Aus der Universitätsklinik für Thorax-, Herz- und Gefäßchirurgie
Tübingen

Ärztlicher Direktor: Prof. Dr. med. Dr. h.c. Chr. Schlensak

# Aortic elongation as a potential risk factor for aortic dissection: evaluation of aortic morphology in three-dimensional computed tomography studies

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Jose Rodrigo Sandoval Boburg

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Dekan: Professor Dr. B. Pichler

1. Berichterstatter: Professor Dr. Med. Dr. h.c. Chr. Schlensak
2. Berichterstatter: Privatdozent Dr. R. Hoffmann

Tag der Disputation 28.09.2020

*Für meine Familie, ohne welche ich hier nicht sein wurde…*

**Inhalt**

## 1. Introduction

### 1.1 Definition and epidemiology of acute aortic dissection

Aortic dissection is classified as a subtype of the acute aortic syndromes (Erbel et al., 2014, Erbel et al., 2001). It occurs if blood leaves the normal aortic lumen through an intimal tear and consecutively dissects the inner from the outer layers of the media to produce a false lumen (Kouchoukos N, 2013, Kim, 2017). Figure 1 depicts an arterial dissection, in which, through a tear in the intima and media layers, blood will flow between the media and adventitia (Kouchoukos N, 2013).

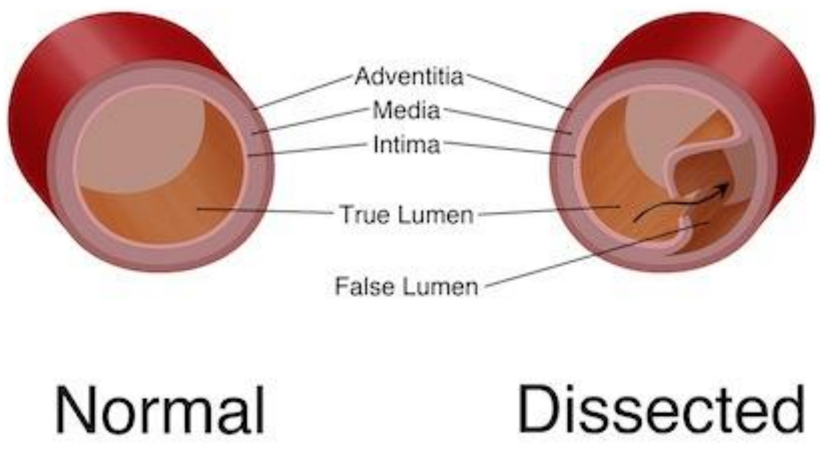


*Figure 1 Arterial dissection(Kouchoukos, 2013)*

Aortic dissection is the most common aortic emergency, with a reported incidence of 6 cases per 100,000 patients each year (Erbel et al., 2014). However, the reported incidence is probably underestimated because of the difficulty of the diagnosis in the acute setting and because a relevant number of patients die prior diagnosis (Erbel et al., 2001, Hiratzka et al., 2010, Erbel et al., 2014). Aortic dissection is most common in men and the incidence appears to have been increasing over time (LeMaire and Russell, 2011, Meszaros et al., 2000, Weigang et al., 2010).

### 1.2 Classification

Several classification systems for aortic dissections exist (Erbel et al., 2001, Kouchoukos N, 2013, Kruger et al., 2012). For the classification, it is crucial to determine the duration of existence of the dissection, the anatomical site of the intimal tear and the involvement of the different aortic segments. According to the duration of the dissection, it can be classified in acute, subacute and chronic (Kim, 2017). A dissection is classified as acute, if it is less than 14 days old; subacute if it has been present between 2-6 weeks and chronic thereafter (Kim, 2017).

With respect to the involvement of the different anatomical segments of the aorta, two different classifications are widely used, DeBakey and Stanford (Erbel et al., 2014, Erbel et al., 2001, Kim, 2017, Kouchoukos N, 2013).

### 1.2.1 DeBakey classification (De Bakey et al., 1955, Debakey et al., 1965)

DeBakey classifies the dissection based on two aspects, the origin of the intimal tear and the extent of the dissection. Based on this classification system, there are three different types of dissection. Type I dissections, are those in which the intimal tear takes place in the ascending aorta and the dissection involves the arch and descending aorta. Type II are dissections in which the intimal tear takes place in the ascending aorta and does not involve the arch or descending aorta. Type III dissections are those that originate and extend distal to the left subclavian artery; they are subdivided into IIIa, which are limited to the descending aorta, and IIIb which extend below the diaphragm (Erbel et al., 2014, Erbel et al., 2001, Kim, 2017).

### 1.2.2 Stanford classification (Daily et al., 1970)

The Stanford classification subdivides dissections into two categories, independent of the extent. The defining factor is, the involvement of the ascending aorta. Stanford type A dissections (TAD) are defined by involvement of the ascending aorta regardless of the site of origin, this entails DeBakey types I and II. Stanford type B dissections do not involve the ascending aorta and the aortic arch but are limited to the descending aorta, this group entails DeBakey types IIIa and b. Acute TAD dissections are responsible for more than 60% of all aortic dissections and are considered surgical emergencies. Type B dissections (TBD) are further subclassified into complicated and uncomplicated, determining the therapy. Complicated Type B dissections include those with refractory pain, malperfusion syndromes and progressive aortic dilatation, indicating imminent or evident rupture, they entail approximately 20% of the cases. Patients presenting any of these should be treated with either surgical or endovascular therapy. Patients with an uncomplicated Type B dissection can be managed with medical therapy (Kim, 2017). The therapeutic strategies are discussed later in detail (see chapter 1.5).

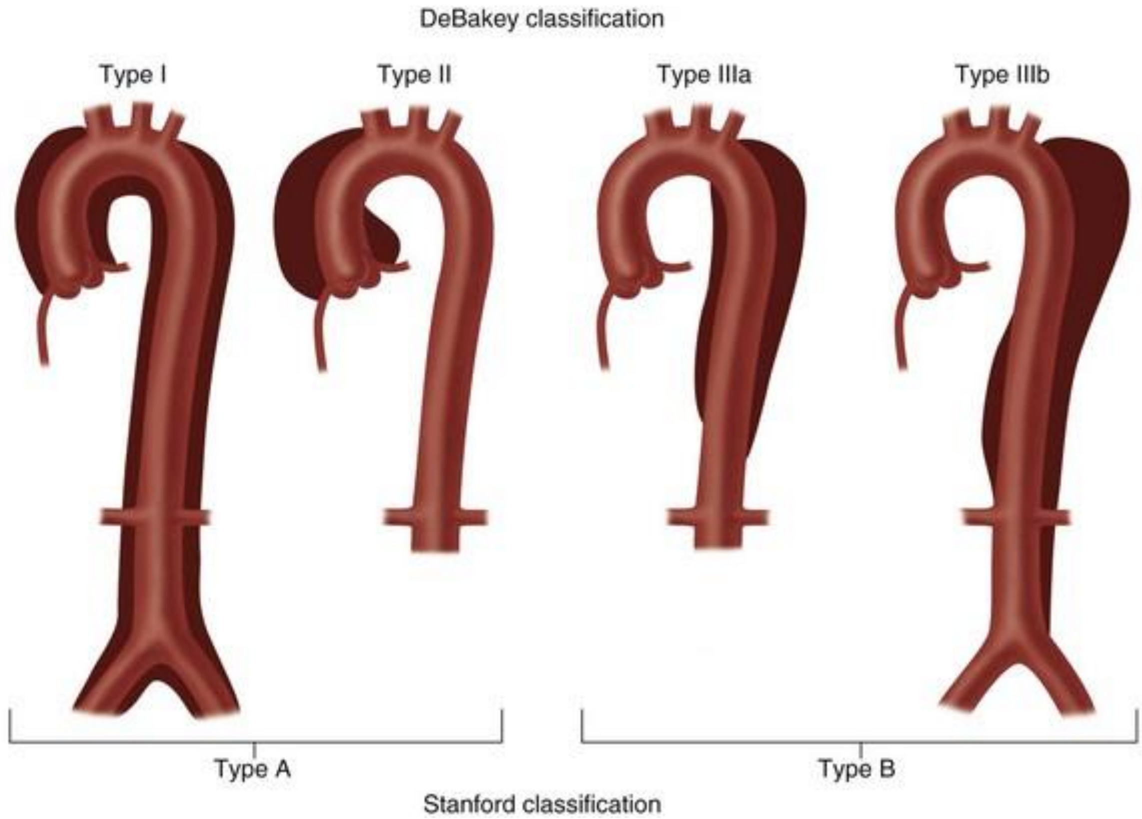


*Figure 2 Type of Aortic Dissections according to DeBakey and Stanford (Kouchoukos N, 2013).*

### 1.3 Risk factors of aortic dissection

Howard and colleagues performed a study, in which they analyzed risk factors in patients who suffered an acute aortic dissection. They showed, that the most prevalent risk factors affecting the incidence of an acute aortic dissection were hypertension and smoking (Howard et al., 2014). Among the patients that were included in their study, 67.3% had an uncontrolled hypertension and 61.5% admitted having smoked throughout their lives. In their study, they could determine that the age onset for an aortic dissection was earlier in men than women, but at an age of 75 years the rates were similar (Howard et al., 2014).

Aside from the previously mentioned risk factors, there are genetic disorders which predispose patients to an acute aortic dissection. Such is the case in patients with syndromes like Marfan (MFS), Loeys-Dietz (LDS) among others (Van Laer et al., 2014, Verstraeten et al., 2016). Patients suffering from these connective tissue disorders may show enlargement of the aorta and even aneurysms from an early age and must undergo aortic segment replacement operations early in their lives (Minatoya K, 2018).

### 1.4 Diagnosis of aortic dissection

Patients suffering from an acute aortic dissection frequently present with sudden and severe thoracic pain. The pain is described as interscapular and it may irradiate to the neck and arms which may make it difficult to distinguish from acute coronary syndrome (Erbel et al., 2014, Erbel et al., 2001, Hirst et al., 1958, Kouchoukos N, 2013). As the dissection occurs, occlusion of aortic branches such as coronary-, carotid-, mesenterial-, renal- or iliac arteries may occur which can exacerbate malperfusion syndromes. An aortic arch vessel occlusion may lead to a stroke; iliac artery or aortic bifurcation occlusion may cause pain, pulselessness, and numbness in one of the lower extremities; occlusion of the renal arteries may lead to an acute kidney injury. If any of these symptoms appear in combination with thoracic pain, the differential diagnosis of acute aortic dissection should be considered and a radiologic diagnostic imaging should be performed as quick as possible (Elefteriades, 2002, Erbel et al., 2014, Erbel et al., 2001, Kim, 2017, Kouchoukos N, 2013).

#### 1.4.1 Chest X-Ray

According to the 2015 Thoracic Aorta Imaging Guidelines, a chest X-ray, although useful in drawing attention to any abnormalities in the aorta and lung parenchyma, has a low sensibility and specificity when diagnosing TAD, and is therefore not a reliable study (Erbel et al., 2014, Goldstein et al., 2015, Hiratzka et al., 2010).

### 1.4.2 Transthoracic echocardiography

Transthoracic echocardiography (TTE) is a useful tool when evaluating the aortic root and the ascending aorta in most patients; the aortic arch can be evaluated in patients with good acoustic windows. The descending aorta however, is difficult to evaluate with a TTE, especially the distal descending segment. This imaging method is an excellent screening tool for upper abdominal aorta aneurysms. Figure 3 shows a TTE from the suprasternal notch view, where the ascending aorta, arch and supraarotic vessels can be visualized and assessed; the descending aorta on the other hand, is only partially visible and can´t be reliably evaluated for any condition. The operator-dependency of the TTE and the inability to assess the complete ascending and descending aorta make it unreliable when diagnosing TAD (Erbel et al., 2014, Erbel et al., 2001, Goldstein et al., 2015, Hiratzka et al., 2010).

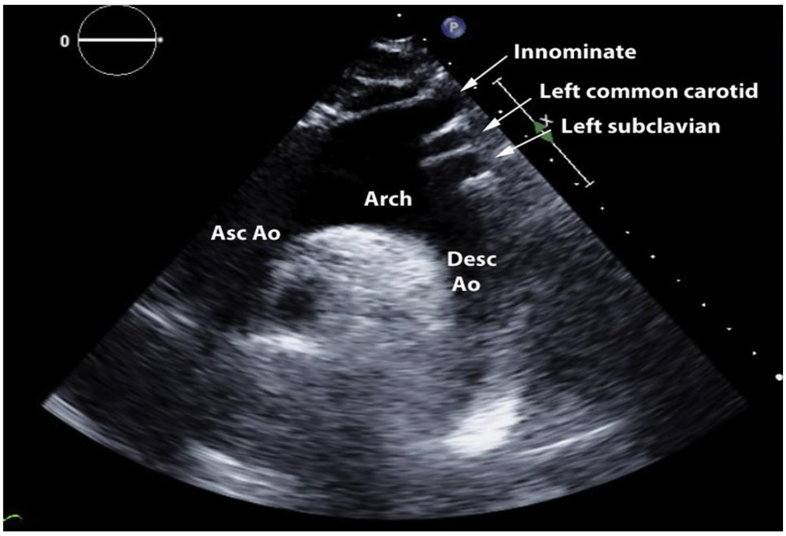


*Figure 3 Transthoracic echocardiography image of the ascending aorta (Asc Ao), aortic arch (Arch), and the descending aorta (Desc Ao) with the supraaortic branches (Erbel et al., 2014).*

### 1.4.3 Transesophageal echocardiography

Transesophageal echocardiography (TEE) has some advantages over TTE. Especially because of a better image quality and a closer proximity to the aorta. This facilitates the evaluation of the ascending and descending aorta; the abdominal aorta however, cannot be visualized. Figure 4 shows a TEE in which a part of the left ventricle, the aortic root and ascending aorta can be seen (Erbel et al., 2014, Erbel et al., 2001, Goldstein et al., 2015). A TEE is of way more value than a TTE when evaluating a TAD, however it is an invasive procedure, time consuming and operator dependent (Erbel et al., 2014).

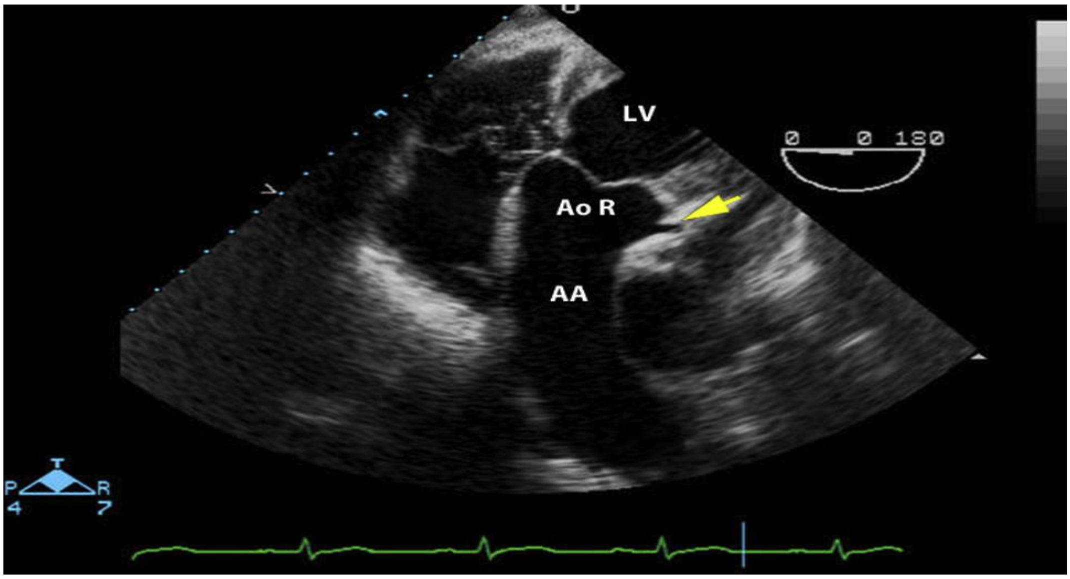


*Figure 4 Transesophageal echocardiographic view in which the left ventricle (LV), the aortic root (Ao R), ascending aorta (AA) and the left coronary (yellow arrow) are imaged (Erbel et al., 2014).*

### 1.4.4 CT-Scan

Computed tomographic angiography (CTA) is the preferred imaging method for diagnosis and follow up of TAD (Agarwal et al., 2009, Bhatia et al., 2010, Erbel et al., 2014, Erbel et al., 2001). CTA acquisition is quick, broadly available, can be performed in even hemodynamically unstable patients, and bearing in mind the relative contraindications renal insufficiency, hyperthyreosis and contrast-agent allergy, it can be performed in practically all patients in the emergencysituation. CTA enables evaluation of both, vessel anatomy and organ-perfusion and is an operator independent diagnostic procedure (Elefteriades et al., 2015).

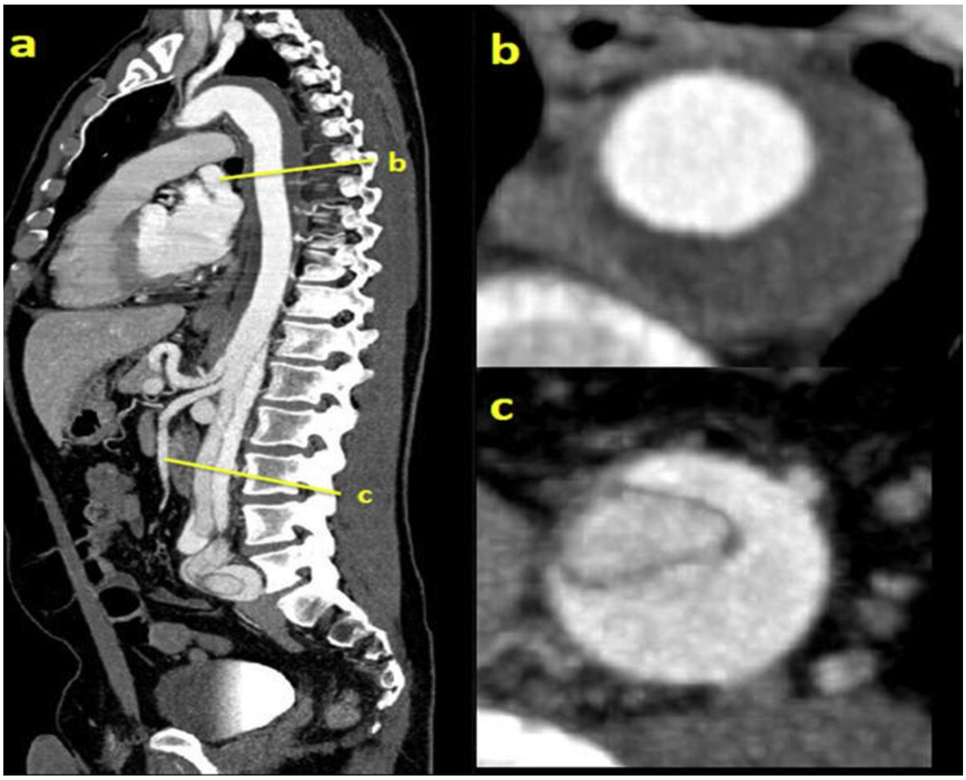


*Figure 5 Sagittal view of the aorta (a), transversal view of an intramural hematoma (b), transversal view of a type B dissection (c)(Erbel et al., 2014).*

CTA has been experiencing important developments in the past years (Agarwal et al., 2009, Bhatia et al., 2010, Elefteriades et al., 2015). With better scanners providing a better resolution and improved image processing software, the depiction of the anatomy has greatly improved. It is possible to analyze complex 3-dimensional structures, such as vessels, and create a 2-dimensional reconstruction, such as multiplanar reformats (Rosset et al., 2004) (Van der Geest R., 2011).

### 1.4.4.1 Curved multiplanar reformats

The tortuous and irregular characteristics of the blood vessels make it difficult to accurately evaluate the diameter, wall thickness and especially lengths when evaluating a CTA. This may represent difficulties in CTAs of patients with an aortic aneurysm or dissection when a therapeutic decision must be made. In the past decade, an improved method for evaluating vessels was developed. It is known as curved multiplanar reformation (CPR).

CPR is a tool that allows the examiner to straighten a tubular, three-dimensional structure, i.e. the aorta, into a single image, thus allowing for an accurate evaluation of the diameters, lengths and wall-thickness at points of interest. To achieve this, a CTA with its sagittal, coronal and transversal reconstructions should be obtained. Afterwards the central point of the object of interest is marked and followed, in all planes, throughout the desired structure. By doing this the three-dimensional structure is mathematically flattened and displayed as two-dimensional. When the curvature of the structure is eliminated, the only varying parameter is the diameter. This can be evaluated along with accurate lengths of the desired structure. This allows for a more accurate evaluation of pathologies such as aortic dissections and aneurysms in any aortic segment (Kanitsar A, 2002, Van der Geest R., 2011, Makaryus A, 2016).

Although CPRs are a valuable tool when evaluating vessels in a CTA, there is a disadvantage when utilizing them. The obtained image shows a straightened reconstruction of the structure of interest, the spatial relations regarding the side branches and organs may be inaccurate (Kanitsar A, 2002).

Figure 6 shows a CPR, in which a center point is marked in all planes of the CTA; a reconstruction is made in which the aorta is visualized in a single image and straightened into a 2-dimensional plane. This enables an accurate evaluation of the aortic diameter and length at any given point (Kanitsar A, 2002, Makaryus A, 2016, Van der Geest R., 2011).

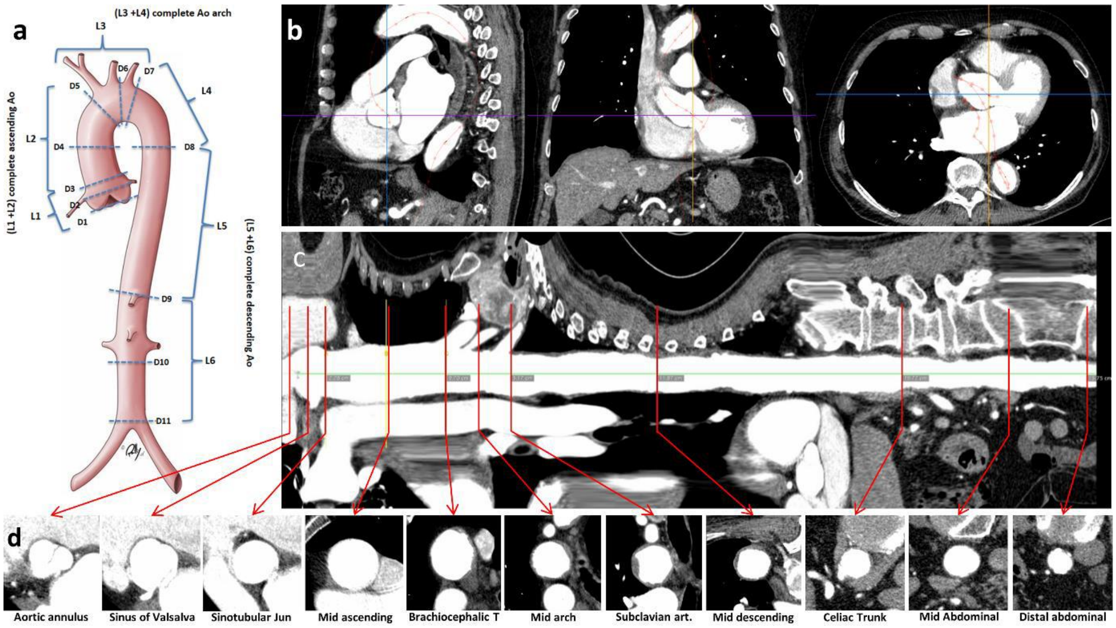


*Figure 6 Representation of a curved multiplanar reformat, (a) representation of the aorta, (b) CTA in sagital, coronal and transversal views, (c) curved multiplanar reformat of the aorta and (d) aortic diameter at the different aortic landmarks (Kruger T, 2018).*

### 1.4.5 Magnetic resonance imaging (MRI)

Like CTA, magnetic resonance imaging is a useful tool for assessing the aorta. It can evaluate aspects such as location and extent of aneurysms, dissections, intramural hematomas and wall irregularities as well as flow direction. This can be attained without the need for ionizing radiation and even without contrast agents. Although it has a very high sensitivity and specificity which is comparable to that of the CTA and TEE, it has inherent drawbacks: acquisition times are very long which is problematic especially in hemodynamically instable patients. Additionally, it is of reduced availability and comparatively expensive. For this reason, it is rarely used in the acute setting, however it is a valuable tool in long term follow up of aortic patients, especially in young ones, who potentially undergo decades of follow up and for whom reducing radiation exposition is prognostically relevant.

## 1.5 Treatment

If a TAD is diagnosed, there is an indication for immediate surgery (De Bakey et al., 1955, Elefteriades, 2002, Elefteriades et al., 2015, Hiratzka et al., 2010). The aim of TAD-surgery is to resect the primary entry tear, which is usually located in the ascending aorta, to stabilize the aortic wall, prevent rupture, depressurize the false lumen, repair the insufficient aortic valve and to treat imminent or evident complications such as pericardial tamponade, coronary, cerebral and peripheral malperfusion syndromes (Kruger et al., 2012).

The extent and the pathoanatomy of the dissection dictate the exact surgical procedure: In patients in which the ascending aorta is dissected, and the aortic valve and root are intact, the proximal segment of the dissected aorta should be resected and replaced with a vascular prosthesis. If the dissection involves the aortic root, resuspension of the aortic valve with preservation of the sinuses is a possibility (De Bakey et al., 1955, Debakey et al., 1965, Hiratzka et al., 2010, Kallenbach et al., 2013). However, if the aortic sinuses and the aortic valve are compromised, an aortic root replacement is needed. There are various operative techniques that may be performed to repair or replace the aortic root with or without the aortic valve. The most common procedures are the Bentall, David and Yacoub procedures (Chiu P, 2016, David TE, 1992, Sarsam MA, 1993).

In the Bentall procedure, the aortic valve, root and the ascending aorta are replaced by a composite graft, the coronaries are re-implanted into the graft and the proximal end of the graft is sutured to the aorta past the main entry tear (Chiu P, 2016, Braverman A, 2019). An aortic valve re-implantation, or David procedure is used in patients who suffer from a TAD that affects the aortic root and show a dilated aortic annulus causing a moderate to severe aortic valve regurgitation. For this procedure, the aortic annulus is measured and a dacron graft is sutured to the aortic annulus, the aortic valve is resuspended in the graft and the coronary arteries are re-implanted. The distal end is sutured to aortic tissue past the main entry point. The objective of this procedure is not only to replace the damaged ascending aorta but to also repair the incompetent aortic valve. This procedure is recommended in patients who show a dilated aortic annulus in order to avoid a valve replacement (David TE, 1992, TE, 2012). The Yacoub procedure is also a valve-sparing procedure, recommended for patients with an aortic regurgitation with a normal sized aortic annulus. This constellation implies that the regurgitation is caused by the aortic dissection, which causes an enlargement of the sinuses, rather than by an incompetent valve. To perform this procedure, the cusps of the aortic valve are preserved whilst the rest of the aortic root tissue is resected, a dacron graft is tailored in such a way, that the cusps can be re-implanted.  The coronary arteries are re-implanted into the graft and the distal end of the graft is sutured to the aorta (TE, 2012, Chiu P, 2016, Sarsam MA, 1993, Zong M, 2016).  Figure 7 depicts the result of the Bentall, David and Yacoub procedures respectively.

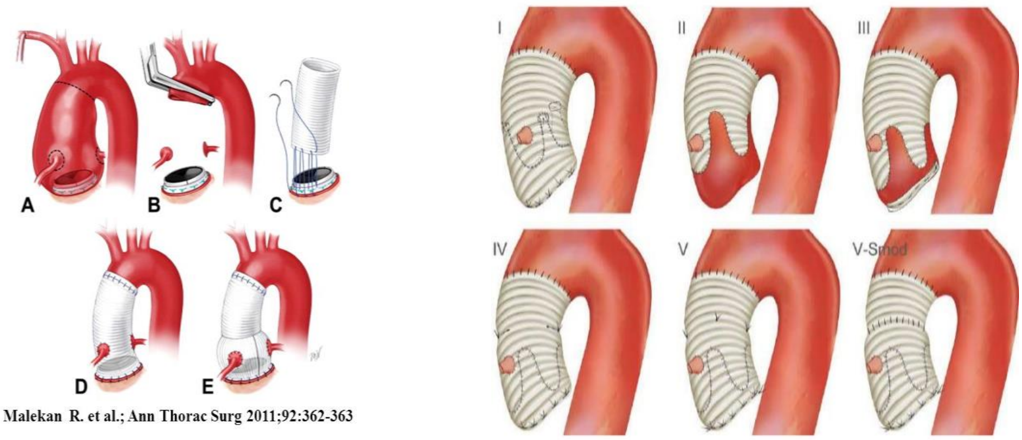


*Figure 7 Left: Depiction of the Modified Bentall procedure.  Right above depiction of the Yacoub procedure.  Right below depiction of the David procedure (Malekan R, 2011).*

If additional dissection-entries are located in the aortic arch, or if this segment is dilated, it is necessary to replace the affected segment.  There are different approaches to this surgery, the operative, the interventional and the hybrid approach (Chiu P, 2016).  The operative procedure is done under a cardiopulmonary bypass, deep hypothermia and cannulation of the axillary artery to allow for a selective brain perfusion and cell protection (Braverman A, 2019). Depending on the degree of arch affection, a partial or total arch replacement may be performed.  The affected arch segment is resected and replaced by a dacron graft; in a total arch replacement, the supra aortic vessels are re-implanted as an “island” into a vascular graft; in an alternative approach, a special trifurcated graft may be used where the supra-aortic vessels are anastomosed independently from each other.  (Braverman A, 2019, Chiu P, 2016, Zong M, 2016).

If replacement of the aorta distal of the left subclavian artery is desired to treat or prevent dilatation in this segment, the frozen elephant trunk (FET) procedure may be performed. A hybrid prosthesis consisting of a covered stent and a conventional vascular prosthesis is placed into the descending aorta during circulatory arrest, then the arch is replaced usually using the afore described island-method (Chiu P, 2016, Zong M, 2016). Should the dissection affect a longer segment of the descending aorta, additional stents may be placed secondarily in the downstream aorta. (Braverman A, 2019, Chiu P, 2016, Zong M, 2016).

**1.6 Prevention of aortic dissection**

TAD is a disease with many complications, high mortality and high neurological morbidity, which makes prevention of utmost importance. The question results, which signs and symptoms allow prediction of TAD with adequate reliability to warrant prophylactic surgery. Elefteriades and colleagues extensively studied this topic. They determined that patients suffering from an asymptomatic ascending aortic aneurysm exceeding a 60 mm diameter have a 31% of rupture or dissection per year. They also established the measures in the descending aorta and found a 70mm diameter being correlated with a yearly rupture risk of 43% (Elefteriades, 2002, Elefteriades et al., 2015). Consequently to these findings, they recommended a prophylactic resection of the dilated aorta to avoid the potentially lethal complications; the threshold was set at 55mm and 60mm at the ascending and descending aorta respectively (Elefteriades, 2002, Elefteriades, 2008). The threshold diameter of 55 mm for prophylactic ascending aorta replacement was established in both, the European- (Erbel, 2014) and the American (Hiratzka, 2010) aortic guidelines, however, in the American guidelines a Class-I-recommendation and in the European guidelines a Class-IIa recommendation is formulated (Kruger et al., 2017).

These measures however, just apply in patients without connective tissue disorders. In patients suffering from connective tissue disorders (i.e. Marfan-Syndrome, Loeys-Dietz-Syndrome) or having a bicuspid aortic valve, the threshold is reduced to 50 mm accounting for the increased rupture- and dissection risk in these patients (Elefteriades et al., 2015, Erbel et al., 2014, Van Laer et al., 2014, Verstraeten et al., 2016).

In patients undergoing cardiac surgery on extracorporeal circulation due to other indications such as aortic- or mitral valve stenosis or insufficiency, prophylactic ascending aorta replacement is recommended at even at 45 mm, the same is true for patients with an aortic growth rate of over 2mm per year (Elefteriades, 2008, Elefteriades et al., 2015, Leontyev SM, 2014).

The diameter is the only established morphological risk factor for TAD. However, there have been studies lately, which question that theory. Importantly, different independent authors described that the majority of TAD occur in aortas clearly below the threshold of 55 mm (Kruger T, 2018, Neri E, 2005, Pape LA, 2007, Rylski et al., 2011). This, and the observation that most TAD entry tears do have a horizontal-, and not a longitudinal orientation, which suggests a longitudinal- rather than a circumferential material failure, led to the hypothesis that aortic elongation, which is longitudinal dilatation, might be a risk factor for TAD as well. Our group recently performed a study in which we measured the aortic diameter of patients who suffered a TAD, a group of patients who had a CTA before suffering a TAD and a control group. They established that the patients in the control group had significantly smaller diameters when compared to the other two groups. They could also determine that 93% of the pre-TAD and 68% patients in the TAD group had aortic diameters of <55 mm; which renders the TAD prediction based solely on the diameter an ineffective method for determining prophylactic surgery (Kruger et al., 2012, Kruger et al., 2016b, Kruger et al., 2017). Further, it was shown that aortas before TAD (pre-TAD group) and after TAD (TAD group) were significantly elongated compared to the healthy control group (Kruger et al., 2016b, Kruger et al., 2017). This supported the hypothesis that the aortic morphology changed in patients with a TAD, not only in width but also in length before it dissects (Kruger et al., 2017, Kruger T, 2018).

Afterwards, other groups confirmed these findings: Adriaans et al. showed that aortic length increases with age, the same group supports ascending aorta length as an independent predictor of TAD (Adriaans BP, 2018).

After the aforementioned studies, the relationship of circumferential dilatation and longitudinal elongation of the ascending aorta still remained unclear, likewise it was unknown to what extent, ectatic and aneurysmatic aortas are elongated. If, as depicted before, most TAD occur in aortas below 55 mm diameter (ectatic), the question arises if there is a subgroup of ectatic and elongated aortas is identifiable, with an elevated risk for TAD.

### 1.7 Hypothesis of this thesis

Based on the body of evidence and the preliminary studies presented in the previous chapter (1.6 Prevention of aortic dissection) we formulated the following hypothesis for this thesis:

1) Dissected aortas (TAD)-, and aortas shortly before dissection are elongated compared to healthy aortas.

This Hypothesis should be investigated with larger cohorts compared to previous studies.

2) Aortic elongation is detectable in ectatic and aneurysmatic aortas. Ectatic and aneurysmatic aortas are elongated compared to healthy aortas.

3) There is a subgroup of ectatic and elongated aortas which matches morphological features of the pre-TAD group, and which is at a certain risk for TAD.

To study these hypotheses, we analyzed aortic morphology in ectatic and aneurysmatic aortas and compared them with healthy controls as well as pre-TAD and TAD aortas.

## 2. Materials and methods

### 2.1. Type of study, formal aspects and approval of the local ethics committee

This study was designed as an observational, non-interventional, monocentic and retrospective clinical study. Computer tomography angiographies (CTAs), which were acquired in routine diagnostics and follow ups were analyzed. The analyzed computer tomographies were from patients who, by any reason other than a vascular disease or who, by suspicion of an aortic dissection had to undergo the diagnostic study.

During the study there were no blood analyses, interventions or diagnostic studies performed on the patients for study-reasons. There were no probes or biopsies taken, no probes were stored in a blood or tissue bank. Neither diagnostic nor therapeutic decisions were made or altered because of the results of this study. All the CTAs performed were part of the standard routine diagnostics, the respective evaluations of the CTAs were performed by certified physicians.

The ethics committee of the medical faculty of the Tübingen University granted the approval to perform this study and reproduce the data in this thesis (No. 766/2017BO2). Because of its retrospective observational character patients informed consent was not required.

### 2.2. Definition of study groups, exclusion and inclusion criteria

For this study we compared the morphology of the aorta in five different patient groups. The groups were defined as follows:

a) Patients treated for a Stanford Type A Aortic Dissection (TAD).
b) Patients who had an adequate CT scan within 24 months before a TAD (pre-TAD group).
c) Patients who were diagnosed with an aneurysm of the ascending aorta (Definition: ascending aortic diameter ≥ 55 mm (Elefteriades, 2002)).
d) Patients diagnosed with ascending aortic ectasia (Definition: ascending aortic diameter 45-54 mm (Elefteriades, 2002, Erbel et al., 2014)).

e) Patients diagnosed in our emergency department for a non-aortic emergency with a CT scan.

In the TAD group we included patients who, were treated in our center because of an acute TAD between January 2016 and March 2017. Patients with the diagnosis of connective tissue disorders, whether clinically or genetically defined, and patients with an iatrogenic or a traumatic TAD were excluded from this study. Within the TAD group we identified patients who in the previous 24 months underwent an adequate CT scan, these patients conformed the pre-TAD group (n=17). In this group the median time between the both CT scans was 5.1 months. The remaining (n=166) patients formed the TAD group and both groups were treated as statistically independent (Kruger T, 2018).

Patients who were diagnosed with an aneurysm (diameter ≥ 55mm) or ectasia (diameter 45-54mm) of the ascending aorta (n=38 and n=102 respectively) in our center from January 2009 to March 2017 were included in the respective groups (Kruger T, 2018). Patients with connective tissue disorders, either diagnosed or suspected, again, were excluded from the study. Coincidental diagnosis such as aortic valve stenosis, regurgitation or a bicuspid aortic valve were not exclusion criteria.

All the patients from the pre-TAD, TAD and aortic aneurysm group had to undergo surgery, some of the ectasia patients as well, however the perioperative data is irrelevant for this study.

The control group was composed by patients who came to our emergency department and underwent an adequate CT scan between March 2014 and March 2016 (n=271) (Kruger T, 2018). In this group the patients were admitted with a diagnosis other than aortic pathologies, any patients who were admitted because of an acute TAD or a symptomatic or ruptured aneurysm were excluded. The data documented from this cohort was also used to establish correlations between age and body dimensions and aortic morphology. The range of age of the patients in this cohort was greater than in the other groups. The youngest patient in the TAD group was 23 years old, for this reason all patients under this age were excluded from the control group to gain comparability (age homogenization).

Table 1 summarizes the exclusion- and inclusion criteria of the patients.

*Table 1: exclusion- and inclusion criteria of the study (Kruger T, 2018).*

| **Inclusion Criteria** | |
|---|---|
| All groups | Age ≥ 18 years |
| Control group | Adequate CT- angiography performed for a non-aortic emergency |
| TAD group | CT-angiography establishing the diagnosis of a TAD |
| pre-TAD group | CT-angiography establishing the diagnosis of a TAD and a CT-angiography performed ≤ 24 month before for another reason |
| Ectasia group | CT-angiography establishing an ascending aorta diameter 45-54 mm |
| Aneurysm group | CT-angiography establishing an ascending aorta diameter ≥ 55mm |
| **Exclusion Criteria** | |
| All groups | Age < 18, clinical or genetical diagnosis of a connective tissue disorder. |

### 2.3 Comparability of study groups

In order to prove comparability of the different cohorts, we documented a series of demographic and clinical parameters. Among the demographic parameters were age, weight, height and date of CT scan; the clinical parameters we recorded were taken from the medical files from the patients. We also recorded the presence of a known, diagnosed hypertension and a massive hypertension which was defined by treatment with three or more of the following drug groups (Mancia, 2013, Kruger et al., 2016a):

- ACE-inhibitors
- B-blockers

- AT-II receptor antagonists
- Vasodilators
- Calcium channel blockers

Although diuretics are classified as drugs to treat hypertension (Mancia, 2013), we decided not to include them in the criteria for massive hypertension definition; so that patients with a complete heart failure therapy wouldn´t be classified under this subgroup. This was relevant, because patients with refractory or massive hypertension would typically be classified as high-risk patients for aortic pathologies. If there was no record of the patient suffering from hypertension in the medical files, the patient would be classified as non-hypertensive. There were no further measurements made to corroborate the diagnosis.

### 2.4. Computer tomography

All the patients included in this study underwent a computer tomography angiography (CTA) of the aorta. Patients who were admitted via the emergency unit were scanned with the with a second generation Dual-Source CT Scanner (Somatom definition Flash, Siemens Heathcare, Erlangen, Germany). A high iodinated contrast (Ultravist, Bayer) was adjusted to height and weight for every patient and administered intravenously at a high flow rate (> 4-5 ml/s). An automated bolus triggering a region of interest, which we defined as the ascending aorta, was used. The layers were no greater than 3mm.

### 2.5. Image analysis, definition of aortic landmarks and segments

The image and CT dataset analysis were performed using the OSIRIX-MD (PIXMEO; Bernex, Switzerland) PACS-viewer and image-processing software package. Curved multiplanar reformats (1.4.4.1 Curved multiplanar reformats) were produced by manually defining the aortic central line with a 3-D Bezier path in frontal, sagittal and transversal CT-reconstructions. At defined landmarks (Kruger et al., 2016b, Kruger et al., 2017, Kruger T, 2018), cross-sectional reconstructions were produced. We followed international standards to define the different aortic landmarks, which represent a clinical relevance (Erbel et al., 2014, Kruger et al., 2016c, Kruger et al., 2017) at which the diameter was measured, the landmarks we used were the following:

- Aortic valve annulus (AV)
- Sinus of Valsalva (midway between AV and STJ)
- Sinotubular junction (STJ)
- Mid-ascending aorta (midway between STJ and BCT)
- Orifice of the brachiocephalic trunk (BCT)
- Mid-aortic arch (midway between BCT and left subclavian artery orifice)
- Distal aortic arch (directly after the left subclavian artery orifice)
- Descending aorta (at the pulmonary artery bifurcation)
- Thoraco-abdominal aorta (at the height of the celiac trunk)
- Mid-abdominal aorta
- Distal abdominal aorta (directly before the aortic bifurcation)

We identified the aortic segments (length parameters) and corresponding values as follows:

- Aortic root (AV to STJ)
- Ascending aorta (STJ to BCT)
- Aortic arch (BCT to distal of subclavian artery)
- Distal aortic arch (subclavian artery to the pulmonary artery bifurcation)
- Descending aorta (pulmonary artery bifurcation to the celiac trunk)
- Abdominal aorta (celiac trunk to aortic bifurcation)

We identified the landmarks and measured the length parameters along the centerline in the curved multiplanar reformats.  To ensure a homogeneous measuring technique, and to reduce the error secondary to not exactly circularly

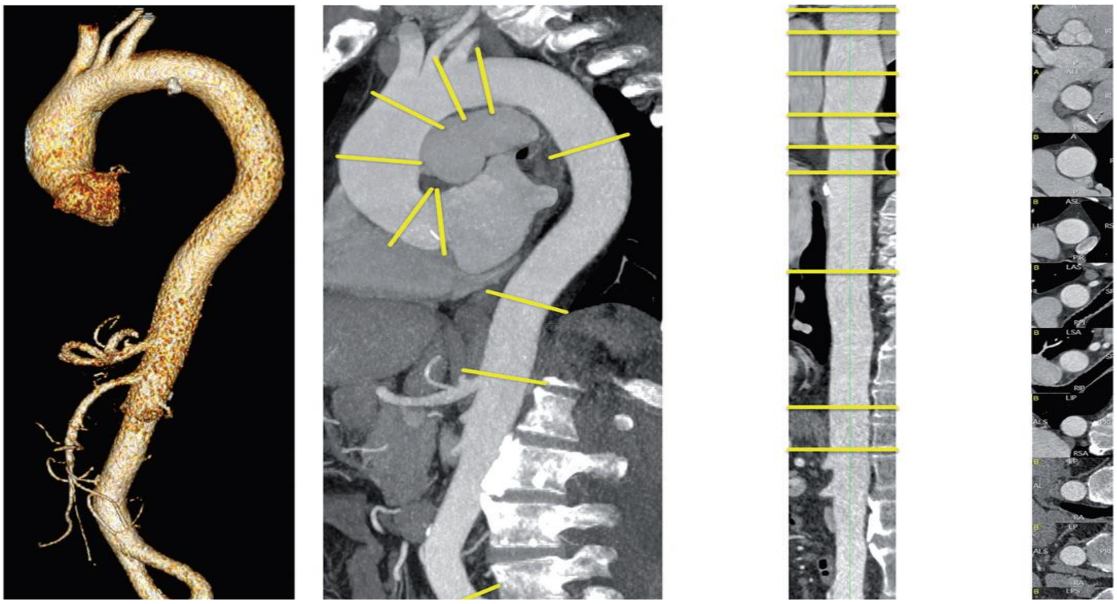

*Figure 8 Aortic segments (Erbel, Aboyans et al. 2014)*

shaped aortas, we measured the aortic perimeter and calculated the mean derived diameter. The measuring tool was placed within the aortic wall. The shape of the aortic wall was retraced with the measuring tool, true lumen as well as false lumen and thrombus were included in the measurement as well (Kruger T, 2018).

Apart from the diameter and lengths of different aortic segments, we also analyzed aortic arch morphology.  Nathan et al (Nathan et al., 2011) defined two different types of aortic arches which can be assessed in the sagittal plane of a CT scan, the defining factor between them is where the highest point of the aortic arch lies. In the aortic arch type I, the highest point lies between the supraaortic vessels, in the type II aortic arch the highest point lies distal to the supraaortic vessels (“gothic arch”).

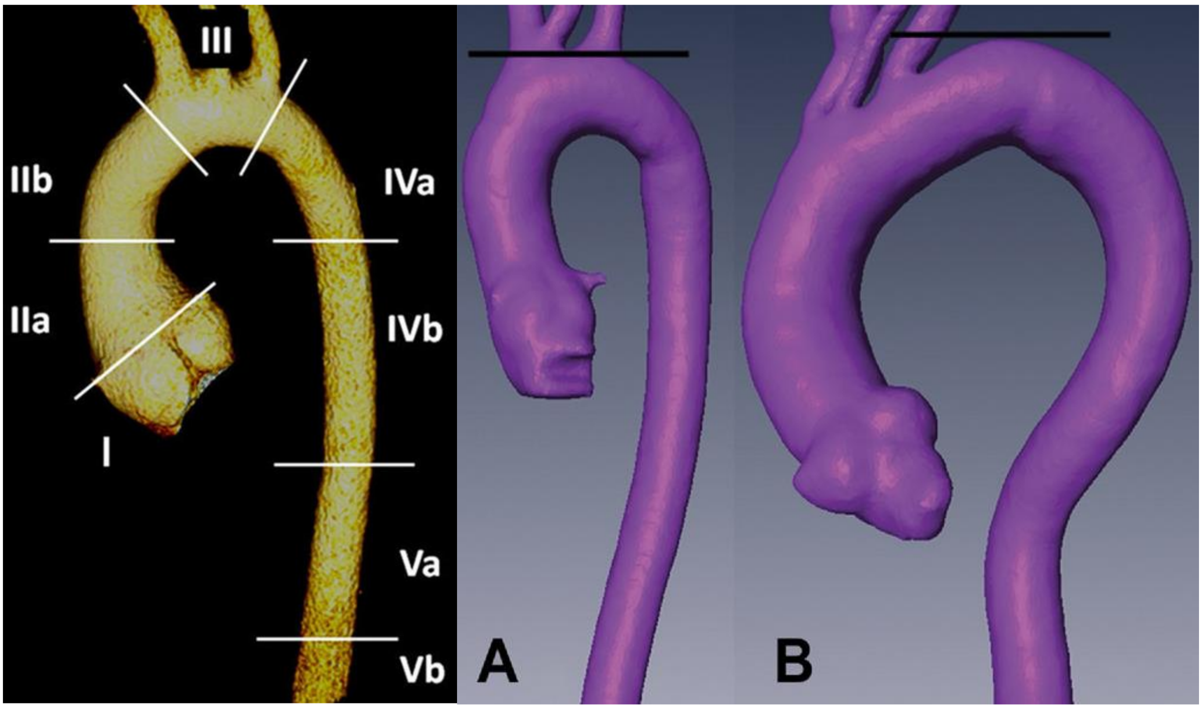

*Figure 9 : Left: Aortic segment illustration. Right: Aortic arch classification (Nathan et al., 2011).*

### 2.6. Analyst training

For this study, the CT scans were analyzed and measured by two medical doctors with a German medical license. Before the analysis of the CT-scans started, both analysts trained the measuring protocol until there was a minimal difference in the measurements between them. During the time the CT-scans were analyzed, if there was a discordance between the data from both analysts, the questioned measurements would be reviewed and with both parties present, repeated and the data obtained would be used and the former data discarded. Both analysts would review the data obtained in a regular time interval to minimize inter-observer variability. Twentyfive randomly picked CTAs were analyzed by both authors throughout the analysis to ensure a low inter-observer variability.

### 2.7. Statistical analysis

For this study we performed no formal sample size analysis, all patients who met the above-mentioned inclusion- and exclusion criteria were included in the study. Data was described depended on its scaling: categorical data was presented with percentages, which were later compared using *chi*-squared tests. Continuous data was presented with box-and-whiskers plots, in which the range (minimum and maximum value), median, first (Q1) and third (Q3) quartiles are represented; Spearman's rank correlation coefficient was used to determine any correlation between these variables. For inferential-statistical comparisons of the multiple study groups, we used a closed testing procedure: the first step was performing a Kruskal-Wallis test, if the result was significant, pairwise Mann-Whitney-Wilcoxon rank sum tests were performed. All reported p-values < 0.001 were considered significant (Kruger T, 2018).

The statistical analysis adhered to the guidelines of the European Association for Cardio-Thoracic Surgery, EACTS (Hickey et al., 2015). The software used for the statistical analyses was SSPS 23.0 (IBM Corporation, Armonk, NY, USA); to present the data we used Microsoft Excel 2010 (Microsoft, Redmond, WA, USA).

# 3. Results

## 3.1. Demographic and anthropometric variables

In all patients, we recorded the gender, age, height and weight and subsequently calculated the body mass index (BMI) and the body surface area (BSA). The objective was to ensure homogeneity and comparability of the study groups. A total of 594 patients were included in the study. Of those, 271 individuals were recruited via the emergency department, having no known aortic condition. After age-homogenization (see chapters 2.2 and 3.1.1), and the consecutive exclusion of 12 very young individuals, 259 patients were included in our control group which can be regarded as healthy with respect to aortic conditions. In the ectasia group (45-54 mm diameter) 102, and in the aneurysm group (>55 mm diameter) 38 patients were included, the preTAD group comprised 17 and the TAD group 166 patients respectively (also see Table 2, page 24).

### 3.1.1 Age

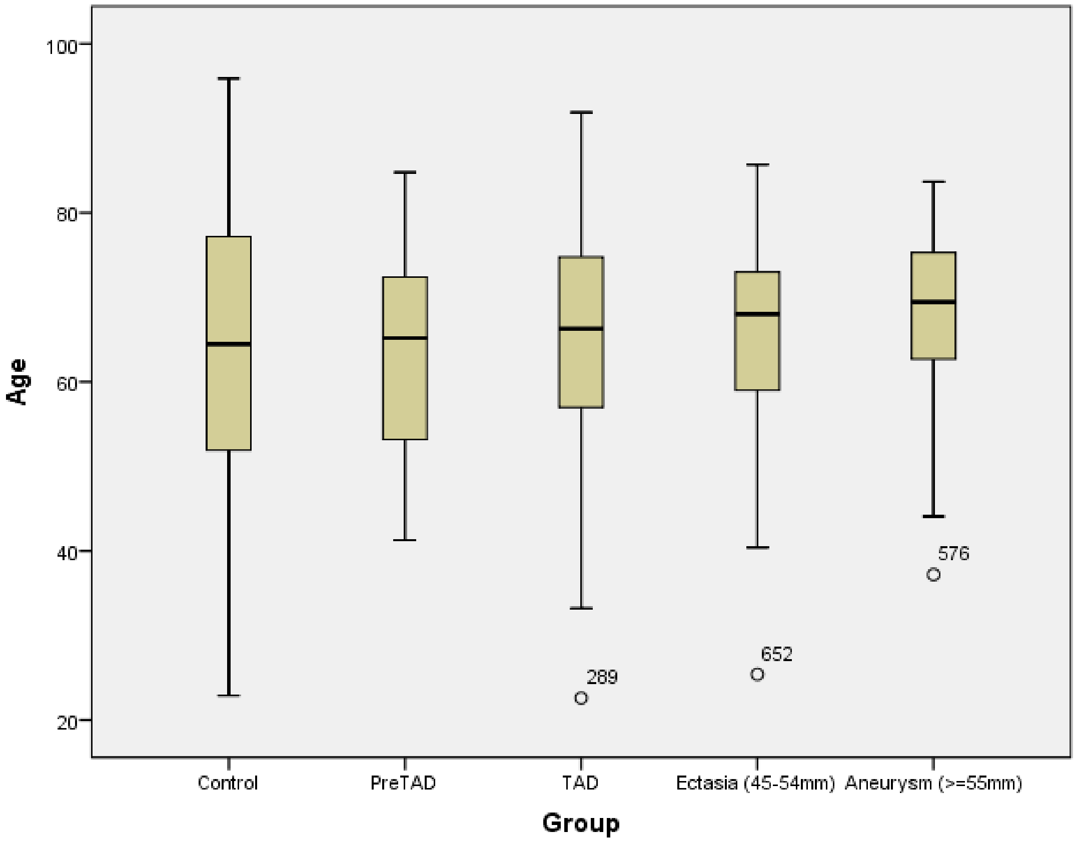


*Figure 10 Age distribution.*

Figure 10 depicts the age range and quartiles of the different study groups. As mentioned earlier, the youngest patient in the emergency department group was 19 years old, in the TAD group the youngest patient was 23 years old. To achieve comparability with respect to patients age, we excluded all patients younger than 23 years from the study (age-homogenization), which is why the youngest control group patient is also 23 years old.

In the Kruskal-Wallis Test comparing age distributions between all groups, the p-value was 0.727, confirming that there was no relevant age-difference between the cohorts.

### 3.1.2 Gender

Table 2 shows the gender distribution in the study groups. Within all groups, there was a tendency to a predominance of male patients, with 63.2% male patients in the aortic aneurysm group, to as much as 76.5% in the pre-TAD group. Between the different groups, chi-square test with a p = 0.9 did not show significant differences in gender distribution.

*Table 2: Percentage of male patients in the different cohorts.*

| | **Control** | **Ectasia** | **Aneurysm** | **pre-TAD** | **TAD** | **p** |
|---|---|---|---|---|---|---|
| N | 259 | 102 | 38 | 17 | 166 | |
| Number of male patients | 173 | 66 | 24 | 13 | 110 | |
| Male % | 66,8 | 64,7 | 63,2 | 76,5 | 66,3 | 0.9 |

### 3.1.3 Height

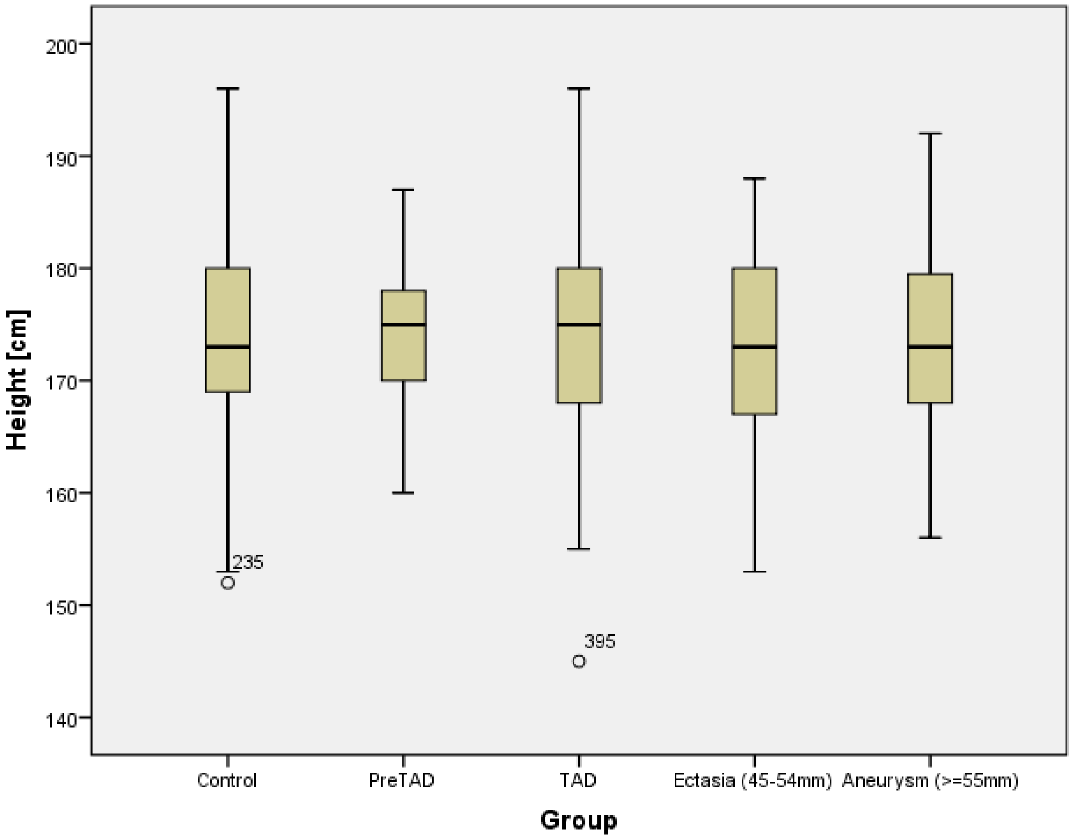


*Figure 11: Height distribution.*

Figure 11 shows the distribution of body-height in the different groups. The median height in all cohorts was between 173-175 cm, and the range of height was between 150 cm and 196 cm. In the Kruskal-Wallis-Test, the p value was 0.826, excluding significant differences between the different groups.

Two outliners were present: In the TAD group, one patient just had a body height of 145 cm, in the control group, another person had a height of just 152 cm.

### 3.1.4 Weight

The median weight in all the cohorts was between 76 - 83 kg, and weight ranged from 46 kg to 140 kg, see Figure 12. The differences in the weight distributions between the groups did not reach statistical significance with a p-value of 0.189 in the Kruskal-Wallis Test.

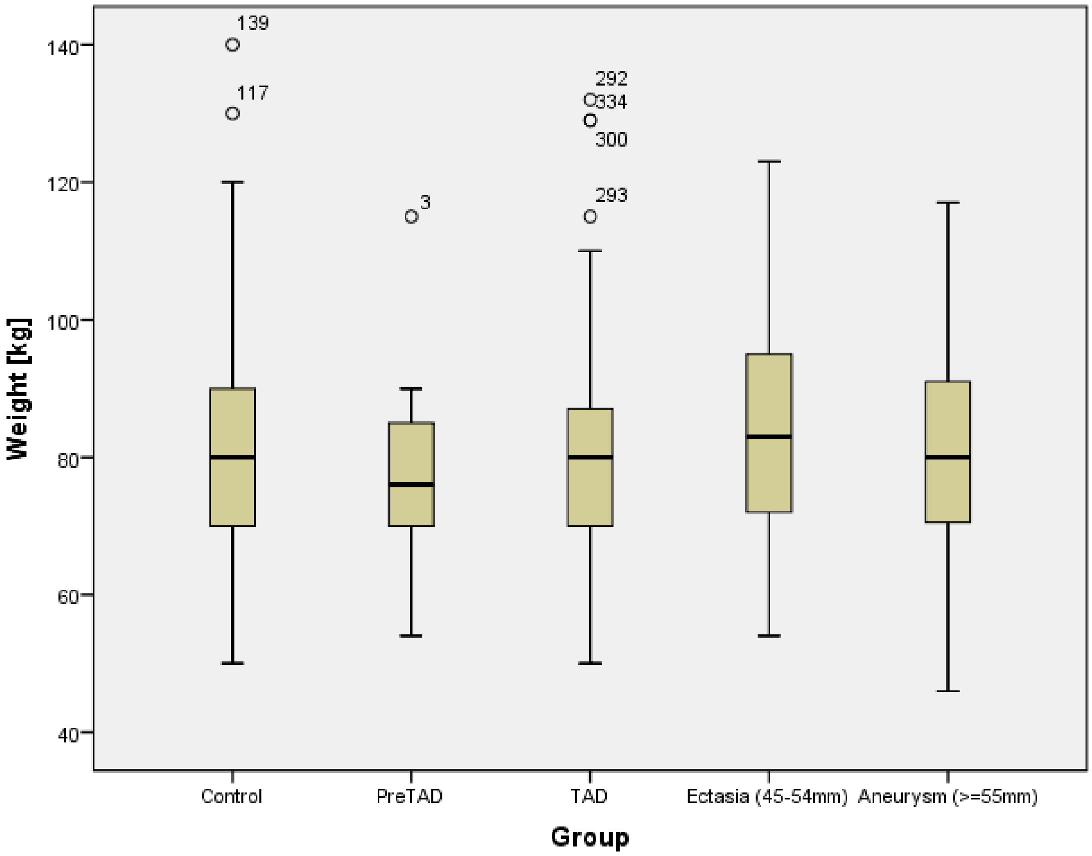


*Figure 12 Body weight distribution.*

### 3.1.5 Body mass index and body surface area

We calculated the body-mass Index (BMI) as an index for obesity- and the Body Surface Area (Mosteller, 1987) (BSA) as a measure of body size.

$$BMI\left[\frac{kg}{m^2}\right] = \frac{weight\ [kg]}{height\ [m]^2}$$

$$BSA[m^2] = \sqrt{\frac{height[cm] * weight[kg]}{3600}}$$

*Formula 1: Body mass index and body surface area formulas (Mosteller, 1987).*

Figures 13 and 14 show the distribution of BMI and BSA in the study groups, respectively.

There was no statistically significant difference in the BMI of patients in the control group compared to the aneurysm, pre-TAD and TAD cohorts. However, a p value of 0.046 was found between the control and aortic ectasia groups. Further analyzing, the difference was 1 kg/m$^2$, when working with an α-value of 0.05 significance can be discussed, although the absolute difference in BMI is irrelevant. When using an α-value of 0.01 the difference between both groups is not significant.

Figure 13 shows the similar median in BMI between all cohorts, the range in the ectasia patients and the control patients is wider than the other cohorts. It is also evident that in the control group there were more outliers with a high body mass index.

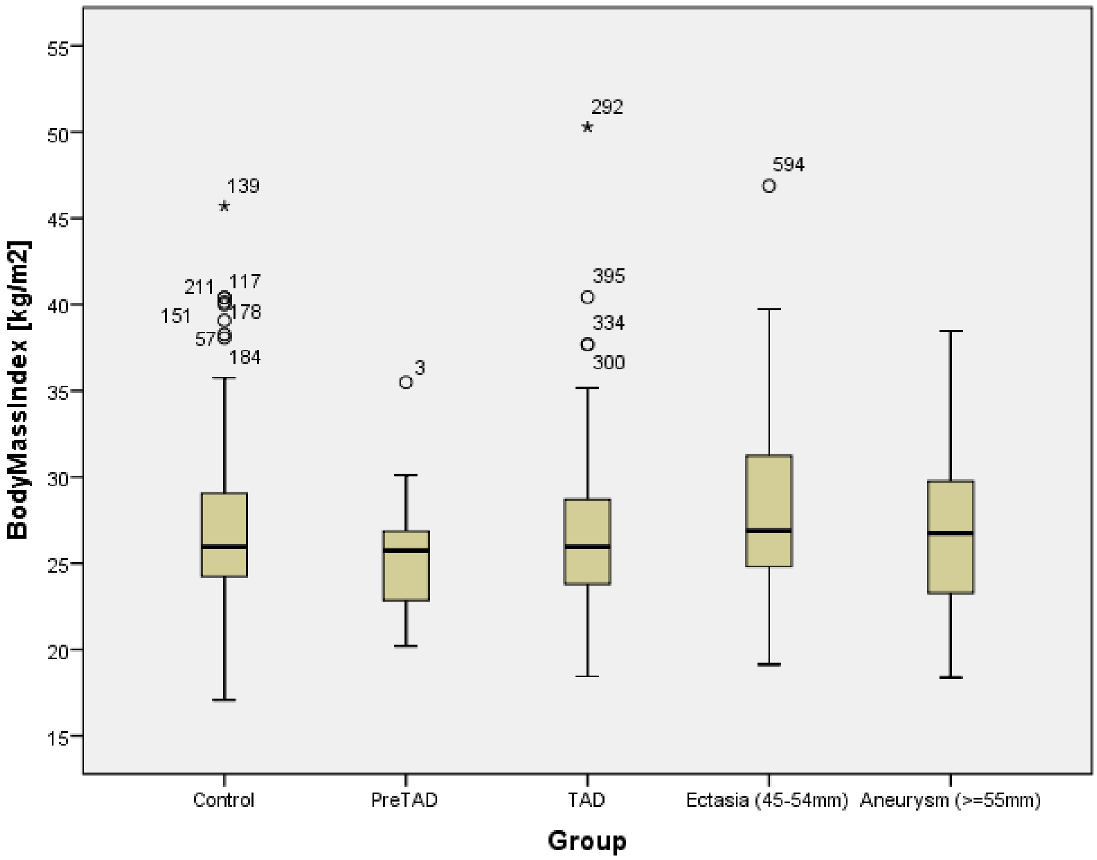


*Figure 13: Body mass index.*

Figure 14 depicts the distribution of BSA in the groups. When comparing the BSA in the different cohorts there was no significant difference (p-value 0.395). It is evident that the control group, as well as in case of BMI, shows the widest range of the cohorts.

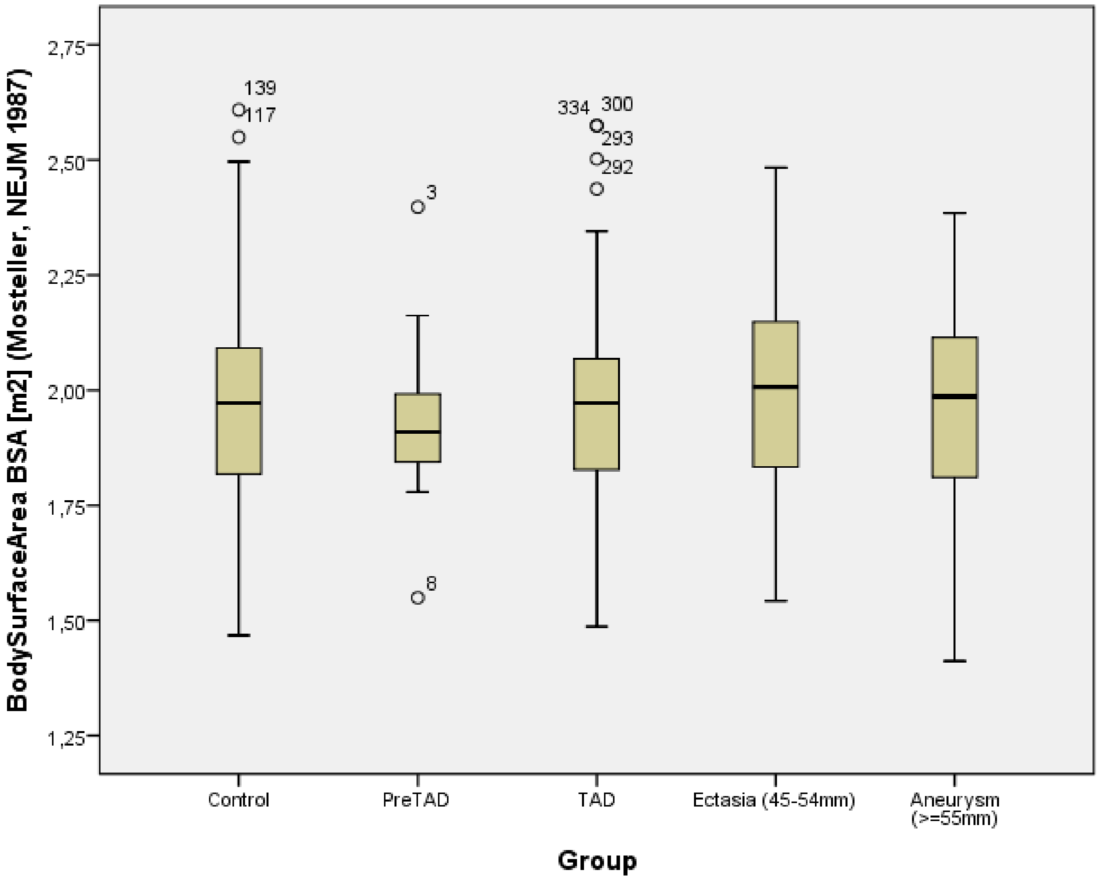


*Figure 14: Body Surface Area.*

### 3.1.6 Hypertension

Hypertension is an acquired risk factor for aortic aneurysm and TAD. We studied the prevalence of hypertension in the different study groups. Hypertension was defined as the presence of the diagnosis in the clinical files of the patient. We furthermore studied the prevalence of massive hypertension, which was defined as hypertension under the chronic medication of three or more antihypertensive drugs (see chapter 2.3) (Mancia et al., 2013). Table 3 shows the distribution of hypertension and massive Hypertension in the study groups. Importantly, both values are not additive, people suffering from massive hypertension are already included in the percentage with the diagnosis hypertension.

Comparing the pathological cohorts to the control group reveals that the prevalence of hypertension in the control group was significantly lower compared to the ectasia, aneurysm, pre-TAD and TAD groups (p< 0.05) (Kruger T, 2018). Between the groups with an aortic pathology there was no significant difference.

We also compared the prevalence of massive hypertension among all groups. Patients in the control group, again, had the lowest prevalence, the highest prevalence, on the contrary, was found in the pre-TAD and TAD cohorts. In all pathological groups, the prevalence of massive hypertension was significantly (p<0,05) higher compared to the control group. Especially in the pre-TAD and TAD groups, the prevalence for massive Hypertension was particularly high (Kruger T, 2018).

*Table 3: Hypertension and Massive Hypertension. P-values were calculated with the Kruskal-Wallis Test.*

| | **Healthy Controls** | **Aortic Ectasia (45-54 mm)** | **Aneurysm (> 55 mm)** | **preTAD** | **TAD** | **p-value** |
|---|---|---|---|---|---|---|
| **N** | 259 | 102 | 38 | 17 | 166 | |
| **Hypertension** | 40.54% | 61.77% | 63.16% | 88.2% | 65.66% | <0.05 |
| **Massive Hypertension** | 6.18% | 17.65% | 7.90% | 41.18% | 26.51% | <0.05 |

### 3.1.7 Comparability of study groups

In summary there were no medically relevant- or statistically significant differences between the study groups with respect to demographical and anthropometric variables as depicted in Chapters 3.1.1 to 3.1.6. Structural equality can be assumed for all study groups, enabling further comparisons regarding aortic morphology.

### 3.3 Aortic diameters

After establishing structural equality between groups, we compared the different aortic measures, diameter- and length parameters (see chapter 2.5), between them. We compared the control cohort with the rest of the cohorts as well as the pathological groups among each other. A special focus was on the comparison between the ectasia- and the aneurysm group on the one hand, and the pre-TAD group on the other hand, to identify potential similarities.

### 3.3.1 Aortic annulus (D1)

Figure 15 displays the aortic annulus diameters in the different groups. The control group, when compared to the rest of the groups had a statistically significant ($p<0.001$) smaller aortic annulus, with a median diameter of 2.72 cm. The median diameter in the ectasia group, on the contrary, was 3.01 cm, which was comparable ($p>0.05$) with the median annulus diameters in the aneurysm group (3.08 cm) and the pre-TAD (3.13 cm). In figure 15, it becomes evident that the range of aortic annulus diameter in the ectasia, aneurysm and pre-TAD groups are similar, with the lowest value corresponding to the pre-TAD group with a diameter of 2.20 cm and the highest to the aneurysm group with just over 4.0 cm.

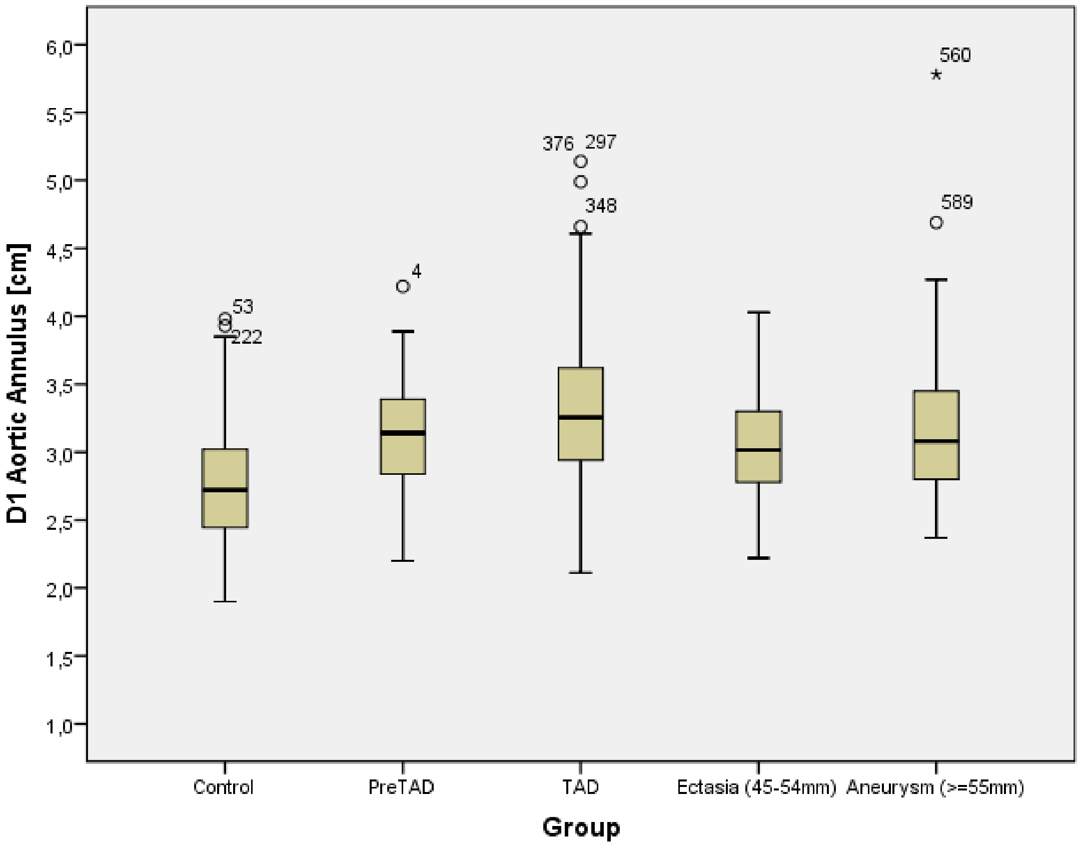


*Figure 15: Aortic annulus diameter in cm.*

### 3.3.2 Aortic sinus (D2)

In the control group, the median diameter of the aortic sinus was 3.63 cm, which was significantly smaller, with a p-value < 0.001, when compared to the respective diameters in the pathological groups. Namely, the median diameters of the aortic sinus were 4.30 cm in the ectasia- and 4.31 cm in the aneurysm groups. These values were comparable to the 4.22 cm median diameter in the pre-TAD group. The median sinus diameter in the TAD group was even larger with 4.46 cm, which was just significant (p=0.049) when compared to the pre-TAD group.

The pre-TAD group has the smallest range of diameters whereas the aneurysm group has the largest. All diameters are displayed in figure 16.

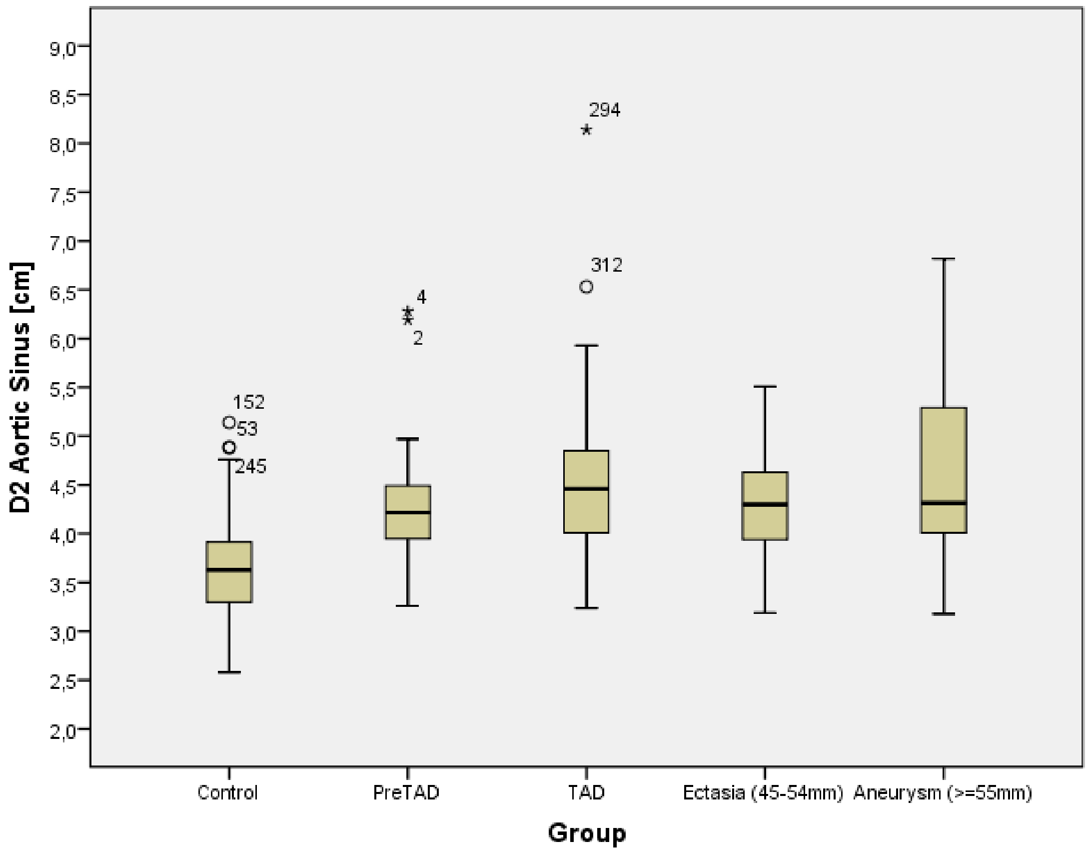


*Figure 16: Aortic sinus diameter in cm.*

### 3.3.3 Sinotubular junction (STJ) (D3)

In the control group the median diameter of the sinotubular junction was 3.05 cm. This was significantly smaller compared to the other groups, with a p-value

<0.001. The ectasia group was characterized by a median STJ diameter of 4.05 cm, which was significantly larger compared to the control group, but significantly smaller when compared to the aneurysm group (4.55 cm).

The STJ median diameter of the pre-TAD group with 3.87 cm, as well as the diameter distribution of this group was comparable to the ectasia group – but not to the other groups. In the TAD group the median diameter was 4.49 cm, larger than in the pre-TAD and the ectasia groups.

Two aspects must be highlighted: first, the STJ diameter in the control group was smaller than the sinus-diameter of the same group. This means that the classic tallied shape of the aorta is preserved. This was also the case in most ectasia- and pre-TAD patients. However, the median STJ diameter in the Aneurysm- and TAD groups is larger than the respective sinus-diameter, indicating that in these groups the sinotubular junction is flattened, the gross shape of the aorta has changed substantially, it is not tallied anymore. Secondly the STJ in the TAD group is significantly larger than in the pre-TAD group, indicating an enlargement of this segment during the actual process of dissection.

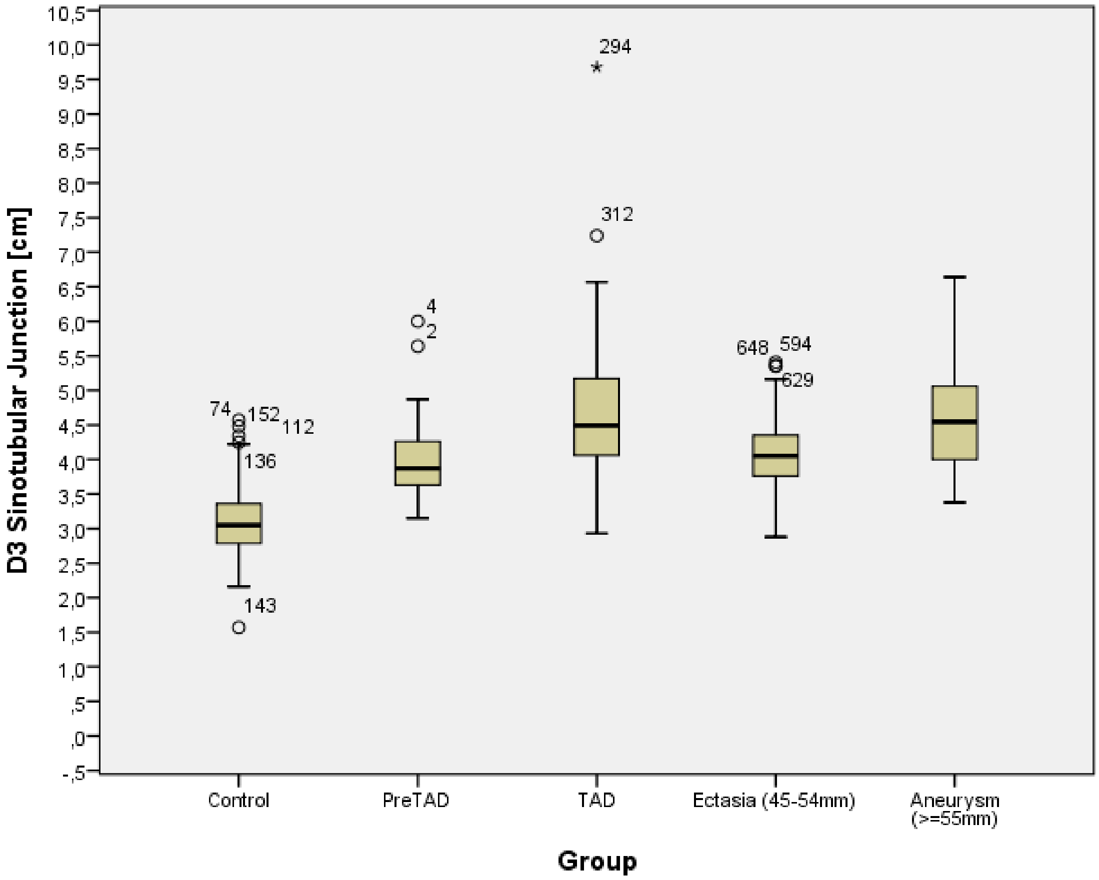


*Figure 17: Sinotubular junction diameter in cm.*

### 3.3.4 Ascending aorta

The ascending aortic diameter is of special interest in this study because it is the parameter traditionally used for indicating prophylactic ascending aorta replacement. Furthermore, the ectasia group and the aneurysm group were defined by this diameter, by 45-54 mm and by >55 mm respectively, and, last but not least, the ascending aorta is the segment which mostly contains the primary entry of a TAD.

The distribution of the ascending aortic diameter in the different groups is shown in figure 18. The control group, with a median diameter of 3.45 cm, showed the smallest diameters when compared to the rest of the groups ($p < 0.001$). The diameters of the ectasia- and the aneurysm groups were predefined.

The median ascending aortic diameter in the pre-TAD group was 4.27 cm (Q1-Q3 3.99-4.67 cm, range: 3.67-7.74 cm) and it was 4.99 cm (Q1-Q3 3.99-4.67 cm, range: 3.67-7.74 cm) in the TAD group, which were both significantly larger than the control group (p<0.001). However, 90% of the pre-TAD patients and nearly 70% of the TAD patients had ascending diameters <55 mm (Kruger T, 2018). By that, both, the TAD and the pre-TAD group were much more comparable with the ectasia than with the aneurysm group.

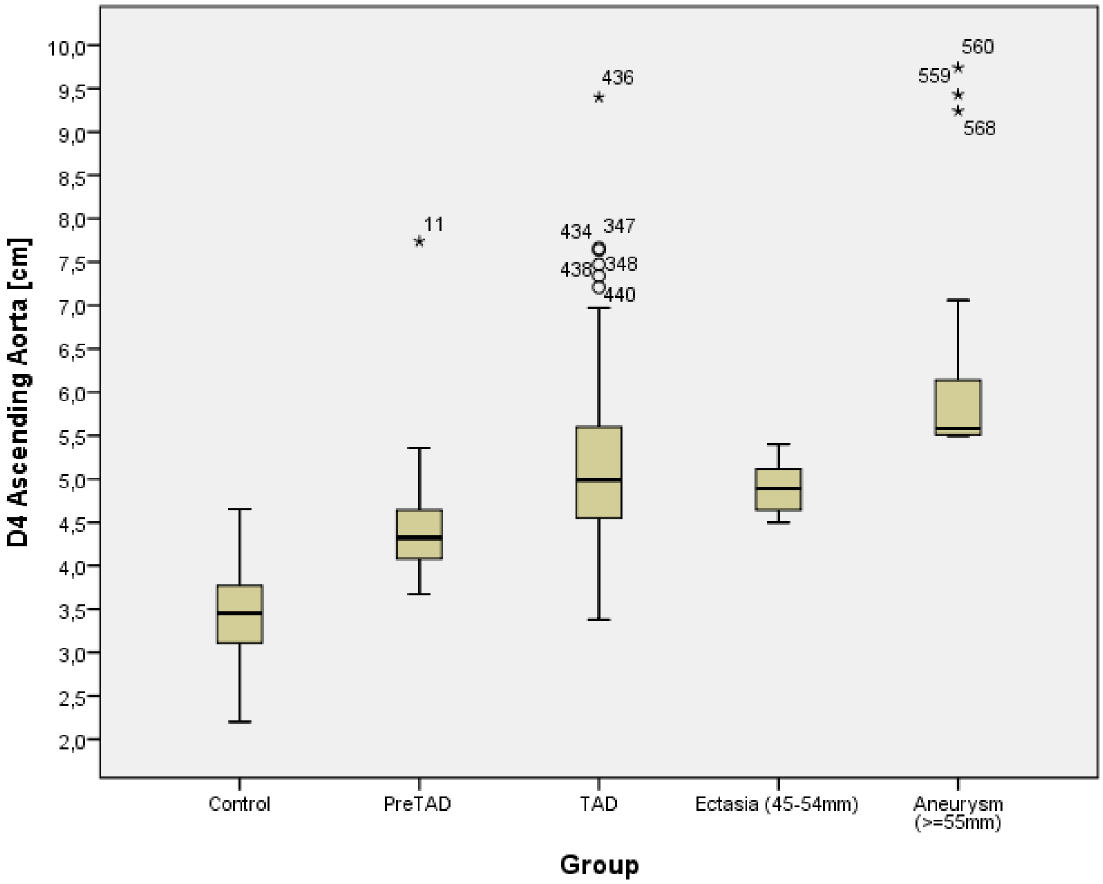


*Figure 18: Ascending aorta diameters in cm.*

In the aneurysm cohort, 5.58 cm was the median value and the maximum value was 9.5 cm.  Considering that none of the aneurysm patients suffered from TAD at the time of the CT-scan, other factors beside the ascending aortic diameter seem to play a role in the pathomechanism of TAD.

### 3.3.5 Brachiocephalic trunk

At the level of the brachiocephalic trunk, there was a significant difference in the median diameters between the control group (3.29 cm) and the rest of the groups (p-value <0.001). The ectasia group had a median value of 3.98 cm and showed a significant difference when compared to aneurysm (4.46 cm) and TAD (4.41 cm) group (p <0.001). However, when compared to the pre-TAD (3.96 cm) group, there was no significant difference (p-value 0.293). When compared to the aneurysm and TAD groups, the pre-TAD group showed a significant smaller median value (p-value < 0.001 and 0.005 respectively).

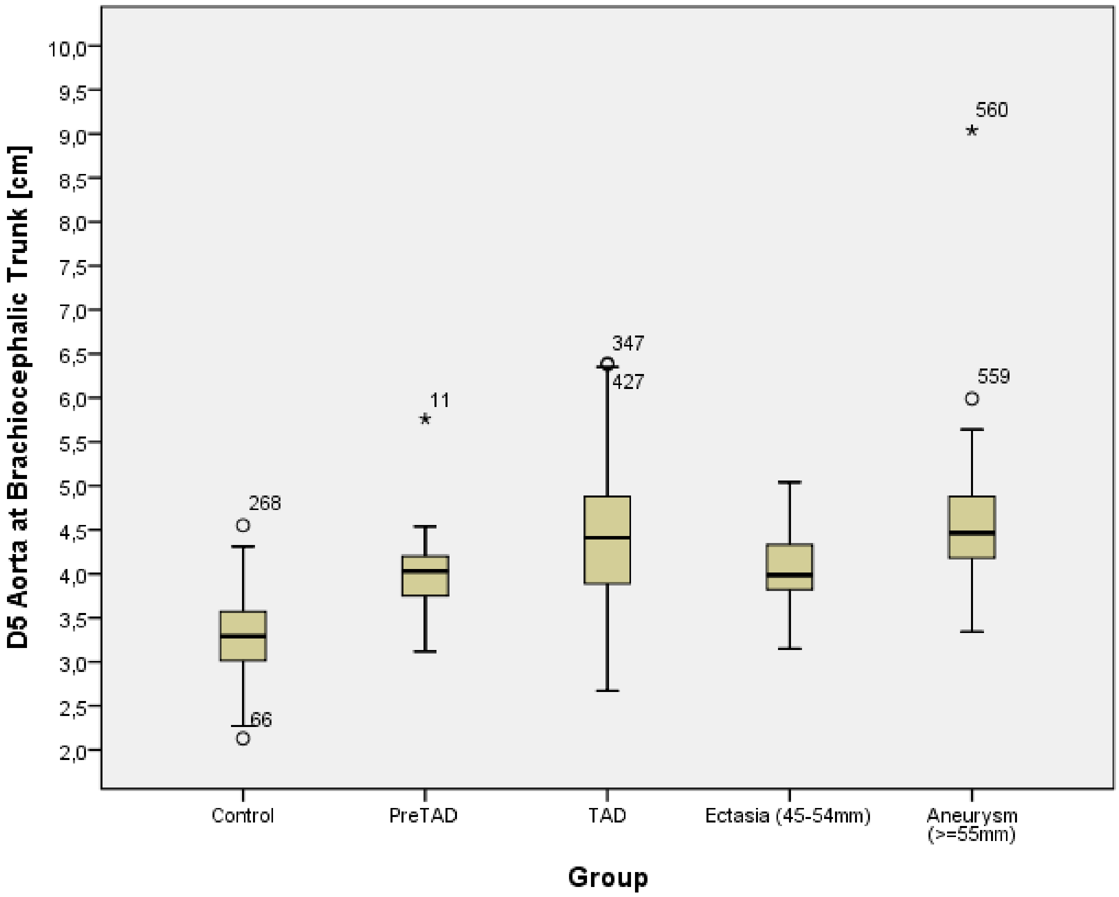


*Figure 19: Brachiocephalic trunk diameter in cm.*

The results are depicted in figure 19, it is evident that the TAD and aneurysm groups have the largest overall values. The graph, also, shows the similarity between the pre-TAD and ectasia groups.

### 3.3.6 Mid aortic arch

The diameter of the mid aortic arch was measured midway between the brachiocephalic trunk and the left subclavian artery. As shown in figure 20, at this level, there was a significant difference between the control group and the rest of the groups with p-value < 0.001. The patients in the ectasia group had a smaller median diameter when compared to the aneurysm (p-value < 0.001) and TAD (p-value < 0.001) groups but no significant difference when compared to the pre-TAD (p-value 0.656). The patients in the pre-TAD group showed a significant difference when compared to the aneurysm and TAD groups (p-value >0.05). However, the aneurysm and TAD groups showed no significant difference (p-value 0.238). In figure 20, it can be appreciated that the patients in the aneurysm group belonging to the 25%-ile (3.33cm) have similar diameters when compared to the 75%-ile of the pre-TAD (3.63 cm) and ectasia (3.51 cm).

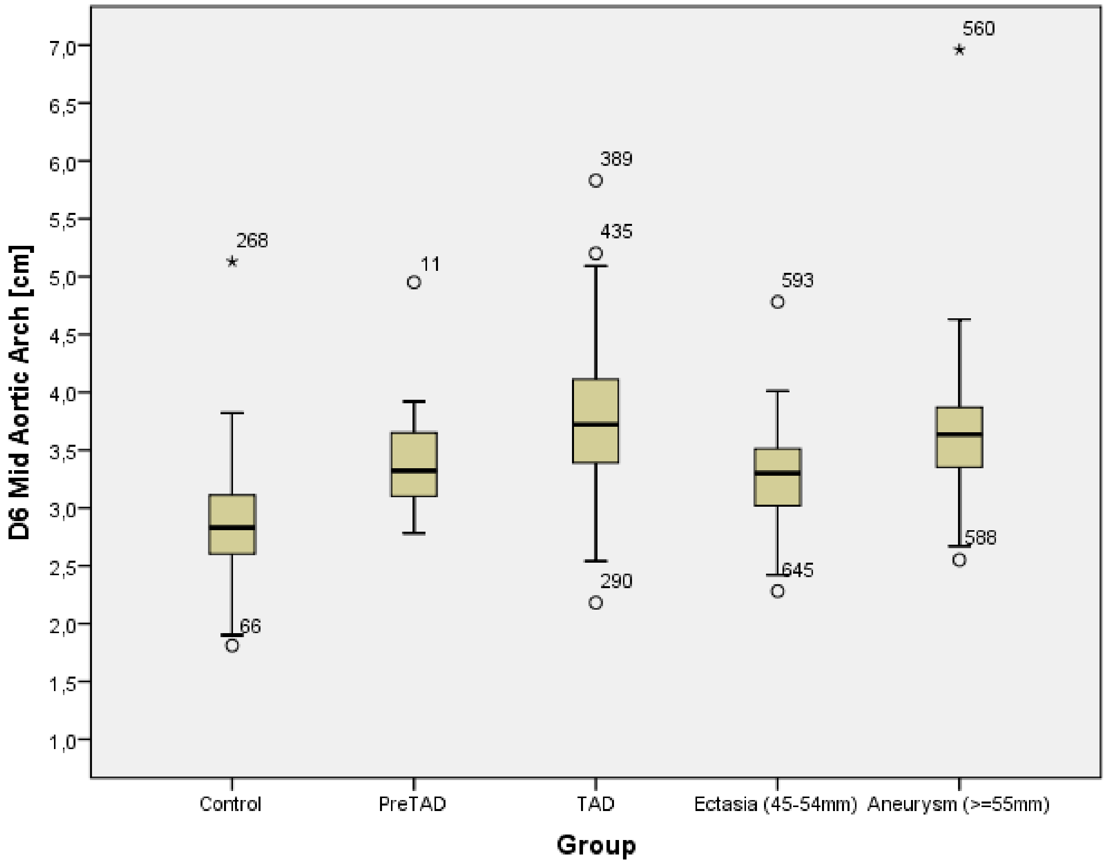


*Figure 20: Measures of the mid aortic arch in cm.*

### 3.3.7 Distal aortic arch

Figure 21 depicts the results of the distal aortic arch diameters in all the groups. With a median of 2.66 mm, the control group had significantly ($p<0.001$) smaller diameter compare to the other groups. There was no significant difference in the median diameters between the ectasia (2.95 cm) and pre-TAD (3.10 cm) groups (p-value >0.05). The aneurysm, pre-TAD and TAD groups showed no significant difference between each other.

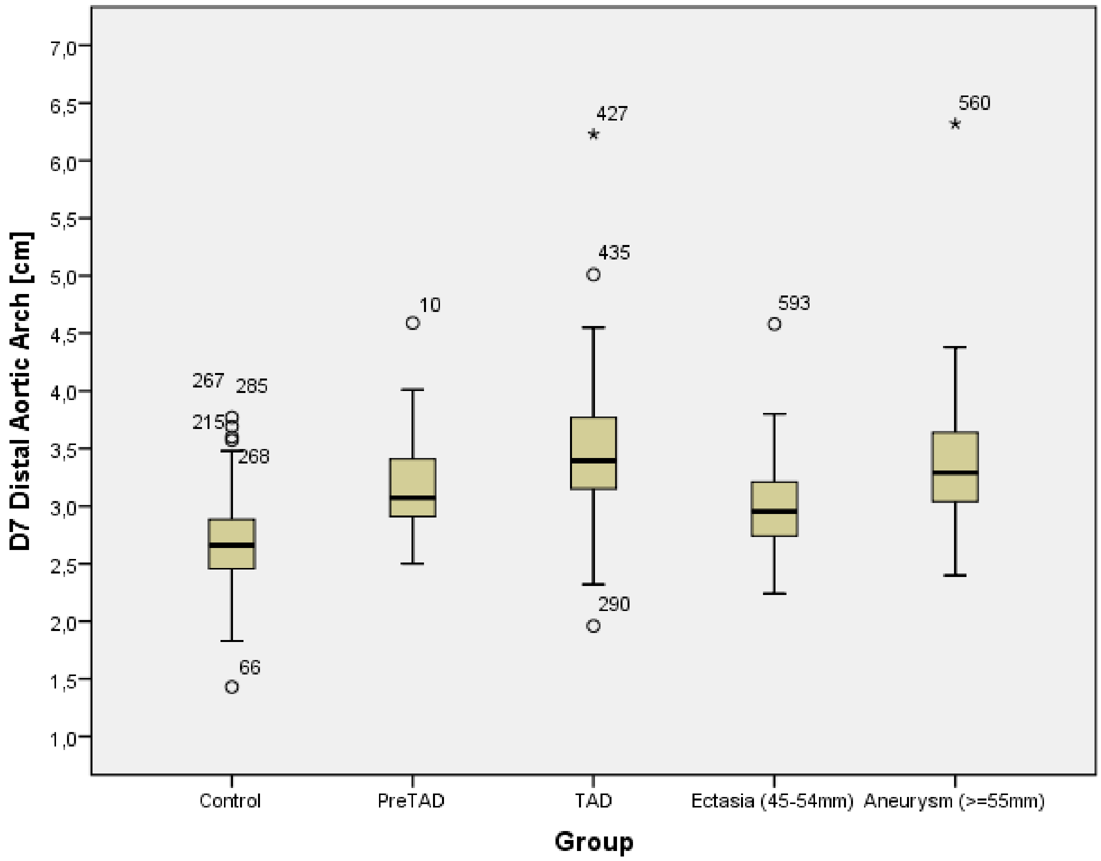


*Figure 21: Measures of the distal aortic arch in cm.*

### 3.3.8 Descending aorta

Figure 22 depicts the descending aortic diameters. The patients in the control group showed a median diameter of 2.57 cm, which is clearly (p-value <0.001) smaller compared to the rest of the groups. The patients in the ectasia group had a median diameter of 2.88 cm, which, compared to the pre-TAD group (3.05 cm), showed no significant difference; whereas compared to the TAD (3.26 cm) and aneurysm (3.40 cm) groups it was significantly smaller (p-value <0.001).

Between the aneurysm, pre-TAD and TAD groups, there was no difference with respect to descending aorta diameters. Figure 22 shows a greater number of outliers than the other diameters depicted so far. The group showing the greatest amount was the TAD group, this may because the TAD began in the ascending aorta, and in most cases, reached at least the descending aorta, enlarging the diameter.

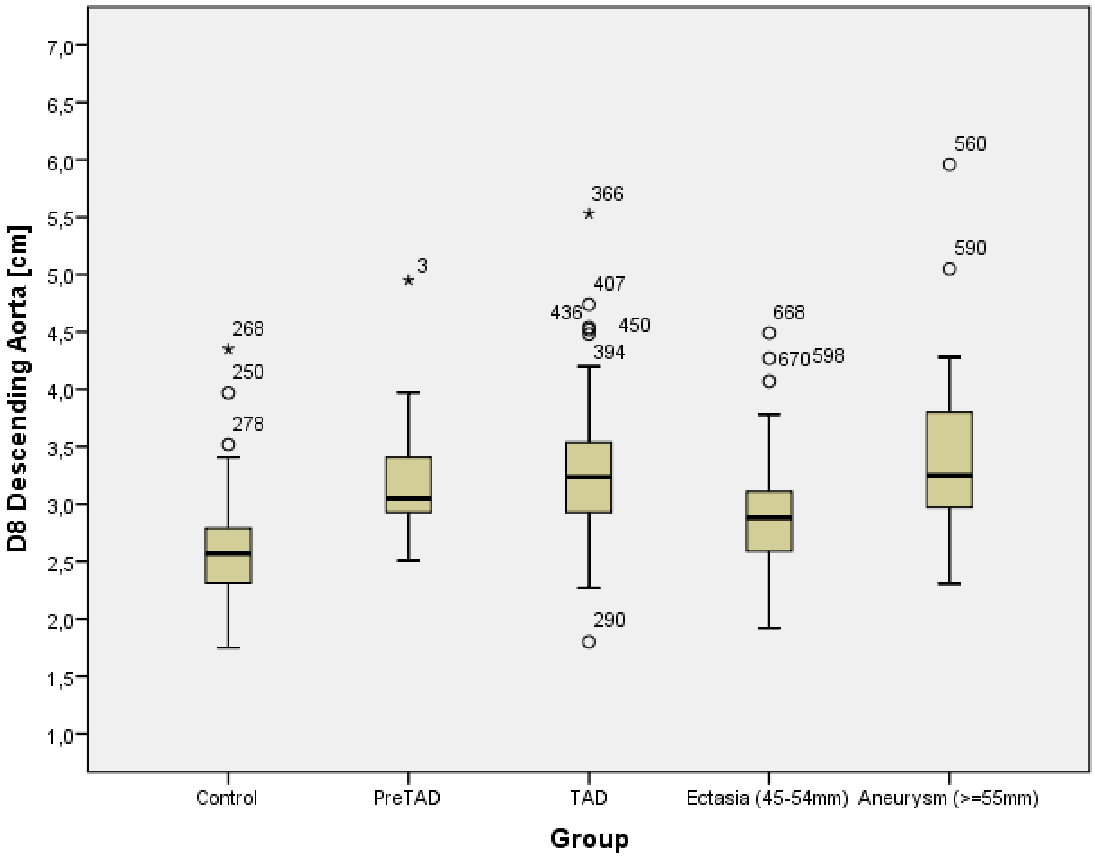


*Figure 22: Descending aorta diameters in cm.*

### 3.3.9 Celiac trunk

At the height of the celiac trunk, the differences between the groups are smaller but still significant. The diameters are presented in figure 23. The control group with a median descending aorta diameter of 2.22 cm at the height of the celiac trunk was significantly smaller when compared to the rest of the groups. The ectasia group had a median diameter of 2.48 cm; when compared to the pre-TAD group (2.63 cm), it showed no significant difference. When compared to the aneurysm- (2.85 cm) and the TAD group (2.76 cm), the ectasia group showed significantly smaller diameters. When comparing the aneurysm, pre-TAD and TAD groups there was no significant difference between them. Like in the measurement of the descending aorta, when measuring the celiac trunk, it is evident, that there is a relevant number of outliers, especially in the control, aneurysm and TAD groups. Like in the previous measurement, the patients in the TAD group in whom the dissection involved the aorta all the way to the abdominal segment and the iliacal vessels (DeBakey I), the diameter was greater than in those with dissections restricted to the ascending aorta (DeBakey II). In the aneurysm and the control group, the number of outliers found was due to the incidential finding of abdominal aortic aneurysms.

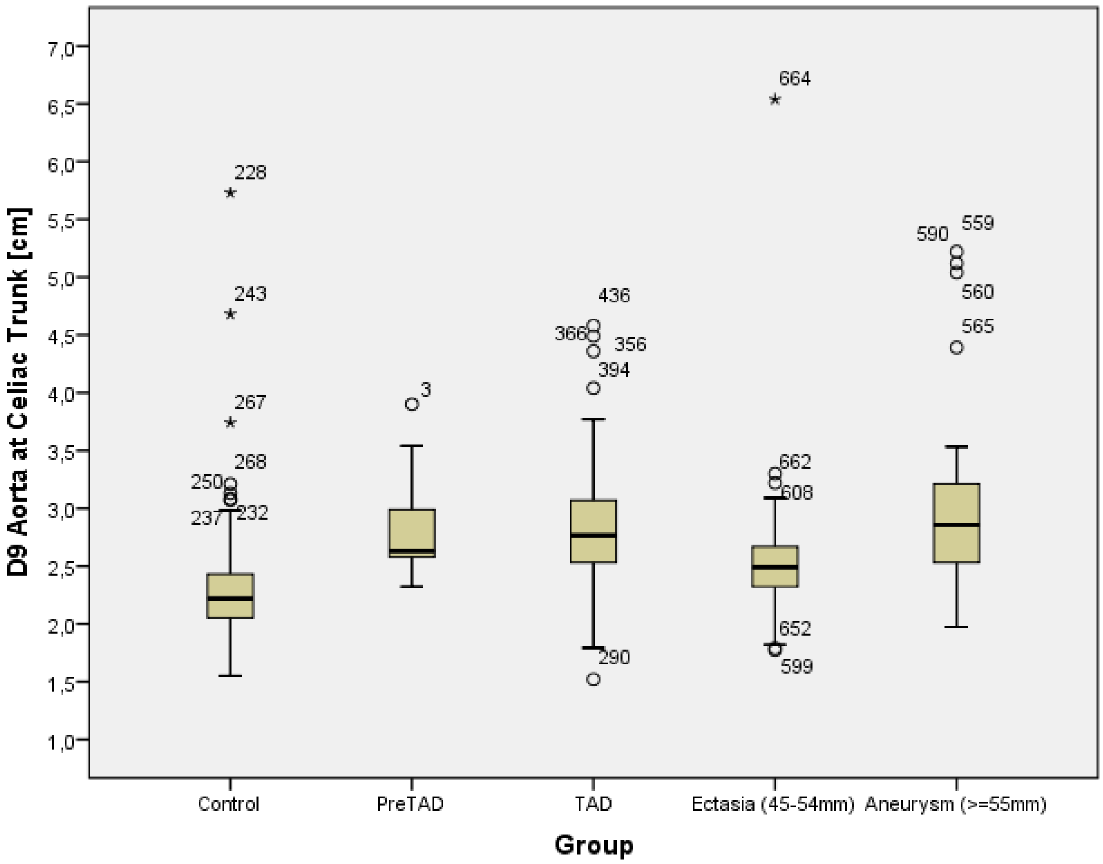


*Figure 23: Celiac trunk diameter in cm.*

### 3.3.10 Abdominal aorta

At the height of the abdominal aorta, the control group again had the smallest median diameter (1.77 cm). Unlike the other measurements, when comparing the ectasia group (2.01 cm) to the pre-TAD (2.07 cm) and aneurysm (2.05 cm) groups there was no significant difference in the median diameter, only in comparison to the TAD group (2.20 cm), the difference reached significance ($p < 0.05$). When comparing the aneurysm, pre-TAD and TAD groups, there was no significant difference between the median diameters at this landmark.

Again, the number of outliers especially in the control group is noteworthy, which is due to incidental findings of abdominal aortic aneurysms.

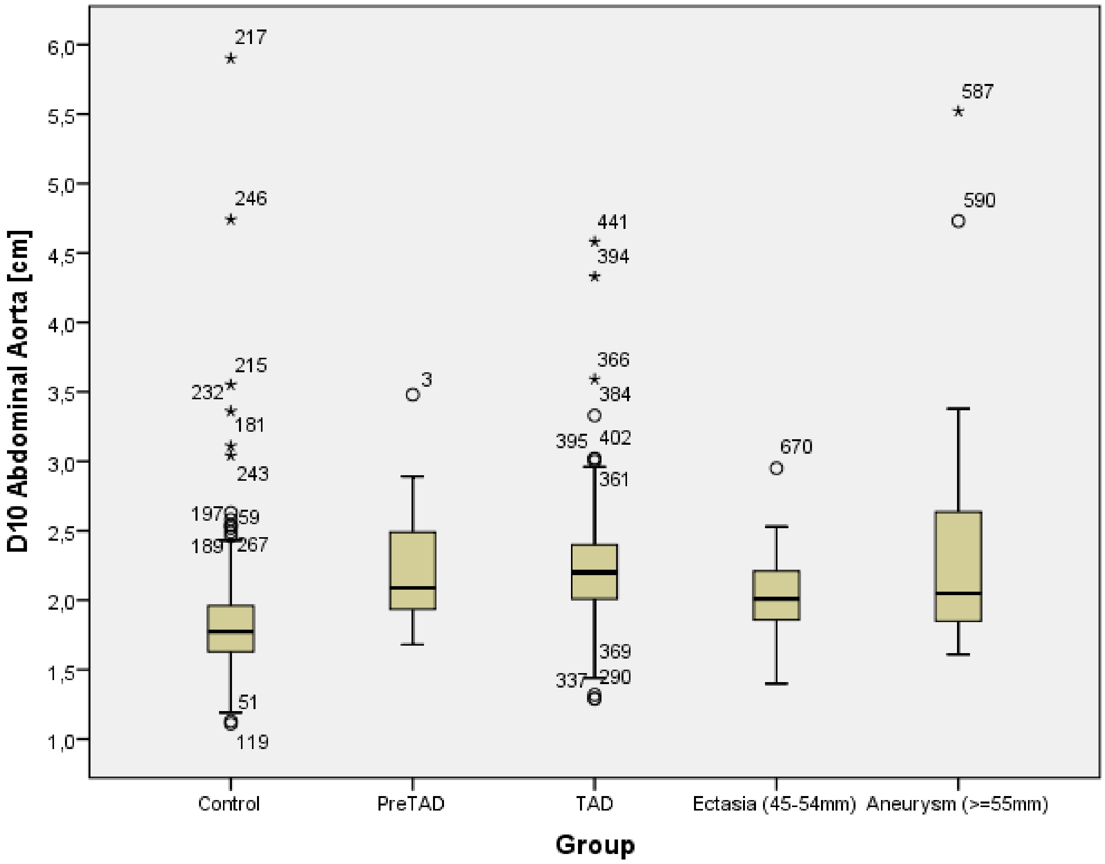


*Figure 24: Abdominal aorta diameter in cm.*

### 3.3.11 Aortic bifurcation

The last diameter was measured at the height of the aortic bifurcation. In the control group, the trend did not change, it was the smallest median diameter when compared to the rest of the groups (1.66 cm); the difference, was statistically significant. When comparing the rest of the groups, there was no significant difference in the measure of the median diameters between them, ectasia (2.00 cm), aneurysm (1.94 cm), pre-TAD (1.98 cm) and TAD (2.03 cm) groups. Again, the control group shows a large number of outliers when compared to the rest of the groups, due to incidental findings of abdominal aneurysms.

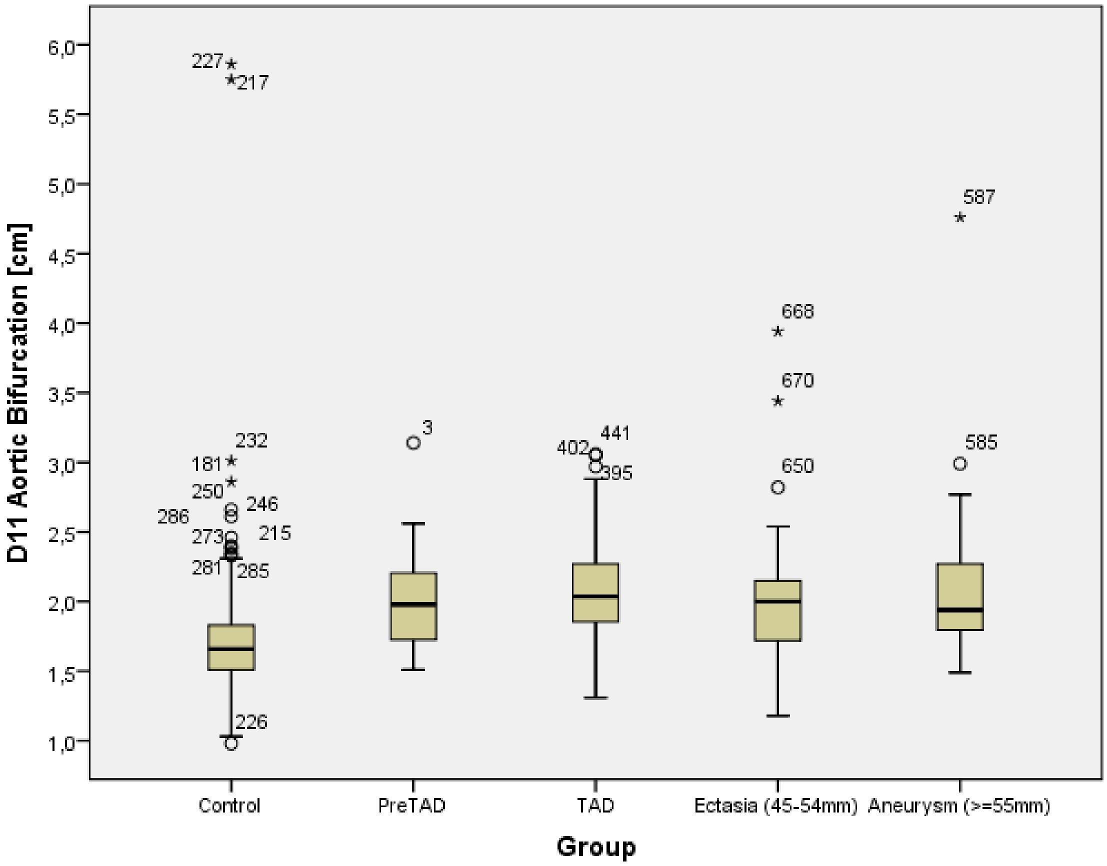


*Figure 25: Aortic bifurcation diameter in cm.*

### 3.4 Aortic Lengths

We measured the aortic segments´ length. Aortic segments were defined by the same landmarks as aortic diameters (Chapter 2.5). We utilized the same procedures to measure the parameters and to statistically compare the groups.

#### 3.4.1 Aortic Root Length

The aortic root comprised the distance between the aortic valve and the sinotubular junction. Unlike the aortic diameter measurements, in the aortic root length, there was no significant difference between the control, aneurysm and pre-TAD groups, the median values were 2.27 cm, 2.48 cm and 2.41 cm respectively (p-value > 0.01); the ectasia and TAD groups showed a significant difference when compared to the control group with median values of 2.53 cm and 2.56 cm, respectively ($p < 0.001$). The comparison of the median lengths of the aortic root between the ectasia vs. aneurysm and ectasia vs. TAD groups, showed no significant difference (p-values of 0.699 and 0.968). When comparing the ectasia and the pre-TAD groups there was a significant difference (p-value 0.047) with the ectasia group having the larger length. At last we compared the aneurysm, pre-TAD and TAD groups between each other and there was no significant difference to be seen, with p-values of > 0.05 in all cases. The results are represented in figure 26, it is evident that the TAD and aneurysm groups show the greatest number of outliers among the groups (Kruger T, 2018).

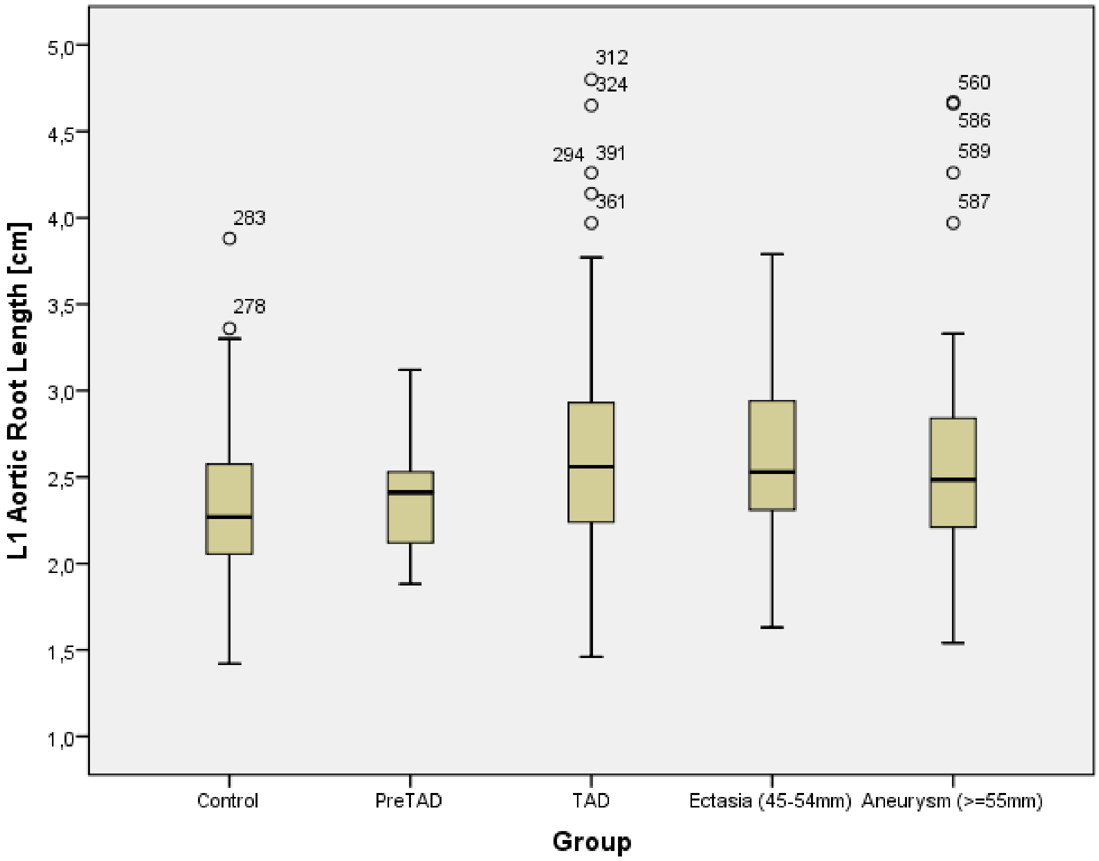


*Figure 26: Length of the aortic root in cm.*

### 3.4.2 Ascending aorta length

The length of the ascending aorta was of utmost interest in the actual study. It was defined as the distance from the sinotubular junction to the offspring of the brachiocephalic trunk.

The median length of the control group ascending aorta was significantly shorter compared to all other groups (p-value < 0.001) (Kruger T, 2018). The control group showed a median ascending aortic length of 6.9 cm with a minimum value of 3.71 cm and a 75th percentile at 7.55 cm. The ectasia group had a median length of 8.73 cm, a minimum value of 5.20 cm and a 75th percentile of 9.47 cm; when compared to the pre-TAD group, with a median value of 8.43 cm, minimum 5.50 cm and 75th percentile of 9.06 cm, there was no significant difference (p = 0.160). The aneurysm group showed the largest values, when compared to the rest of the groups, a median value of 9.75 cm, minimum value of 6.33 cm and a 75th percentile of 10.6 cm. It showed a significant difference when compared to all the groups except the TAD group (median 9.75 cm, minimum 3.46 cm and 75th percentile 9.91 cm) (Kruger T, 2018).

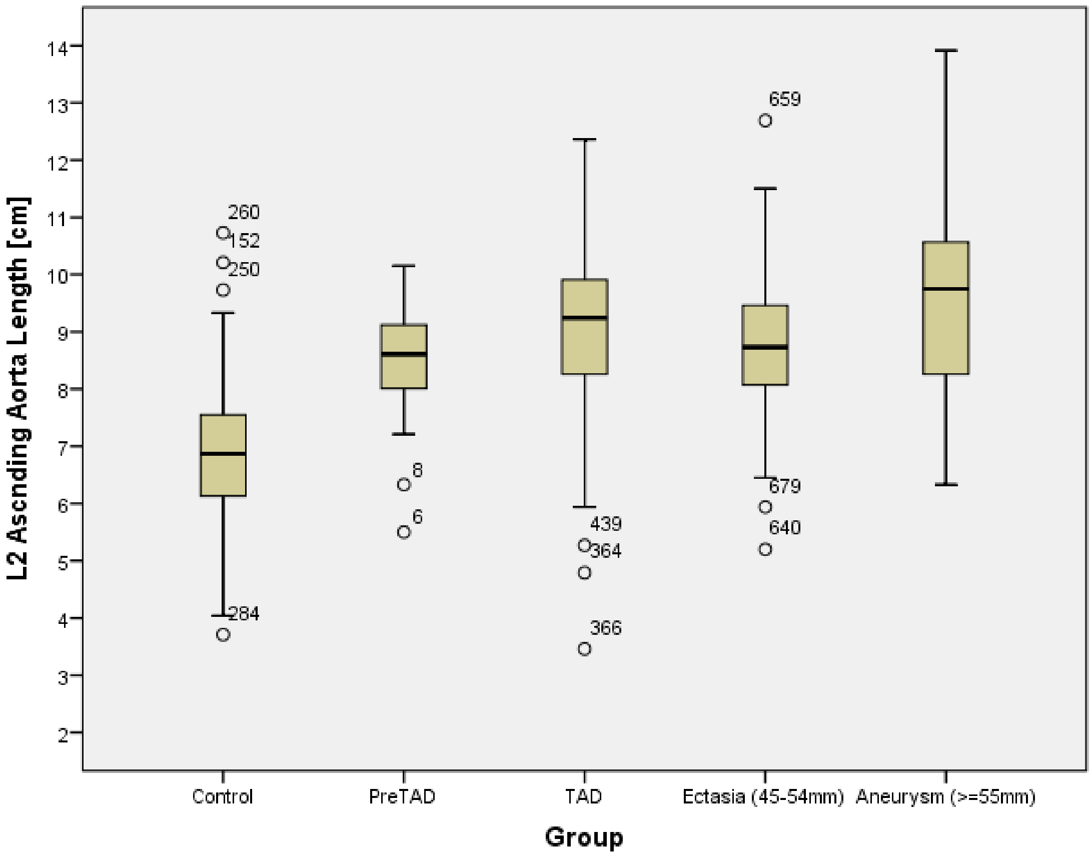


*Figure 27 Ascending aortic length in cm.*

As seen on figure 27, there are two pairs of groups that show similar values. The first pair is the TAD and aneurysm groups, the second the pre-TAD and ectasia groups. This supports the premise, that as the ascending aorta increases in width, it also increases in length. It is noteworthy that the greatest lengths and diameters of the ascending aorta occurred in the aneurysm group, in patients who at the time of the CT-scan did not suffer from a TAD, rather than the patients in the TAD group. It is also noteworthy that even though there is a significant difference between the pre-TAD and TAD groups in the ascending aorta in terms of length, the range of the length measurements in the pre-TAD group is smaller than that of the patients in the ectasia group; the values of the ectasia group relate to those of the TAD group (Kruger T, 2018).

### 3.4.3 Complete ascending aorta length

We measured the aortic root and the ascending aorta individually (Chapters 3.4.1. and 3.4.2.). However, we came across the problem that in some cases it is difficult to exactly identify the STJ because it is flattened and not tallied. Especially in aneurysmatic and dissected aortas (see Chapter 3.3.3), the distinct division of the aortic root and the ascending aorta may not be possible. For this reason, we decided to calculate the distance from the aortic valve to the brachiocephalic trunk and labeled it as complete ascending aorta (L1+L2) (Kruger T, 2018). The patients in the control group showed with a median of 9.2 cm the shortest lengths, with 75% of the values being under 10.01 cm; they showed a significant difference when compared to all other groups ($p < 0.001$). The pre-TAD group (median 10.67 cm and 75-percentile 11.63 cm) showed the smallest length values amongst the pathological groups, and although the difference to the ectasia group formally reached statistical significance ($p = 0.05$), the medians and the distributions appear comparable (see figure 28). The median length of the complete ascending aorta in the ectasia group was 11.31 cm and 75% of the values fell under 12.15 cm. The aneurysm and TAD groups showed the largest complete ascending aorta length values with medians of 12.19 cm and 11.18 cm respectively, and the difference was insignificant ($p = 0.232$). By the way, when compared to the aneurysm and TAD groups, the pre-TAD group showed a significant difference with smaller values than both groups (p-values $< 0.05$) (Kruger T, 2018).

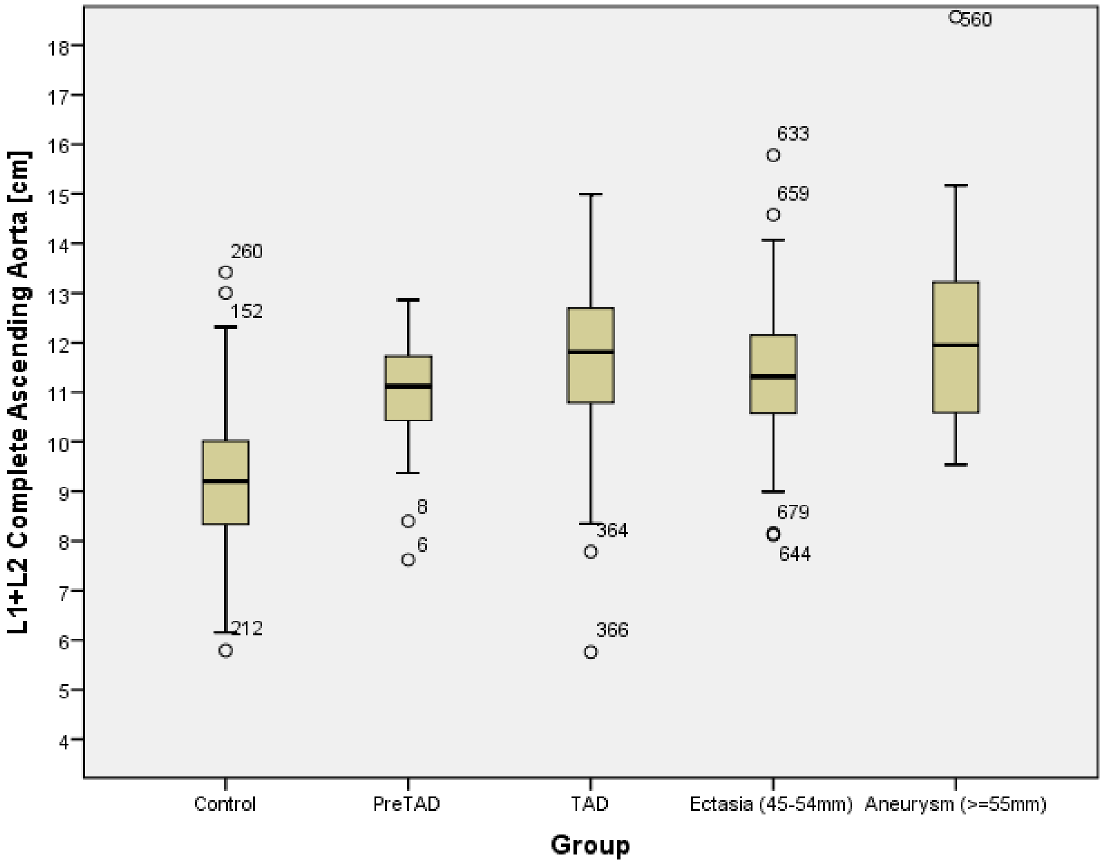


*Figure 28: Complete ascending aortic length measurements in cm.*

### 3.4.4 Aortic arch length

The aortic arch was measured from the offspring of the brachiocephalic trunk to the point exactly distal of the subclavian artery, comprising all supraaortic branches. Figure 29 depicts the length of the aortic arch in the different groups, and it is evident that the differences between all the groups are not as large as in the more proximal segments.

When comparing the control group to the rest of the groups, the control group showed a significantly smaller median length of the aortic arch (3.64 cm) (p-value < 0.01) (Kruger T, 2018). When comparing the ectasia group (4.35 cm) to the rest of the groups, there was no significant difference compared to the aneurysm (4.69 cm), pre-TAD (3.94 cm) and TAD (4.39 cm) groups p-value >0.05 in all cases. Between the aneurysm, pre-TAD and TAD group there was no significant difference in aortic arch length. As shown in the graph, the TAD and aneurysm groups have the greatest values, and again, the aneurysm group has a greater length at the 75th percentile mark, when compared to the TAD group (Kruger T, 2018).

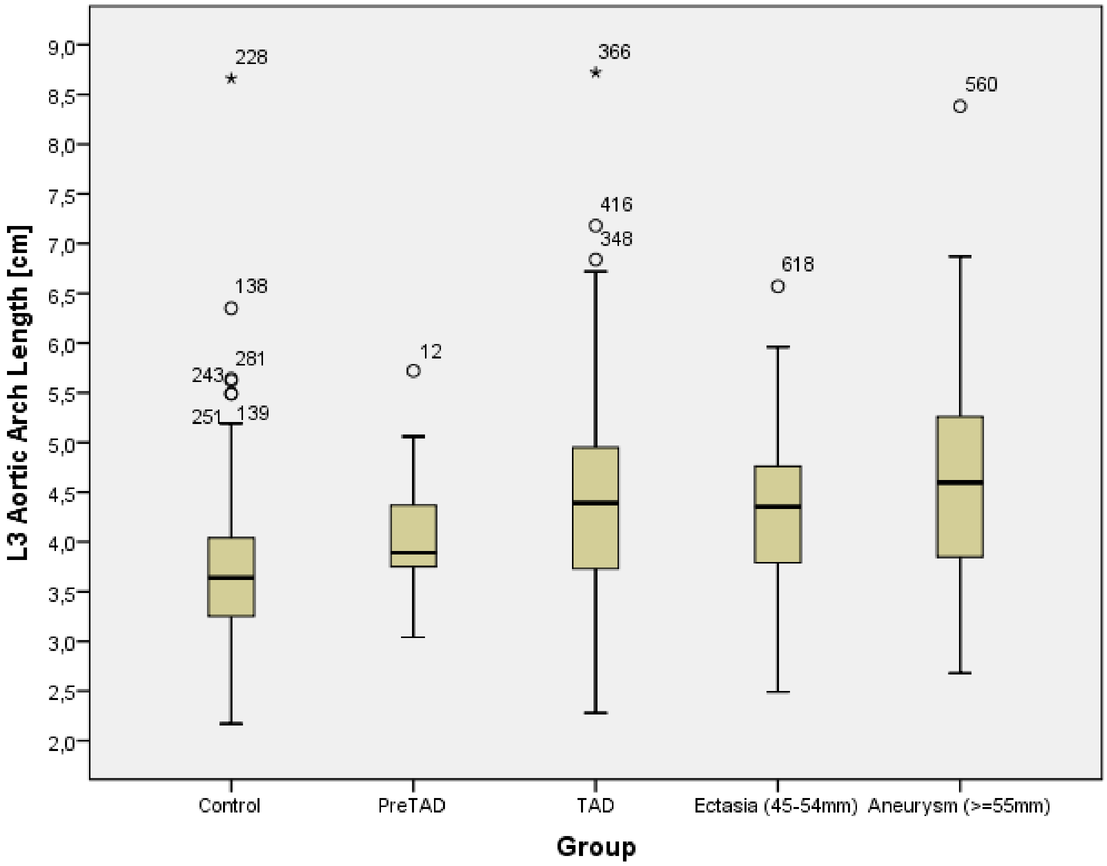


*Figure 29: Aortic arch length in cm.*

### 3.4.5 Distal aortic arch length

The distal aortic arch length was measured from distal of the subclavian artery to the pulmonary artery bifurcation. The control group, again, showed the smallest median values (6.13 cm) when compared to the rest of the groups (p-value < 0.001). The ectasia group had a median value of 7.56 cm. When compared to the pre-TAD (7.85 cm) and TAD groups (7.29 cm), there was no significant difference (p-value > 0.05). The aneurysm group had a median length of 8.30 cm, it showed a significant difference when compared to the ectasia (p-value = 0.003) and TAD groups (p-value = 0.001). The pre-TAD group showed no significant difference when compared to the aneurysm and TAD groups (p-value >0.05).

As seen in figure 30, without the outliers seen in the control and TAD groups, the aneurysm group had by far the greater lengths when compared to the rest of the groups. When comparing all the aortic segments measured, the ascending aorta and the distal aortic arch were the segments that showed the greatest morphologic change (Kruger T, 2018).

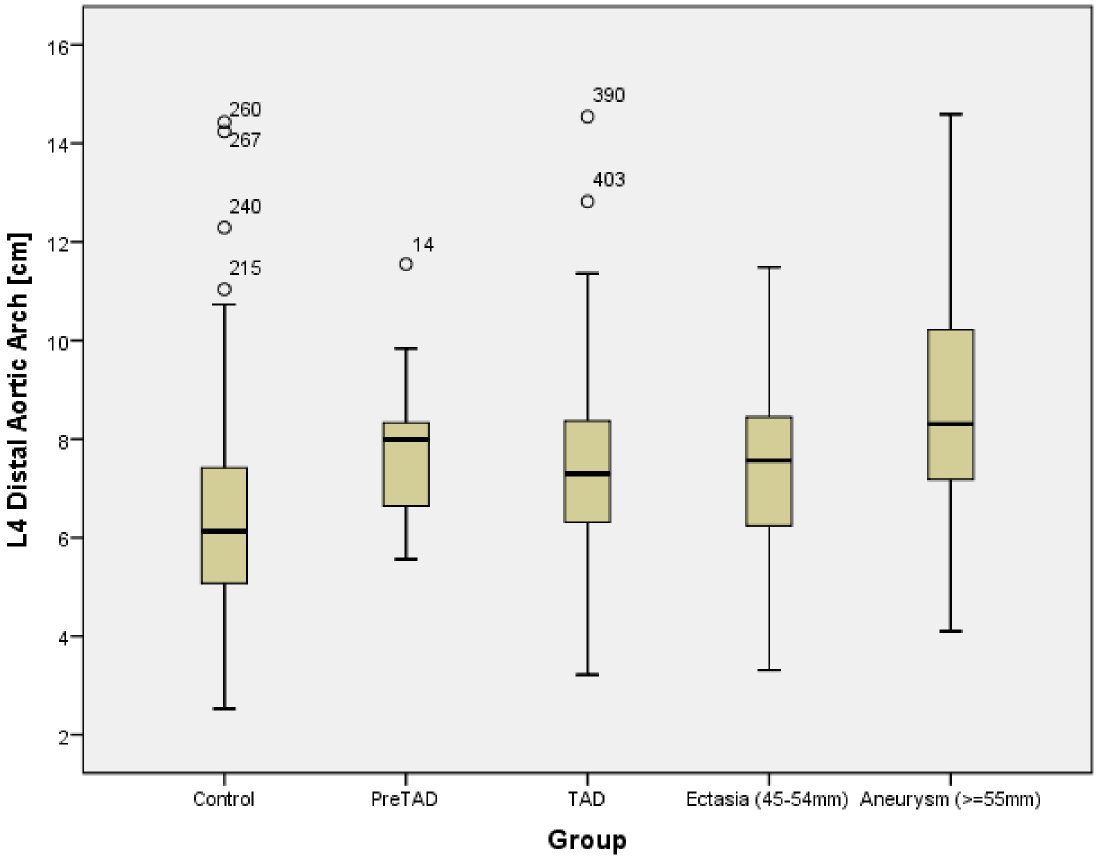


*Figure 30: Distal aortic arch in cm.*

### 3.4.6 Complete Aortic Arch Length

As with the complete ascending aorta (Chapter 3.4.3), we combined segments L3, aortic arch, and L4, distal aortic arch, to a combined segment complete aortic arch by simply adding the values L3 and L4. Figure 31 shows the length values, and a substantial and statistically significant ($p<0.001$) length difference between the control group (median = 9.8 cm) and all the pathological groups becomes evident. However, among the pathological groups there was no significant difference with respect to this parameter. Again, the outliners in the control group must be mentioned, showing that healthy individuals incidentally do have strikingly elongated aortic arches (Kruger T, 2018).

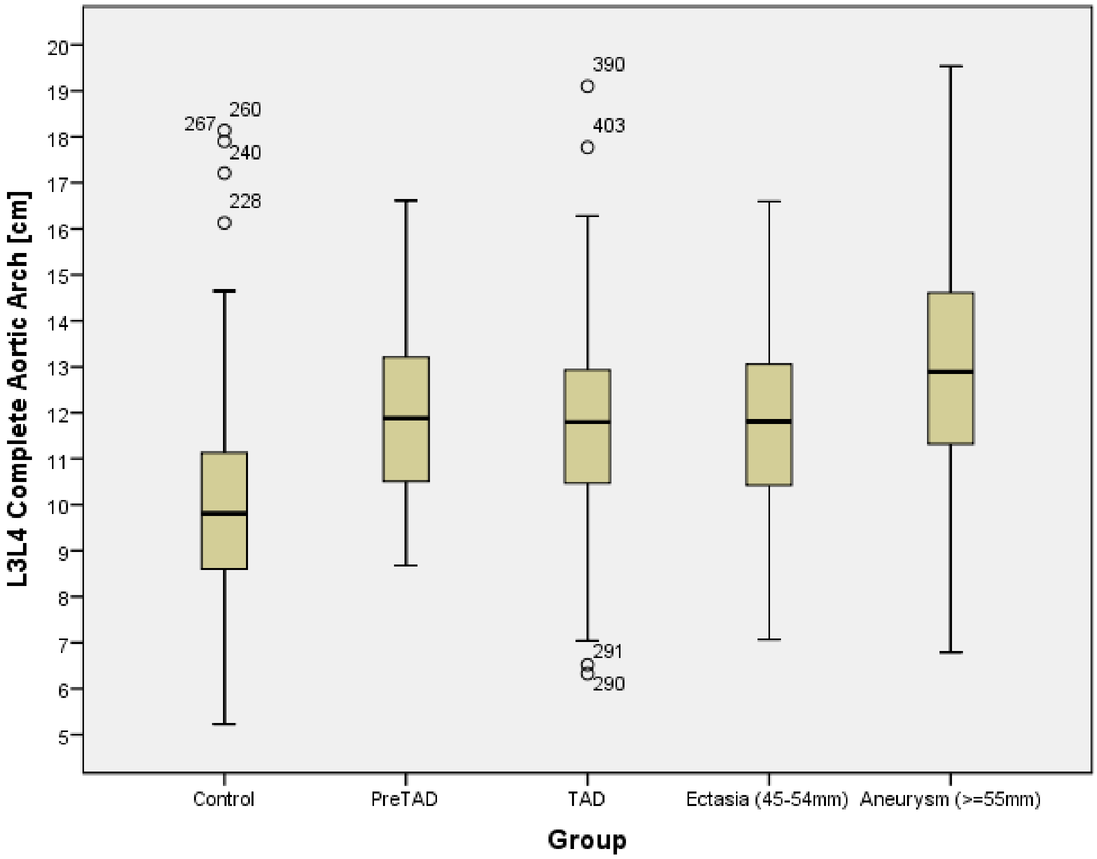


*Figure 31: Complete aortic arch measurements in cm.*

### 3.4.7 Descending aorta

The descending aorta was measured from the pulmonary artery bifurcation to the celiac trunk. In this segment, the median lengths were similar with no significant differences between groups (Figure 32). The median lengths of the descending aorta were the following: Control group 17.47 cm, Ectasia group 17.38 cm, Aneurysm group 17.99 cm, pre-TAD group 18.20 cm, and TAD group 18.59 cm (Kruger T, 2018).

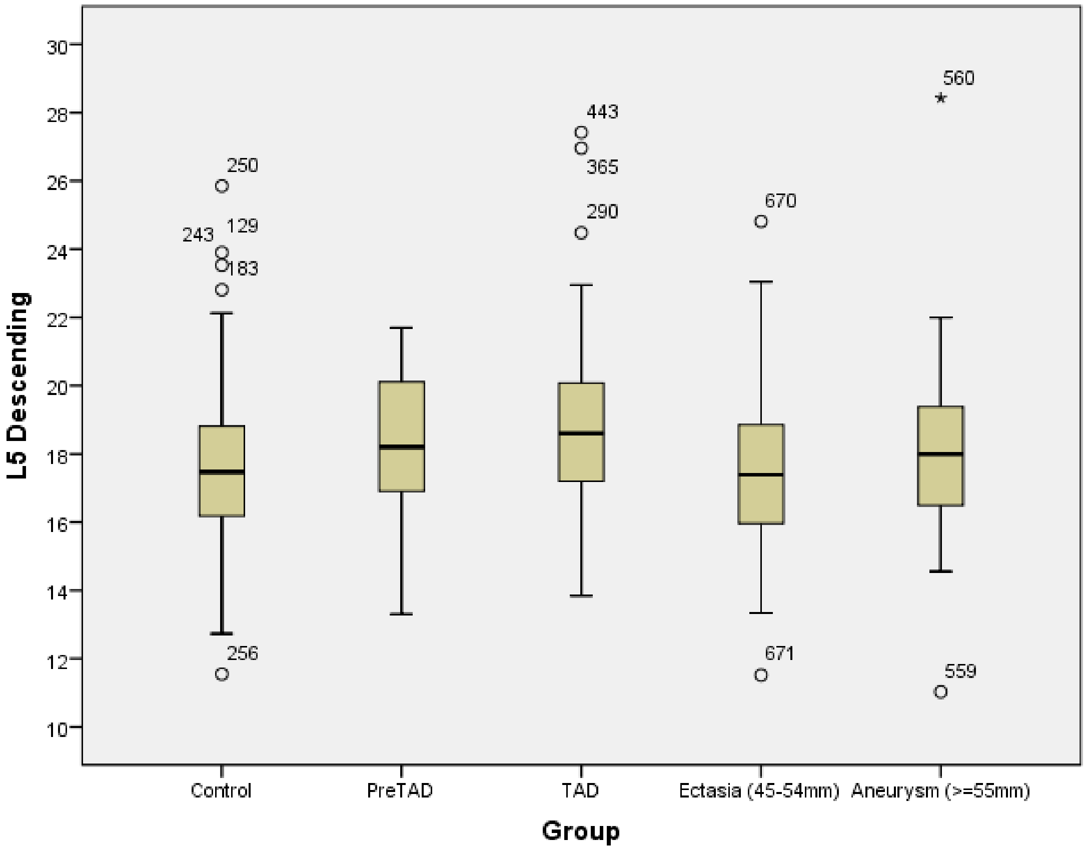


*Figure 32: aortic length measurements in cm.*

### 3.4.8 Abdominal aorta

The abdominal aorta was measured from the celiac trunk to the aortic bifurcation. Like in the descending aorta, the differences between the medians of the different groups were not as large when compared to other segments. The control group showed a statistically significantly smaller median when compared to the rest of the groups (p-value < 0.05). Between the rest of the groups there was no significant difference when comparing the median values. The TAD group showed the highest values and the pre-TAD group showed the smallest range of values among all the groups. The results are depicted in figure 33. However, even if statistically significant, comparing the distributions of the abdominal aorta length reveals no striking differences between the control group and the pathological groups (Kruger T, 2018). The outliers especially in the control group represent individuals with incidentally found abdominal aortic aneurysms and ectasias (Kruger T, 2018).

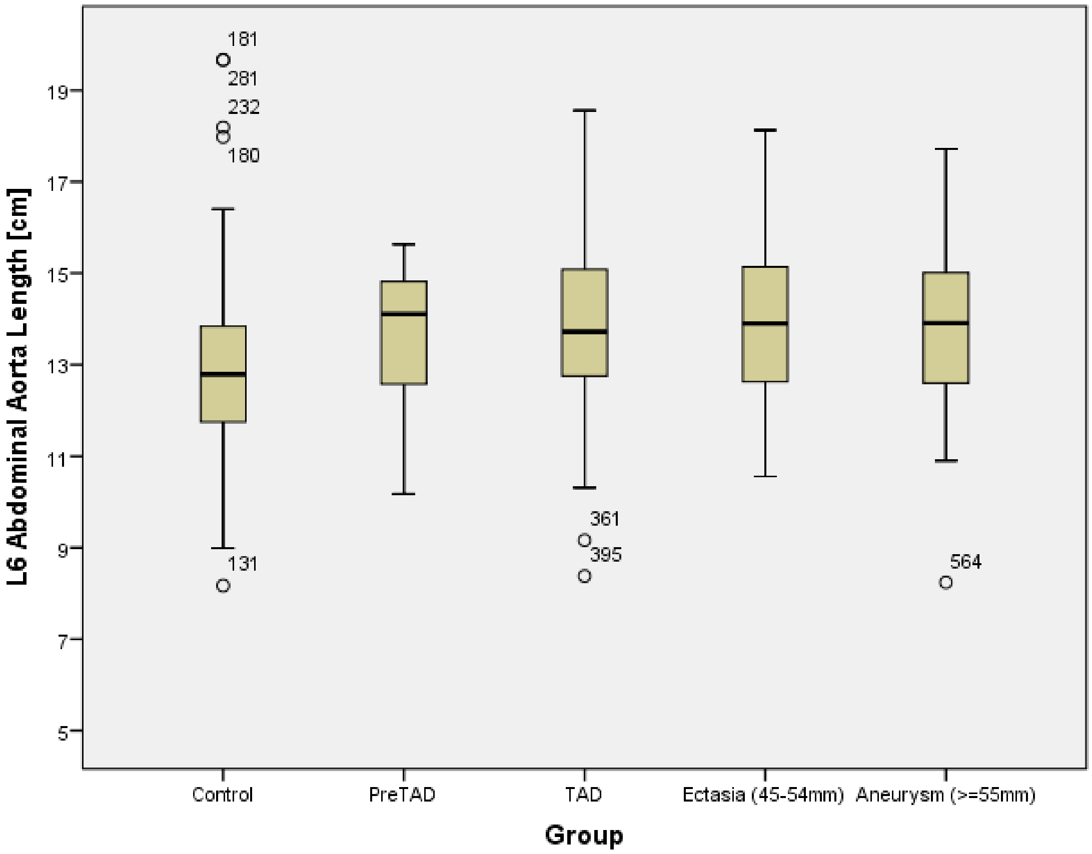


*Figure 33: aorta length measurements in cm.*

### 3.5. Arch morphology

Aside from the diameter and length of the different aortic segments, we also classified the patients depending on the type of aortic arch (Nathan et al., 2011). Type I arch represents the “normal” configuration of the arch, Type II arch the elongated, “gothic” configuration where the inflection point is distal of the left subclavian artery. When comparing the frequencies of the different aortic arch types between the groups, the control group showed a significantly lower type 2 arch frequency (23.17% and p-value < 0.001) compared to the pathological groups (Table 4). In the pathological groups the frequency of Type II arches ranged from 45% up to 62% with the highest values in the aneurysm group (Kruger T, 2018). There was no significant difference when comparing the pathological groups (p-value > 0,05). The distribution of Arch morphology is similar that of complete aortic arch length (See chapter 3.4.6) (Kruger T, 2018).

*Table 4: Type 2 aortic arch in the cohorts.*

| | **Control group** | **Ectasia group** | **Aneurysm group** | **Pre-TAD** | **TAD** |
|---|---|---|---|---|---|
| N | 259 | 102 | 38 | 21 | 166 |
| Number of type 2 Arch | 60 | 46 | 23 | 13 | 75 |
| Type 2 Arch in % | 23.17 | 45.10 | 60.53 | 61.91 | 45.18 |

## 4. Discussion

### 4.1.1 Comparability of the groups and the distribution of hypertension

The objective of this study was to analyze different aspects of the aortic morphology. It was necessary to generate comparable study groups and to ensure that anthropometric or demographic differences would not bias the outcome. Sex, age, height, weight, BMI and BSA were documented in all patients, and the distributions were compared between groups. Additionally, we recorded and documented which of the patients was previously diagnosed with hypertension and which of them had massive hypertension, defined as hypertension under medication with 3 or more different antihypertensive drugs (Mancia et al., 2013). Importantly, for the massive hypertension definition, diuretics were not included as an antihypertensive drug group, by doing this, we avoided patients receiving a maximal heart insufficiency therapy to be classified in this group.

Age distribution in the patients recruited in the emergency room differed from that of TAD patients. This is not surprising because trauma has a high incidence in patients in their second and third decade. The youngest TAD-Patient was 23 years old. Consequently, we excluded all Patients younger than 23 years from the control group. This is an established method in retrospective studies, known as age-homogenization.

Subsequently, we found no significant differences with respect to any of the aforementioned anthropometrical parameters between all the study groups. This structural comparability of the groups is the basis to perform meaningful comparative analysis with respect to aortic morphology.

Hypertension is well established risk factor for aneurysm and acute aortic syndromes (Elefteriades, 2008) (Erbel et al., 2014) (Kouchoukos N, 2013) (Kruger et al., 2016a, Kruger et al., 2017). This became evident in our analysis as well: In the groups in which there was a pathological aortic diameter i.e. ectasia, aneurysm, pre-TAD and TAD, most patients suffered from hypertension, whereas in the control group the percentage was clearly lower. The same pattern could be seen in patients with massive hypertension; the groups with the highest percentages were the aneurysm and TAD group. Our results with respect to the distribution of hypertension are in compliance with the literature (Erbel et al., 2001, Erbel et al., 2014).

### 4.1.2 Curved multiplanar reformats

In the clinical setting of suspected acute aortic syndrome, the diagnostic method of choice because of availability, acquisition-speed, sensitivity, specificity and low cost is the CTA (Agarwal et al., 2009) (Bhatia et al., 2010, Elefteriades et al., 2015, Erbel et al., 2014). It provides reliable diagnosis of TAD and aneurysm in conventional, two-dimensional transversal, frontal and sagittal projections of the CTA data. However, in these projections, it is difficult to accurately measure the aortic diameter and length, especially in curved segments. Inexact orthogonal slicing of the aorta results in oval projections leading to potential overestimation of the diameter. Imprecise placement of linear measuring tools in circularly shaped aortic projections leads to underestimation of the diameter. The measurement of aortic segments´ lengths in frontal or sagittal projections leads to systematic underestimation of the real values, because one dimension is always neglected in the pictures (“depth”).

These sources of error are overcome by three dimensional techniques of aortic analysis, these however require post-acquisition processing with specialized software.

The curved multiplanar reformation (CPR) technique uses a straight line (central line) traced in a non-linear structure in all 3 projections (sagittal, transversal and coronal). Subsequently, the structure (aorta) is stretched out and reconstructed as a linear structure (Makaryus A, 2016). This facilitates the exact measurement of length along the central line in complicated curved structures such as blood vessels and therefore provides accurate measurements of the aortic segments needed (Bhatia et al., 2010, Erbel et al., 2014, Makaryus A, 2016, Lell et al., 2006). Additionally, true short axis views of the structure (aorta) may be reconstructed, enabling the exact measurement of diameter. Measuring the perimeter and secondarily calculating the diameter further increases exactness of diameter measurement. The Osirix software (Pixmeo, Switzerland), we used in this study, was developed and validated to perform the aforementioned reconstructions and measurements in the clinical setting (Rosset et al., 2004).

### 4.1.3 Pathophysiology of aortic aneurysm and dissection

The exact pathophysiological processes leading to aortic dissection are not fully understood, however, main factors are the increased aortic wall-tension due to high internal pressures, increasing diameters and decreasing wall thickness. Additionally an increased stiffness of the aortic wall due to loss of elastic fibers composing the vessel is an important factor (Hickson et al., 2010, O´Rourke, 2008) (Hickson, 2010, O´Rourke, 2005). Diameter, length and stiffness of the aorta increase with each decade in a patient’s life(O´Rourke, 2008, Hickson, 2010, O´Rourke, 2005). It has further been described, that the process of widening and elongation of the ascending aorta is occurring in every aging aorta, however, the rate at which this process occurs is influenced by other factors such as blood pressure and genetical predispositions. The fastest aneurysm development usually can be observed in patients suffering from hereditary connective tissue disorders such as Marfan´s Syndrome, Ehlers-Danlos Syndrome and Loeys-Dietz Syndrome(Verstraeten, 2016, Van Laer, 2014, Iselbacher, 2016). O’Rourke et al. numbered the average rate of aortic growth with 3% in diameter and 12% in length per decade of life(O´Rourke, 2008). Figure 35 shows a comparison between the size of the aorta of a 20-year old vs. an 80-year old person and the differences in diameter and length(O´Rourke, 2008). The graphs on the right represent pulse-wave velocity measurements at different aortic segments in patients from different age groups. The graphs show an increase in the flow velocity with an increase in age, this is represents vessel wall stiffening and the decrease in elasticity(Hickson, 2010, Garcia-Herrera, 2012).

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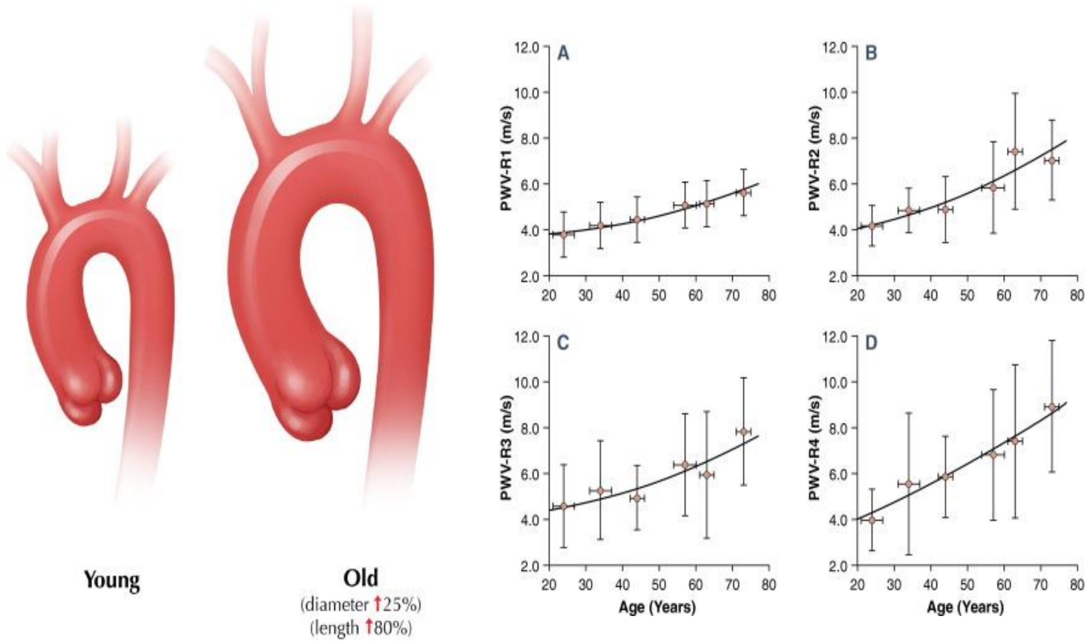


*Figure 35: Change in length of the aorta between a 20-year old (left) and an 80-year old (right)(O´Rourke, 2008). Right: Age vs Pulse-wave-velocity in different aortic segments. A, thoracic arch, B, thoracic-descending region, C, mid-descending region, D, abdominal aorta(Hickson, 2010).*

With the increase in diameter and length, the aorta undergoes a morphologic transformation: a progressive angulation and sometimes kinking can be observed in the ascending and especially the descending aorta. The highest point of the aortic arch in the young is usually found between the supraaortic vessels (type 1 arch). With increasing length of the aorta, the aortic arch increases its radius, and the most cranial point and reversal point of the arch shifts to distal of the supraaortic branches (type 2 arch). This could also be observed in our data, aortic dilatation causes a change in the tension exerted on the aortic wall which may lead to the increased TAD events occurring in these patients(Morrison, 2009, Rylski, 2014).

It has been proven, that at the time a dissection occurs the tear in the intima is mostly transverse, not longitudinal (Hirst et al., 1958, O'Rourke et al., 2008, Robicsek and Thubrikar, 1994, Thubrikar et al., 1999). This is a strong hint toward a predominantly longitudinal material failure of the aortic wall intima in the process of dissection entry formation (Kruger T, 2018). The coincidence of longitudinal wall material failure and elongation is palpable; however, causality is not proven yet. Additionally, presupposed a constant internal pressure, aneurysm formation leads to a disproportional increase in longitudinal wall tension exerted on the aorta (O'Rourke et al., 2008). This causes a stretching of the longitudinal fibers and may lead to a tear causing a dissection

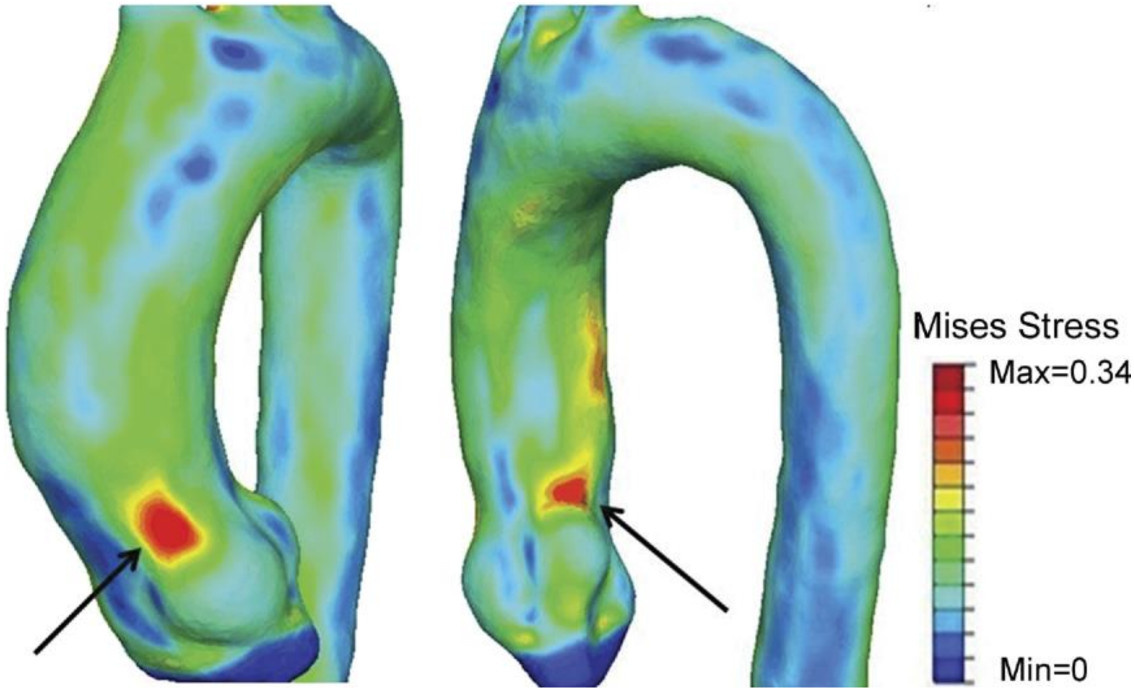


*Figure 36: Three-dimensional wall stress distribution for the normal ascending aorta. Stress in mega-pascal (Nathan et al., 2011).*

Aside the aforementioned factors influencing wall stress, the blood flow itself creates shear stress on the aortic wall. Figure 36 shows a model of the aorta representing shear stress suffered by the aorta from the aortic root to the descending aorta, showing a maximum right above the STJ (Nathan et al., 2011).

When measuring the diameters of the TAD group, we expected them to be greater than the rest of the groups except for the aneurysm group in the aortic root, aortic sinus and ascending aorta. This is because of the change in morphology the aorta undergoes when it dissects. As the intima tears and blood flows into the false lumen of the aorta, the morphology in a CTA changes increasing in diameter until the dissection stops (Rylski et al., 2014). We found out, that these two groups had the largest diameters, throughout the entire aorta; for the TAD group this can be explained by the dissection affecting the aorta all the way to the aortic bifurcation. The larger diameters in the more distal segments in the ascending aorta aneurysm patients, however, is an expression of the generalized character of the vascular wall weakness and the aneurysm predisposition (Garcia-Herrera et al., 2012, Hickson et al., 2010, O'Rourke et al., 2008).

According to the actual guidelines, the aneurysm group is the only group who should undergo prophylactic surgery because of an increased risk of suffering a TAD in comparison to the rest of the groups described in this study (Elefteriades, 2002, Elefteriades et al., 2015, Erbel et al., 2001, Erbel et al., 2014).

Since the year 2002, when Elefteriades et al. published their landmark papers describing the process of an aortic aneurysm and the subsequent rupture if not treated early enough, guidelines have made the recommendation of prophylactically operating a patient with an aortic aneurysm greater than 55 mm (Elefteriades, 2002, Elefteriades et al., 2015, Erbel et al., 2014). These recommendations are based on the augmenting risk of an untreated growing aneurysm which can lead to rupture, dissection and in worst cases death if not treated at the right time (Davies et al., 2002).

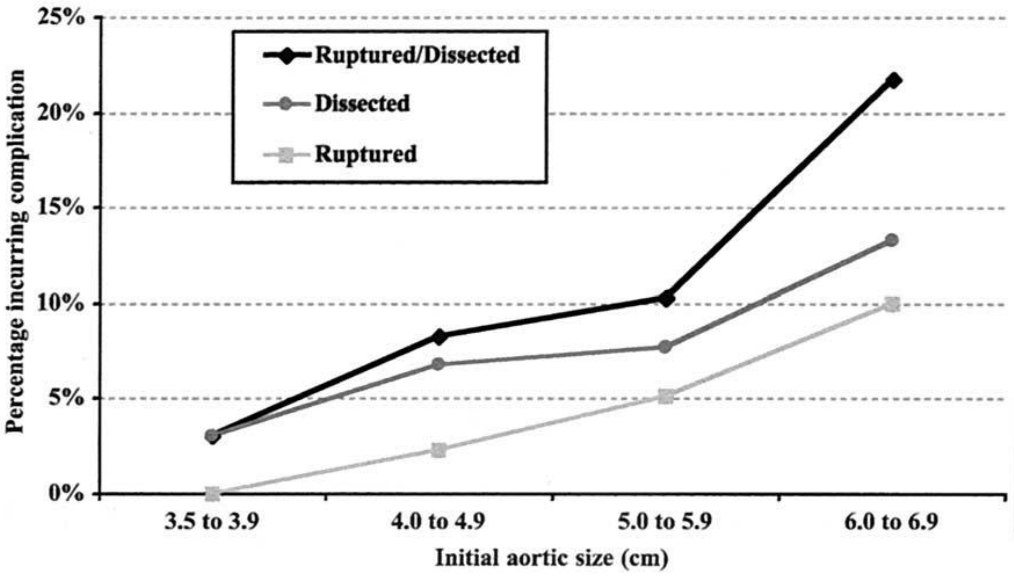


*Figure 37: Cumulative incidence of acute dissection or rupture as a function of initial aneurysm size (Davies et al., 2002).*

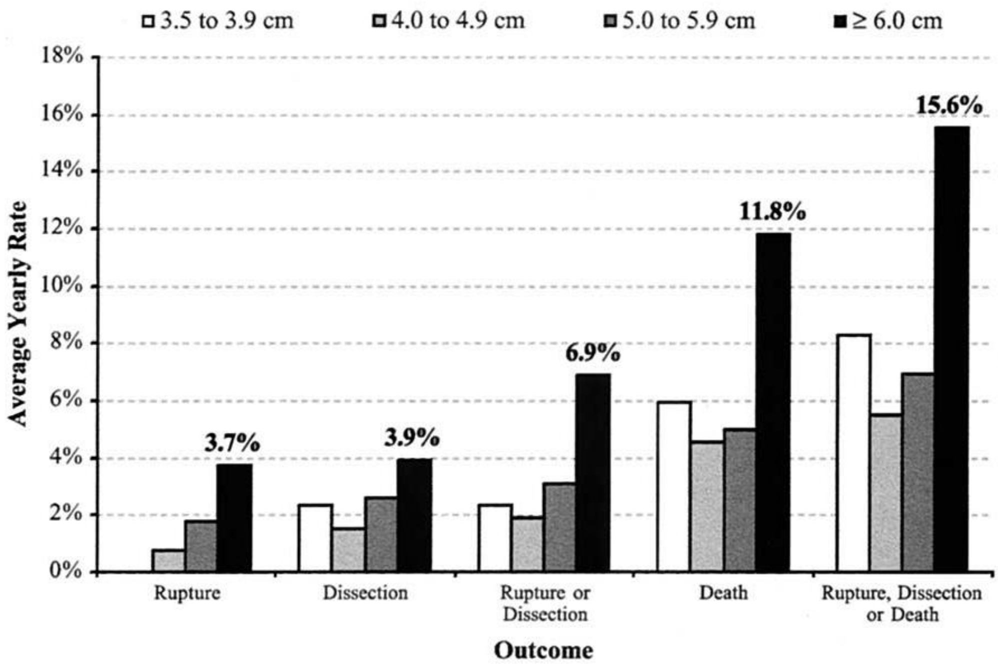


*Figure 38: Average yearly rates of negative outcomes (Davies et al., 2002).*

As shown in figures 37 and 38, the risk of rupture and dissection increases with growing diameter of the aorta, however seldomly but importantly, dissection and ruptures take place in aortas as small as 35-39 mm. It is accurate to say that patients with an aortic ascending diameter greater than 55mm should be prophylactically operated, but other unknown risk factors must be present leading to TAD in small diameter aortas. Our data strongly suggests ascending aortic length being another risk factor, especially because it is present in both, pre-TAD and TAD aortas.

Besides the pre-TAD and TAD groups, our focus of interest was on the aortic ectasia group (diameters of 45-54 mm), since we could demonstrate that absolutely most TAD´s occur in that range of diameters. The diameters and length parameters of the ectasia group where smaller compared to those in the TAD group, but they were very similar to those of the pre-TAD group (Kruger T, 2018). Especially against the background that the aorta undergoes acute diameter changes in the actual process of dissection (Rylski et al., 2014), it is plausible that most dissections emerge from ectatic aortas.

However, this subgroup of patients, according to the actual guidelines, should not be operated on as prophylaxis to avoid a TAD.

Just one of 17 Patients in the pre-TAD group exceeded the threshold diameter of 55 mm. It might be argued that the pre-TAD group was susceptible for selection bias because patients with diameters >55 mm would had undergone surgery prior a TAD, however, even in the TAD group, nearly 70% of patients had ascending diameters <55 mm, and those were certainly not susceptible for selection bias (Kruger T, 2018). Consequently, the diameter alone is an insufficient parameter for TAD-prophylaxis.

This low predictive value of the 55 mm threshold led us to search for other morphological predictors of TAD, and, by that, to measure the length of the different aortic segments. In the literature it has been described, that aortas who suffer from a dissection, undergo morphologic changes in which, they not only grow wider but also longer (Rylski et al., 2014). The control group showed significantly smaller aortic segment lengths throughout all the measurements, this implicates, that an increase in width and length occur simultaneously (O'Rourke and Nichols, 2005, O'Rourke et al., 2008).

In Consequence to our findings, there are several points to be noted. Firstly, as mentioned in chapter 3, when comparing the diameters at the different landmarks, it was remarkable that both, the TAD diameters and lengths were greater than the respective pre-TAD values throughout the ascending aorta, the critical segment for TAD. This shows that during the actual process of acute dissection there are massive changes in the aortic morphology, diameters and segments´ lengths (Rylski et al., 2014). When comparing the length of the segments between the ectasia- and TAD groups, the greatest differences were in the ascending and descending segments of the aorta. Secondly, importantly, the morphology of the ectasia group was very similar to that of the pre-TAD group in terms of both, segment diameters and lengths. This proves that not only patients with aneurysms ≥55 mm diameter are at risk for dissection, but particularly those with ectatic, slightly dilated aortas. Aortic length, the second dimension of aortic morphology probably allows a further stratification and risk prediction in the interesting subgroup of aortic ectasia patients.

### 4.1.4 Prevention of TAD

Based on the data presented herein, we conclude, that the ascending aortic diameter alone is insufficient as an indicator to decide whether a patient needs a prophylactic replacement of the ascending aorta and to prevent TAD. Therefore, special consideration should be given to the aortic length in patients with an ectatic aorta.

Based on our findings, we propose a prognostic score, in which the ascending aorta diameter and length measured in curved planar reformations of CTAs are considered (Kruger et al., 2017). The score is depicted in table 5: depending on the length and width, points are assigned and summed up. A score equal to or greater than two points would be the indication for prophylactic ascending aortic replacement (Kruger et al., 2017). A score of two points can basically be reached in two different scenarios: firstly, if the ascending diameter reaches 55 mm, as in the actual guidelines, and secondly, if the ascending aortic diameter reaches 45 mm and the ascending aortic central line length, measured from the aortic valve annulus to the offspring of the brachiocephalic trunk, simultaneously reaches 120 mm. The latter morphology characterized by ectasia and significant elongation contains a significant risk based on our data and prophylactic surgery should be discussed in the future scientific discourse.

*Table 5: TAIPAN Score (Kruger et al., 2017).*

| Parameters | Length in mm | Points |
|---|---|---|
| Diameter of Aorta ascendens | <45 | 0 |
| | 45-54 | 1 |
| | >55 | 2 |
| Length of Aorta ascendens | <120 | 0 |
| | ≥ 120 | 1 |
| Prophylactic replacement of ascending aorta at ≥ 2 points | | |

The TAIPAN score would have been positive in none of our control group patients, but it would have been positive in 23.5% (4 out of 17) of our pre-TAD patients, and by that in at least twice as many as the 55 mm threshold. In other words, at least twice as many pre-TAD patients would have been identified as risk-patients by the TAIPAN-score as with the diameter alone. Off course, the TAIPAN score was positive in all aneurysm patients, but, however, it would have been positive in 31.4 % of the ectasia patients as well, which means that prophylactic surgery should be discussed for this group of patients as well (Kruger T, 2018). Future studies, possibly prospective and multicenter-based, must evaluate the superiority of the TAIPAN-score over the sole 55-mm-threshold in the prophylaxis of TAD.

#### 4.1.5 Study limitations: study design and analysis

The ideal way to identify and stratify risk factors that may lead to a TAD would be through a prospective study. The unnecessary exposure to radiation and risk of suffering a TAD in patients undergoing such a study make it ethically and clinically problematic. For these reasons, the best tool within our reach nowadays, is a retrospective study of this nature; for this is the only medium available to investigate and study risk factors and causes associated to TAD without exposing the patients to any risks.

The pre-TAD group was evidently smaller than the other groups because patients who received a CTA before a TAD event were quite rare in our experience. However, to our knowledge, this is the largest reported cohort of such patients and we plan to increase the number in a multicenter approach (Kruger T, 2018).

## 5. Conclusion

Acute TAD is a serious condition of the aorta, mortality is quantified with 1-2% per hour (Anagnostopoulos et al., 1972, Erbel et al., 2001, Hirst et al., 1958), and almost all patients die within 14 days after the acute event. The incidence of TAD is estimated 2.9 cases per 100.000 per year (LeMaire and Russell, 2011, Meszaros et al., 2000), about 2500 cases every year are estimated for Germany. Emergency surgery for TAD improves the prognosis, however, postoperative mortality in this scenario is still around 10-20% (Kruger et al., 2011, Rylski et al., 2011, Weigang et al., 2010) and 10% of the survivors suffer from chronic neurological deficits. In contrast to that, electively planned ascending aorta replacement has a postoperative mortality of 5% (Hiratzka et al., 2010). This clarifies the need for a sufficient prophylaxis of TAD, and for reliable predictors of TAD. However, TAD is known to be a multifactorial disease, which may be triggered by genetical mutations, such as syndromes affecting the connective tissue. Age also appears to be a factor that plays a major role, with an increasing age, tissue and fibers gradually and constantly show a decreasing elasticity, mainly due to elastin degradation. In the long term these changes can lead to tears in the intima layer of the aorta leading to a TAD. So far, the only accepted parameter utilized in international guidelines used as a morphologic predictor is the ascending aortic diameter. It is established and accepted, that a patient should undergo a prophylactic replacement of the ascending aorta if the diameter exceeds 55 mm. However, we and other authors could show the insufficiency of this parameter in reliably predicting TAD. Significant aortic elongation can be observed in aortas before and after dissection and in ectatic and aneurysmatic aortas. This and the pathophysiological plausibility of the concept are strong arguments that ascending aorta elongation may be a risk factor for dissection. We could show that most dissections happen in aortas with diameters under 55 mm and we studied aortic length as a potential further predictor of TAD. Ascending aorta length appears to be capable to identify patients with a high risk for TAD (Kruger T, 2018). However, based on our score, prophylactic surgery would have to be discussed for a relevant number of patients, which are classified as having ectatic aortas. Further studies will be conducted to evaluate the prognostic value of ascending aorta length in TAD prevention.

## 6. Zusammenfassung

Die Aortendissektion Typ A nach Stanford (TAD) ist ein akutes Aortensyndrom mit hoher Letalität und vielfältigen, auch chronischen Komplikationen.

Der einzige etablierte morphologische Risikofaktur für eine TAD ist der Diameter der Aorta ascendens. Die europäischen und amerikanischen Leitlinien empfehlen eine prophylaktische Operation der Aorta ascendens, wenn ein Durchmesser von 55 mm erreicht ist. Bisherige Studien sowie unsere eigenen Daten zeigen jedoch, dass die Mehrzahl der Aortendissektionen bei Patienten mit einem Aortendurchmesser von weniger als 55 mm auftreten. Hieraus ergibt sich die Frage nach weiteren morphologischen Prädiktoren einer TAD die eine zukünftig bessere Risikostratifizierung und Prophylaxe erlauben. In der vorliegenden Studie wurde die Aortenmorphologie in aortengesunden-, sowie in Patienten mit Aorta ascendens Ektasien, Aneurysmen und TAD, sowie in solchen kurz vor einer TAD in computertomographischen Angiographien vergleichend analysiert. Zur exakten Vermessung der aortalen Dimensionen kamen multiplanare Rekonstruktionen (curved multiplanar reformation, CPR) zum Einsatz. Neben den Diametern der gesamten Aorta die an etablierten Landmarken gemessen wurden, wurden insbesondere die Längen der Aortensegmente analysiert.

Betreffend die aortalen Diameter konnte gezeigt werden, dass der mediane Diameter der Aorta ascendens in der Kontrollgruppe mit 3,45 cm signifikant kleiner war als in der TAD und Gruppe vor TAD, aber auch dass die Diameter an den anderen Landmarken im Bereich der Aortenwurzel und des Aortenbogens in der Kontrollgruppe signifikant kleiner waren als in Gruppe vor TAD, TAD Ektasie- und Anerysmagruppe, was als Ausdruck einer grundsätzlichen Aortenwandschwäche zu werten ist. Der mediane Diameter der Aorta ascendens in der Gruppe vor TAD lag mit 4,27 cm deutlich unter dem Grenzdiameter für den empfohlenen prophylaktischen Aortenersatz, und entsprach vielmehr dem der Ektasie- als dem der Aneurysmagruppe. Die Länge der gesamten Aorta ascendens, gemessen von der Aortenklappe bis zum Truncus brachiocephalicus betrug in der Kontrollgruppe 9,2 cm und war signifikant länger in der Ektasiegruppe, 11,31 cm, und in der Aneurysmagruppe, 12,19 cm. Derselbe Längenwert betrug 10,69 cm in der Gruppe vor TAD und 11,18 cm in der TAD

Gruppe, beide erneut signifikant länger als in der Kontrollgruppe. Die Distanz, gemessen von der Aortenklappe bis zum Truncus brachiocephalicus, erwies sich als sehr stabil und reproduzierbar messbar, da die genannten Landmarken trotz pathologischer Veränderungen jederzeit identifizierbar waren, wohingegen der sinotubuläre Überang in aneurysmatischen und disseziierten Aorten oft nicht eindeutig identifizierbar war. Die signifikante Längenzunahme der Aorta ascendens ist einerseits pathogenetisch interessant, als dass hiermit die longitudinale Komponente der aortalen Dilatation bei der Aneurysmabildung quantifizierbar und das longitudinale Wandversagen in der Entstehung der TAD erklärbar wird. Andererseits erscheint die Elongation der Aorta ascendens nutzbar als weiterer Prädiktor für eine TAD.

Die signifikante Längenänderung einerseits und die pathogenetische Plausibilität andererseits machen die Rolle der aortalen Elongation als Risikofaktor eine TAD sehr wahrscheinlich. Aufgrund dieses Befundes entwickelten wir einen prognostischen Score, der sowohl den Durchmesser als auch die Länge der Aorta ascendens berücksichtigt. Je nach Durchmesser, <4,5 cm, 4,5-5,4 cm oder >5,5cm werden 0 bis 2 Punkte, je nach Länge zwischen Aortenklappe und Truncus brachiocephalicus, <12 cm oder ≥12 cm, werden 0 bis 1 Punkte vergeben. Wenn der Score gleich oder größer als 2 ist, wird er als positiv gewertet. Das bedeutet, dass der Patient ein erhöhtes Risiko für eine TAD hat und einen prophylaktischen Ersatz der Aorta ascendens diskutiert werden sollte. Angewandt an unseren Studienpatienten hätte niemand aus der Kontrollgruppe ein pathologisches Ergebnis gehabt, 23,5% der Patienten in der Gruppe vor TAD; 31,4% der Patienten in der Ektasiegruppe und alle Patienten in der Aneurysmagruppe hätten einen positiven, pathologischen Score gehabt. Somit scheint der Score eine verbesserte Sensitivität verglichen mit dem Ascendensdiameter allein zu haben, allerdings müsste auch bei einem knappen Drittel der Ektasiepatienten eine prophylakische Operation diskutiert werden.

Zukünftige prospektive Studien müssen die hier erhobenen Befunde verifizieren und die prognostische Wertigkeit des Scores bestätigen, dann wäre ein weiteres Instrument zur verbesserten TAD Prophylaxe gegeben.

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## 8. Wissenschaftliche Veröffentlichungen

Die folgende Originalarbeit entstand aus dem in dieser Arbeit präsentierten wissenschaftlichen Projekt. Der Verfasser dieser Arbeit war ursächlich und umfangreich an der Erstellung dieser Arbeit beteiligt:

Krüger T, Sandoval Boburg R, Lescan M, Oikonomou A, Schneider W, Vöhringer L, Lausberg H, Bamberg F, Blumenstock G, Schlensak C.
Aortic elongation in aortic aneurysm and dissection: the Tübingen Aortic Pathoanatomy (TAIPAN) project. European Journal of Cardiothoracic Surgery 2018; 1;54 (1):26-33.

**9. Erklärung zum Eigenanteil**

Die Idee zu der vorliegenden Studie hatte Dr. T. Krüger, durch ihn erfolgte auch die wissenschaftliche Betreuung des Gesamtprojektes und der vorliegenden Dissertationsschrift.

Herr R. Sandoval Boburg und Dr. T. Krüger konzipierten und planten die Studie, hierbei entfallen relevante Anteile der konkreten Planung des Studienablaufs auf Herr R. Sandoval Boburg.

Alle Computertomograpien und klinischen Daten dieser Studie wurden im Rahmen der standardmäßigen Krankenversorgung erstellt. Herr R. Sandoval Boburg und Dr. T. Krüger werteten die Computertomographien gänzlich neu und eigenhändig aus, wobei auf jede der vorgenannten Personen die Hälfte der CT-Auswertungen entfällt.

Die statistische Auswertung der Arbeit wurde konzipiert von Dr. T. Krüger und durchgeführt von Herr R. Sandoval Boburg.

Die Publikation *Aortic elongation in aortic aneurysm and dissection* wurde geschrieben von Dr. T. Krüger unter Mithilfe von Herr R. Sandoval Boburg, hierbei entfallen relevante Anteile des Textes und die Erstellung der Abbildungen auf Herr R. Sandoval Boburg.

Die vorliegende Dissertation wurde ausschließlich angefertigt von Herr R. Sandoval Boburg.

Die Literaturrecherche zu vorliegender Dissektion wurde angefertigt von Herr R. Sandoval Boburg.

Die Abbildungen dieser Arbeit, die Ergebnisse darstellen wurden entweder für diese Arbeit individuell durch Herr R. Sandoval Boburg oder, für die zugehörige Publikation durch Herr R. Sandoval Boburg und Dr. T. Krüger erstellt. Weitere Abbildungen sind der Literatur entnommen, die entsprechenden Abbildungen sind allesamt mit den zugehörigen Zitaten gekennzeichnet.

Dr. Tobias Krüger hat die vorliegende Dissertationsschrift korrekturgelesen.

gez. R. Sandoval Boburg                gez. Dr. T. Krüger

## 10. Danksagung

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