of yet, few studies have investigated the association between FDG uptake and adverse outcomes in setting of aortic dissection. Kuehl et al. performed PET/CT on 33 patients with acute aortic syndromes within 24h after admission, one third had PET positive finding, and this subgroup, combined with increased D-dimer levels, had poorer prognosis.[129] Complementing that study Kato et al. performed PET/CT on 28 patients, with mostly acute type B dissections (n=26), at a mean of 13 days after onset, and found higher FDG aortic wall uptake in patients with unfavorable outcome compared to patients with more favorable outcome on follow up.[130] Sakalihasan et al. performed PET/CT and analyses of plasma biomarkers on 23 patients with chronic dissections, and found the higher occurrence of complications in PET positive patients as compared with PET negative patients.[131]

Our findings in Paper III agrees with those studies showing a trend towards higher arterial wall TBR values in those patients developing disease progression requiring conversion from medical treatment to surgery, compared to patients that remained stable on medical treatment. In addition, MRI showed that

gadolinium enhancement (GE) was present in the dissected wall in 60% of the patients in acute phase, indicating presence of neo-angiogenesis and macrophage-rich inflammation, which are two histological features commonly found in dissected aortic wall specimens. [50, 94, 97, 132, 133] Furthermore, GE was more frequent in patients that experienced aorta related complications than in patients that did not, suggesting that GE warrants further attention as a possible biomarker of increased risk of adverse events in ADs.

Endovascular treatment of chronic dissection

Endovascular treatment for chronic dissections remains controversial. Favourable aortic remodelling and decreased aorta-related mortality after TEVAR for acute B dissections have been demonstrated in two randomized trials.[134, 135] However, in chronic dissections, possibly due to the presence of a rigid dissection flap, aortic remodelling is more uncertain to occur.[136] Aortic remodeling is important as it has been shown to be a surrogate marker of successful treatment, associated with better survival.[62]

Our findings in paper IV demonstrate that TEVAR was associated with a high rate of false lumen thrombosis when the dissection was limited to the thoracic aorta (90.0% of DBIIIA vs 31% of DBIIIB) and induced aortic remodeling in the treated thoracic aortic segments in extensive dissections (DBIIIB). Aortic remodeling continued throughout the whole follow-up time without cessation, despite that long time had passed after the initial TEVAR procedure, emphasizing the need of long follow up. The aneurysm size in the treated thoracic portion decreased significantly during follow up, which is in line with other reports showing favorable maximum aneurysm sac shrinkage.[137] Reasonable conclusions from these findings are that TEVAR seems to be a good treatment option for local DBIIIA dissections and prevents dilatation in thoracic aorta that is covered by the stent-graft in the more extensive dissections (DBIIIB). On the other hand, in the more extensive dissections false lumen thrombosis was rare after TEVAR (31% for DBIIIB), and abdominal aorta distal to the stent-graft continued to expand, which is in line with other reports.[65] Continued false lumen patency is a predictor for late complications and disease progression, which might reflect the substantial number of aorta-related deaths in our series.[138] In addition, similar to other reports, our re-interventions (one third of cases) were substantial, consisting mostly of stent graft extensions for distal disease progression, emphasizing the high risk of disease progression and thus the need of meticulous imaging surveillance, and perhaps more extensive aortic coverage initially. In a recent study no association was found between extent of initial TEVAR coverage and sac shrinkage and the potential benefits of initial coverage should be balanced with the risk of paraplegia associated with longer coverage of the thoracic aorta.[137, 139] No patient developed permanent paraplegia in our series.

TEVAR for chronic dissections can be performed with acceptable per-operative outcome and long-term survival, which are comparable to endovascular and open repair of chronic type B dissection reported in recent years as presented in Table 7.

Table 7 Treatment outcomes after endovascular and open repair of chronic type B aortic dissections

Author, year	Patients (n)	Type of repair	Perioperative mortality	Stroke	Paraplegia	5-year survival
Lee, 2013	71	TEVAR	1.4%	NR	NR	89%
Anderssen, 2014	74	TEVAR	4%	0%	0%	65%
Bogerijen, 2015	32	TEVAR	0%	3.1%	0%	78.1%
Hellgren, 2021*	50	TEVAR	4%	4%	0%	76.5%
Conway, 2014	86	OR	5.8%	2.3%	2.3%	83%
Estrera, 2015	209	OR	8.6%	2.4%	NR	72%
Corvera, 2017	196	OR	3.6%	1%	NR	79%

*paper IV; NR= not reported; OR = open repair

Our results from Paper IV indicate that for dissection involving visceral aorta (DBIIIB), TEVAR might stop dilatation in thoracic aorta that is covered by the stent-graft, but distally the aorta will continue to dilate which ultimately results in a post-dissection aneurysm of the thoraco-abdominal aorta (PD-TAAA). Song *et al*. showed that distal PD-TAAA occurs in 28% of patient with chronic dissections, irrespective of dissection type or aortic surgery in the acute setting, which underlines the need of subsequent repair.[140] PD-TAAA that include the aortic arch and/or visceral branches are indeed a challenge, and have until recently been treated with open or hybrid surgery. A total endovascular approach with fenestrated and branched stent grafts (F/B-EVAR) has recently been introduced but is still a relatively new technique, limited to a few high-volume centers.[76, 77] In Paper V we evaluated the early and mid-term results after such treatment.

The technical success rate was 89% with 30 and 90-day mortality of 4% and 11%, respectively, which is comparable with previous reports. Lack of technical success was in one case due to retrograde dissection (RTAD), and one death was related to a second retrograde dissection. In total there were six patients without previous ascending repair that underwent arch fenestrated procedures and both RTADs occurred in this subset of patients. This occurrence of RTAD is indeed a major concern and two cases in a small series suggests this complication may occur more frequently after arch fenestrated repair

than after standard TEVAR for chronic dissections, even with proximal landing being in the aortic arch.[141] In their early experience in 2015 Spear *et al.* treated 7 patients with arch branched endografts, six of those seven patients had had previous ascending aorta replacements and the only patient that died (RTAD was highly suspected) had a native ascending aorta.[75] Tsilimparis *et al.* also found arch fenestrated TEVAR to be associated with higher mortality rates as compared to branched TEVAR in chronic dissections (20%vs 0%).[142] Fenestrated TEVAR procedures might aggravate the risk for RTAD in patients with chronic dissections as they require more snare and wire manipulation, and potentially cause aortic wall damage upon bridging stent deployment. In light of these considerations, we believe that total endovascular arch repair with fenestrated/branched endo-grafts for post-dissecting aneurysms in patients with native ascending aortas should be avoided. In contrast, patients with prior type A dissection with graft replacement of the ascending aorta, providing a secure proximal landing zone, may be the optimal surgical candidates for total endovascular arch repair with branched endo-grafts. Recent published series on patients with selected post type A chronic dissections that provide secure proximal landing in a prosthetically replaced ascending graft, have shown excellent mortality and technical success rates.[143]

Re-interventions were 29% for the entire cohort, occurring solely in TAA group (52% of TAA patients undergoing intervention at 36 months), which is in accordance with previous reports with reintervention rates ranging from 19%-47%. Thus, re-interventions after TAA repair can be regarded as part of the surgical strategy, and patients should be informed of this in advance. Apart from one case, all reinterventions were for Ic and IIIc endoleaks, indicating that longer bridging might be advised in dissection setting.

SCI remains significant, with our rates of 11% being in line with previous studies, ranging from 0%-16%, as summarized in table 5. Among our 3 patients (11%) with SCI, none developed permanent symptoms and all recovered fully upon discharge.

Cerebrovascular insults remain a major concern, in our series three patients experienced stroke (11%), however only one was permanent.

Please see table 8 for summary of outcomes after total endovascular repair for chronic dissections, including our results for comparison.

Table 8 Summary of outcomes after total endovascular repair for postdissection aneurysms in arch and thoracoabdominal

Author, Year	Number and type of repair	Technical success	Perioperative mortality	Stroke	SCI	Reintervention
Kitagawa, 2013	1 arch BEVAR, 29 TAAA F/B-EVARs	100%	0%	0%	0%	27%
Spear, 2018	19 arch BEVARs, 24 TAAA F/B-EVARs	93%	2,3%	4.7%	7%	20%
Tsilimparis. 2018	20 arch BEVARs, 0 TAAA F/B-EVARs	95%	5%	5%	0	30%
Oikonomou, 2019	0 arch BEVARs, 71 TAAA F/B-EVARs	94%	5.6%	0%	16%	47%
Law, 2019	0 arch F/B-EVARs, 20 TAAA F/B-EVARs	100%	5%	0%	10%	30%
Verscheure, 2019	70 arch BEVARs, 0 TAAA F/B-EVARs	94%	2.8%	2.8%	0%	29%
Kuzniar, 2021*	13 arch F/B-EVARs 14 TAAA F/B-EVARs	89%	3.7%	11%**	11%	29%

*Paper V; **Permanent stroke 4%(n=1); BEVAR, Branched endovascular aortic repair; F/B-EVAR, fenestrated/branched endovascular aortic repair; SCI, spinal cord ischemia; TAAA, thoracoabdominal aortic aneurysm.

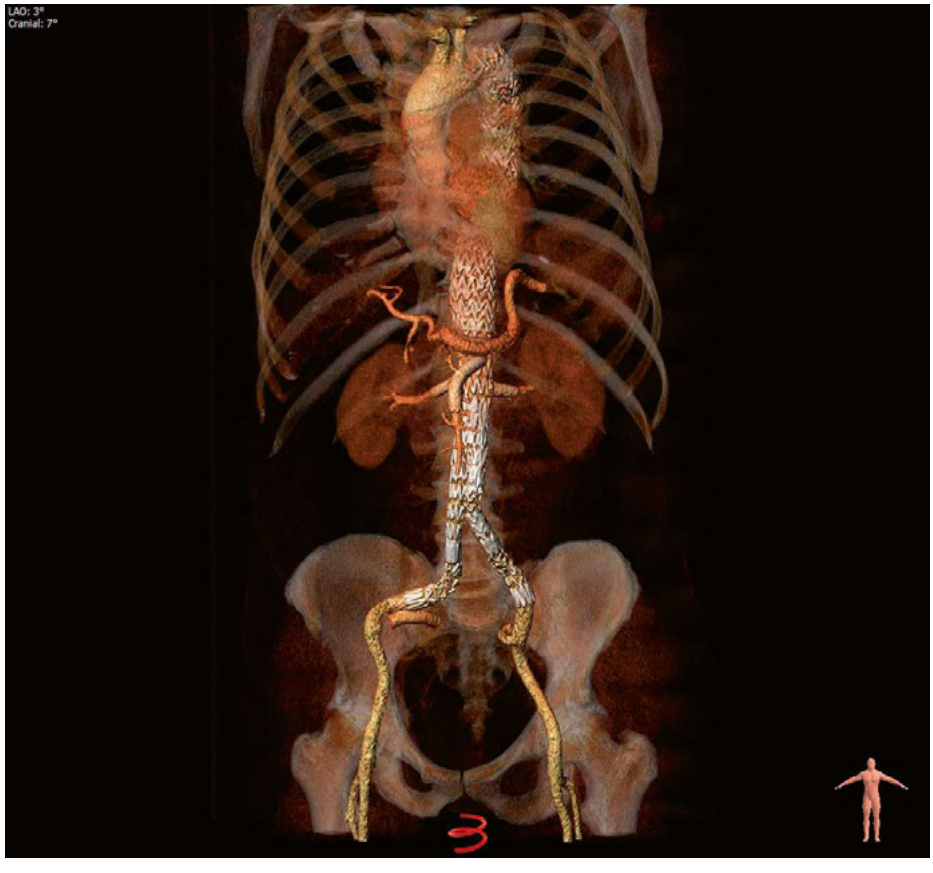

Figure 18 Patient with chronic dissection treated with TEVAR and four fenestrated endovacular aortid repair (4 FEVAR). Bilateral access surgery was performed prior to fenestrated procedure

Future aspects

In paper I our purpose was to show feasibility of PET/MRI as novel technique as a potential imaging modality tool for future studies, which can be directed on smaller and more dormant aneurysms. Screening programs along with the growing use of abdominal imaging for other problems have led to an increase in the identification of patients with small abdominal aortic aneurysms so there is a need for risk stratification of small to medium sized AAA (between 3.0 and 4.5 cm) to identify which subgroup of patients that are in need of more frequent follow-up scans and possibly early intervention. Longitudinal follow-up studies of small aneurysms with assessment of baseline inflammatory activity with PET/MRI and relationship with future aneurysm growth would be of high interest. Future studies should also investigate the potential link between functional imaging markers of aortic wall inflammation and circulating biomarkers for inflammation. Evaluating the future role of PET/MRI in monitoring the clinical response of a medical intervention aiming to reduce disease progression in patients with aneurysms under formation would be of interest. Metformin for Abdominal Aortic Aortic Growth Inhibition Aneurysm Inhibition (MAAGI) trial has been initiated to study the effect of Metformin on aneurysm growth. In a subgroup analyses we aim to evaluate the effect of Metformin on the inflammatory activity in aneurysm wall as assessed with FDG-PET/MRI.

Additionally, development of new, more aneurysm-specific PET tracers for molecular imaging may have great potential. A potential tracer currently under evaluation in our unit is a radionucleotide tracer for elastin degradation. As loss of elastin is one of the early pathologic processes in aneurysm formation, this tracer has the potential to visualize the early processes in the aortic wall that are currently not possible to evaluate with the less specific FDG tracer.

With regards to endovascular treatment of chronic dissections, our single center report on treatment of this pathology with standard TEVAR and complex F/B-EVAR complements previous reports on the topic. However, to further support the use of new techniques in this relatively rare pathology, multicenter or registry-based collaborations could be of great value. Indeed, we are currently collaborating with several vascular institutions to acquire larger multicenter data to confirm the preliminary outcomes after F/B-EVAR treatment for chronic dissections. Furthermore, there is a need for standardized reporting

of outcome in large cohorts to better understand the benefits as well as pitfalls of new treatment strategies.

The high re-intervention rate after endovascular treatment of chronic dissection remains a concern, and development of new disease-specific stentgrafts may be of importance in this aspect. One of the issues with TEVAR in chronic dissection is the risk for distal stent-graft induced new re-entry, which occurs in up to 20% of the cases. At Uppsala university hospital, we are evaluating a dissection-specific TEVAR stentgraft developed on the Cook Alpha thoracic stentgraft platform, which aims to reduce the risk for this complication. This stentgraft has a modified distal landing zone with reduced radial force, with a view to reduce the risk for stent-graft induced new entry at the distal landing zone of the stentgraft. Evaluation of this stentgraft is ongoing. Other possible stentgraft design improvements which may be of value for complex endovascular repair of PD-TAAA include the use of inner-branches for the left subclavian artery or the thoracoabdominal branches of the stentgraft. This design has been used in selective cases, and may reduce the risk for branch endoleaks when compared to fenestrations.[144] However, further evaluation is required.

Neurologic complications after endovascular repair of PD-TAAA is another important area for further future improvement. Operative techniques such as staged repair may be of importance, but currently there is no homogenous definition of what staged repair entails[145] , and further studies of how to best perform staged repair and its potential benefits in terms of reduced SCI rate would be of value. Additionally, development of markers for spinal cord ischemia for early detection prior to clinical manifestation of neurologic deficit, and improved therapeutic strategies for treatment of this catastrophic complication, would be of great value.

Conclusions

Paper I

Assessment of inflammatory activity in medium to large AAAs with FDG PET/MRI is feasible with identification of focal FDG uptake and gadolinium enhancement in the aneurysmal wall. FDG uptake corresponded rarely with mural MRI inflammatory changes.

Paper II

PET/MRI was able to detect focal FDG uptake and gadolinium enhancement as suggested markers of inflammatory activity also in small to medium sized AAAs.

Paper III

The inflammatory activity in the aortic wall after acute type B aortic dissection based on PET/MRI imaging was highest in the dissected descending aorta in the acute phase (<14 days), decreasing radically to subacute phase, but not stabilizing until early chronic phase. Metabolic activity in non-dissected ascending aorta and aortic arch was also increased in acute phase. MRI inflammatory changes were detected in 60% of patients.

Paper IV

TEVAR for chronic dissections was associated with a high rate of false lumen thrombosis when the dissection was limited to the thoracic aorta (DBIIIA), and induced aortic remodelling in the treated thoracic aortic segments. However, in cases of more extensive dissections (DBIIIB), abdominal aorta distal to the stent-graft continued to expand. Re-interventions were substantial (one third of cases). Long term survival was comparable to other series on open repair and TEVAR for chronic dissections.

Paper V

F/B-EVAR of extensive arch and thoracoabdominal post-dissection aneurysms (PD-TAAA) had acceptable short and mid-term outcomes, comparable to other reports. However, retrograde type A dissection following fenestrated arch repair warrants caution. Re-interventions (half of cases) were common, mostly due to leaking bridging stents, occurring solely following thoracoabdominal aortic aneurysm (TAAA) repair.

Sammanfattning på svenska

Abdominellt aortaaneurysm (AAA) och aortadissektion (AD) är två vanligt förekommande, potentiellt livshotande sjukdomar som drabbar stora kroppspulsådern och resulterar i en försvagning och dilatation av kärlväggen med risk för bristning (ruptur). Dessa sjukdomar är ur ett epidemiologiskt perspektiv kopplade till riskfaktorer för generell kärlsjukdom, såsom högt blodtryck, hyperkolestrolemi, rökning, manligt kön och hög ålder. Histologiska prover från manifest sjukdom visar att båda sjukdomarna karaktäriseras av degeneration i kärlväggen med nedbrytning av kärlväggens stödjevävnad, och infiltration av inflammatoriska celler såsom lymfocyter och makrofager samt angiogenes (nybildning av kärl). Dock är patofysiologin bakom sjukdomsutveckling fortfarande okänd och dessutom väldigt svårstuderad.

Moderna funktionella bilddiagnostiska tekniker, såsom kombinationen av positron-emissions tomografi (PET) med spårsubstansen 18-F-fluorodeoxyglucose (FDG) i kombination med magnetresonanstomografi (MRI) kan visualisera biologiska processer, såsom inflammation in vivo, och möjliggör därmed studier av sjukdomsutveckling bland patienter med aneurysm under utveckling eller med aortadissektion.

De flesta patienter som drabbas av akut aortadissektion typ B (där sjukdomen är isolerad till nedåtgående aorta i bröstkorg och buk) har en okomplicerad dissektion i akutskedet. Dessa patienter behandlas primärt med blodtryckskontroll och smärtbehandling enligt gällande internationella riktlinjer. Trots optimal medicinsk behandling utvecklar ca hälften av patienterna en sekundär vidgning av aorta över tid eller påverkan av blodcirkulationen till något av kroppens organ. Dessa är potentiellt livshotande tillstånd som kräver en operation. Traditionellt har man opererat dessa sjukdomstillstånd med öppen kirurgi som varit förenad med hög risk för komplikationer och död. Minimal invasiv kateterburen teknik har utvecklats, så kallad thoracic endovascular aortic repair (TEVAR), där man inplanterar ett så kallat stent-graft via ljumsken upp i aortan för att täcka det sjuka kärlsegmentet från insidan istället. Även om korttidsresultaten är förenade med färre komplikationer och död jämfört med öppen kirurgi så är långtidsresultaten av denna behandling fortfarande begränsade. När aneurysm utvecklingen dessutom sträcker sig ner i bukaortan eller upp i aortabågen och involverar visceralkärlen eller halskärlen försvåras den endovaskulära behandlingen avsevärt. Endovaskulära tekniker med fenestrerade eller grenade stentgrafter (F/B-EVAR) är etablerade

operationsmetoder för aterosklerotiska thorako-abdominella aneurysm (TAAA) men de är kontroversiella och ännu obeprövade vid behandling av TAAA sekundärt till dissektionssjukdom. Det finns idag ingen konsensus för val av operationsmetod vid behandling av patienter med kombinerad aortadissektion och TAAA.

Målsättningen med detta projekt är att studera patofysiologiska processer vid aortaaneurysm och aortadissektion med PET/MR teknik samt att studera resultatet av endovaskulär behandling av dessa sjukdomar.

Delarbete I

I delarbete I, undersökte vi huruvida PET/MRI kunde detektera inflammatorisk aktivitet hos stora (>45 mm) aneurysm (AAA) av bukaorta in vivo (i den levande organismen).

15 patienter med stora asymptomatiska AAA (52-65mm) genomgick PET/MRI undersökning med användningen av spårämnet 18-F-fluorodeoxyglucose (FDG), som är en variant av glukos (socker) men där en hydroxyl grupp ersatts av en radioaktiv isotop, vars sönderfall kan detekteras av PET kameran. FDG ackumuleras i celler med förhöjd sockermetabolism exempelvis kancer celler eller inflammatoriska celler. Alla patienter fick också intravenös injektion av kontrastmedel gadolinium, en metallatom som är paramagnetisk och ger ökad signalintensitet på MR bilder, och tas upp i patologisk inflammerad vävnad.

FDG upptaget i kärlväggen värderades både visuellt och mätningar utfördes (med SUV =standardiserade upptagsmätningar) i aneurysmväggen. MRI bilder granskades avseende förekomst av förtjockning, ödem och gadolinium upptag i aneurysmväggen talande för inflammatorisk aktivitet.

FDG upptag kunde detekteras i aneurysmväggen hos 87% av patienterna. MRI visade förekomst av inflammatorisk aktivitet (ödem, förtjockning och gadolinium upptag) i aneurysmväggen hos 53% av patienterna. Både FDG upptag och MRI inflammatoriska väggförandringar hade positivt samband med den senaste tidens tillväxthastighet av AAA.

Delarbete II

I delarbete II, undersökte vi huruvida PET/MRI också kunde detektera inflammatorisk aktivitet hos små och medelstora (30-50 mm) bukaorta aneurysm (AAA). 10 patienter med relativt små AAA inkluderades i studien och undersöktes med PET/MRI med FDG som spårämne och gadolinium som kontrastmedel. Analyser av FDG upptag och MRI inflammatoriska väggförändringar i aneurysmsäcken genomfördes. FDG upptag i aneurysm vägg kunde

identifieras hos 90% av patienterna och inflammatoriska MRI förändringar (gadolinium upptag) påvisades i aneurysmväggen hos 50% av patienterna.

Delarbete III

I delarbete III användes FDG-PET/MRI att utvärdera inflammatorisk aktivitet i aorta och dess omvandling över tid vid akut aortadissektion. Prospektivt inkluderades 10 patienter med akut typ B aortadissektion och undersöktes med FDG-PET/MRI i olika faser av dissektionssjukdomen, inom 2v från dissektionen (akut fas), 3-4 månader (subakut fas), 9-12 månader (tidig kronisk fas) och 21-24 månader (sen kronisk fas). FDG upptaget och förekomsten av inflammatoriska väggförändringar på MRI undersöktes. FDG upptaget var högst i den dissekerade aortan i akut fasen, och minskade betydligt till den subakuta fasen, men stabiliserades inte förrän i den tidigt kroniska fasen. MRI visade att 60% av patienterna hade gadolinium upptag i den dissekerade aortaväggen tydande på inflammation. PET/MRI inflammatoriska förändringar var vanligare bland patienter som senare utvecklade dissektionsrelaterade komplikationer som krävde en operation.

Delarbete IV

I det fjärde delarbetet undersöktes resultaten efter TEVAR för kronisk aortadissektion. 50 patienter behandlade med TEVAR för kroniska typ B dissektioner vid Akademiska Sjukhuset inkluderas i studien. Data analyserades avseende överlevnad, komplikationer, re operationer, och förändringar i aortans morfologi under uppföljningstiden. 20% hade en dissektion begränsad till thorakalaortan medan 80% hade en mer omfattande dissektion som sträckte sig ner i bukaortan. TEVAR behandlingen stoppade flödet i falska lumen i 90% för dissektioner begränsade till thorakalaortan, men för de mer omfattande dissektionerna endast i 30%. TEVAR resulterade i en minskning av storleken av aneurysmet och gynnsam morfologisk utveckling (minskning av falska lumen och ökning av äkta lumen) i den TEVAR behandlade thorakalaortan, men morfologin och aneurysm diametrarna var oförändrade i den obehandlade bukarotan.

Efter 5 år var överlevnaden 76,5% och en tredjedel av patienterna behövde re opereras, oftast för fortsatt vidgning av aortan nedanför den behandlade delen.

Delarbete V

I delarbete V undersöktes resultatet av komplex behandling av kronisk aortadissektion med fenestrerade och grenade stentgrafter (F/B-EVAR). 26 patienter behandlade med F/B-EVAR för kronisk aortadissektion inkluderades. Anatomiska och kliniska parametrar analyserades med hänsyn till överlevnad, komplikationer och reoperationer och endoläckage. I 11% av fallen uppnådde man inte teknisk framgång med operationen. 11% av patienterna dog inom 90 dagar. Stroke i hjärna och ryggmärg inträffade hos 11% av fallen men de flesta av dessa återhämtade full kroppsfunktion och kunde skrivas ut till hemmet.

3 års överlevnad var 84%. 29% av patienterna som genomgick operation i thorakal och bukaorta behövde reopereras medan ingen patient som genomgick operation i aortabågen behövde reopereras. Nästan alla reoperationer var pga läckande artärgrenar vilket talar för att längre överbryggande stentar behöver användas.

Sammanfattning

FDG-PET/MRI är en lovande bilddiagnostisk metod för att studera inflammation i aorta aneurysm och aortadissektion. Endovaskulär behandling av kronisk aortadissektion resulterade i bra resultat i jämförelse med andra publicerade studier avseende överlevnad och komplikationer, men reoperationer var vanliga vilket understryker vikten av fortsatt radiologisk uppföljning efter behandling.

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