TITLE PAGE

Title:

INFLUENCE OF CARDIOVASCULAR RISK FACTORS ON AORTIC WALL MOTION AFTER REPAIR OF TYPE A AORTIC DISSECTION: AN ECG-GATED CT STUDY

Author:

Mariagrazia Croccia

Institution and Affiliation:

University of Pisa Medical School, Pisa, Italy

Scuola di Dottorato di Ricerca in Fisiopatologia e Clinica dell'Apparato Cardiovascolare e Respiratorio

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ABSTRACT

OBJECTIVES: To evaluate aortic shape changes during cardiac cycle with dynamic computed tomographic angiography at important thoracic aorta anatomic landmarks in patients who previously underwent ascending aorta repair because of type A dissection, and correlate aortic wall motion with several cardiovascular risk factors.

METHODS: From December 2009 to December 2011, 18 patients (14 men and 4 women, mean age 64 ± 12 y.o.) with previous aortic repair, underwent ECG-gated-CT follow-up. Aortic systolic and diastolic diameter and cross-sectional area were measured at 4 levels: 1 cm proximal (level A) and 1 (B), 3 (C) and 10 cm (D) distal to the origin of left subclavian artery. Results were assessed according to presence of diabetes, hypertension, smoking and age (2 groups: ≤ 55 and ≥56 years).

RESULTS: This morpho-functional evaluation of aortic distensibility demonstrated a significant influence ($p<0,05$) on aortic wall-motion of hypertension at level A and diabetes at level D. Smoke has a borderline significance at level C and D. No significant correlation between aortic wall motion and age was evident, being results not significantly different in two age groups.

CONCLUSIONS: Smoking, diabetes and hypertension play a role in impairing aortic distensibility and previous surgical repair does not interfere with vessel wall motion. Aortic distensibility might predict wall structural alteration due to cardiovascular risk factors before they become morphologically evident.

This might influence timing of surveillance, making this specifically tailored for any single subject.

INTRODUCTION

“Aortic dissection” is a disruption of the media layer of the aorta with bleeding inside the wall of the vessel. The term “dissecting aortic aneurysm” is often used incorrectly and should be reserved only for those cases where a dissection occurs in an aneurysmal aorta, since an aneurysm may occur without dissection as well as a dissection may exist without aneurysmatic dilatation [1].

Among aortic disease, dissection is relatively common with an incidence of 2.9 cases per 100000 person-years [2]. Its natural history is characterized by high early and late mortality rates.

Anatomically, acute thoracic aortic dissection can be classified according to either the origin of the intimal tear or whether the dissection involves the ascending aorta (regardless of the site of origin). Accurate classification is important as it drives decisions regarding surgical versus non-surgical management. The De Bakey and the Stanford classifications are the two most commonly used.

The De Bakey classification divides dissections according to the origin of the intimal tear and the extent of the dissection:

- Type I: Dissection originates in the ascending aorta and propagates distally to include the aortic arch and the descending aorta.

- Type II: Dissection originates in and is confined to the ascending aorta.

- Type III: Dissection originates in the descending aorta and propagates most often distally. It could be limited to the descending thoracic aorta (IIIa) or extend below the diaphragm (IIIb).

The Stanford classification categorizes dissections into 2 groups:

- Type A: All dissections involving the ascending aorta regardless of the site of origin.

- Type B: All dissections that do not involve the ascending aorta.

According to guidelines published in 2010 [1], urgent surgical repair is the gold standard for treatment of Stanford type A dissection. The suggested imaging techniques for preoperative and postoperative evaluation and for follow up is computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) of the thoracic aorta [1]. The frequency of surveillance imaging is not clearly defined because no data accurately indicate surveillance intervals. It seems prudent to obtain an initial follow-up imaging study before discharge; at 1, 3, 6, and 12 months postoperatively; and then annually after the thoracic aortic disease is first detected.

Standard imaging techniques, like computed tomography (CT), give a complete diagnostic work-up, but cannot measure dynamic, pulse-associated changes of the aortic geometry, resulting in aortic sizing failures.

During the cardiac cycle, the thoracic aorta has the important role to reduce pulse pressure, smoothen peripheral blood flow and enhance the efficacy of the entire cardiovascular system. Its abnormalities may result in several cardiovascular diseases [3]. Furthermore, aortic elasticity is extensively accepted as an independent predictor of adverse cardiovascular outcomes at an early stage [4]. Hence, the evaluation of aortic elasticity non-invasively is of great interest.

With the development and application of dynamic imaging techniques such as electrocardiography (ECG)-triggered CTA and MRA, it has become possible to study the aortic motion and distention during the cardiac cycle [5-6]. Several research studies showed significant aortic distention at important landmarks in the abdominal, ascending and descending thoracic aorta [5-8]. In other papers, similar observations were made using different techniques, such as M-mode ultrasound and intravascular ultrasound (IVUS) [9-10].

Modern ECG-triggered 64-slide CTA acquires image data at any particular level in a short time with excellent temporal and spatial resolution and may show the aortic diameter and area during cardiac cycle, at diastole, systole, or anywhere in between. This imaging technique offers an exceptional opportunity to study aortic distensibility, giving morphological and functional information at the same time.

The aim of this study was to utilize ECG-gated CTA to examine aortic motion during the cardiac cycle at important anatomic landmarks of the thoracic

aorta in patients who previously have undergone ascending aorta surgery for Stanford type A dissection.

METHODS

Patients previously undergone ascending aorta repair for acute type A dissection were studied using dynamic CTA. Firstly, diameter and cross-sectional area changes were analyzed at different levels, secondly, the correlation between several cardiovascular risk factor (smoking, diabetes, hypertension, age) and aortic wall motion was made to gain a new insight into elastic properties of the thoracic aorta in order to give patients a tailored follow up.

This study was approved by the institutional review board, and written informed consent was obtained from each patient before performing CTA.

PATIENT DATA

From December 2008 to December 2010, 44 patients underwent urgent aortic surgical repair because of type-A dissection at our institution. According to 2010 Guidelines [1], our patients underwent CTA or MRA follow up, before discharge, 1, 3, 6, and 12 months post-dissection and, if stable, annually thereafter. Among them, from December 2009 to December 2011, 18 patients were examined with ECG-gated CTA, selected because of no extension of dissection beyond arch or descending aorta.

At first presentation, all of them were affected by acute aortic dissection and underwent immediate surgery, as shown in Table 1: 11 patients (61.1%) had ascending aorta repair and coronary artery reimplantation according to the

Bentall-DeBono technique, 3 (16.7%) had ascending aorta repair and coronary artery by-pass grafting (CABG), 2 (11.1%) received ascending aorta and aortic arch repair, and 2 (11.1%) had simple ascending aorta repair.

The study population clinical characteristics are summarized in Table 1. There were 14 men (78%) and 4 women (22%), with mean age of 64 ± 12 years (range, 47 to 83 years); considering them as divided into two age-group (those aged ≤ 55 and those ≥56 years), 12 (66.7%) were older than 55 years. All of them were in sinus rhythm. 7 patients (38.9%) had diabetes and it was well controlled with oral therapy, 10 (55.6%) had hypertension (systolic pressure more than 140 mmHg and diastolic pressure more than 90 mmHg) treated with beta-blockers, 6 (33.3%) were smokers and 2 (11.1%) had dyslipidemia. Two patients (11.1%) had received an aortic valve replacement for valve regurgitation prior to acute aortic dissection. No patient had pulmonary disease or extracardiac arteriopathy.

IMAGE ACQUISITION

Patients underwent 64-slice CTA (Light-Speed VCT 64, GE Healthcare, Milwaukee, WI, USA), with the following scan parameters: retrospective ECG gating, 912 channel detectors along the gantry and 64 channel detectors along the z-axis; tube voltage of 120 kV, tube current of 350-750 mA (depending on patient size), scan field of view of 50 cm, gantry rotation of 0.35 s/rotation,

matrix of 512 x 512, slice thickness of 0.625 mm, and range of helical pitch of 0.18–0.24. When appropriate, a single intravenous dose of metoprolol (up to 5 mg) was administered shortly prior to the examination to lower the heart rate below 65 beats per minute. Non-ionic iodinated contrast medium (Iomeprol 400; Bracco International, Milan, Italy) was injected via a peripheral vein. To time the start of the scan, a region of interest was placed in the right ventricular cavity to detect the peak enhancement. Scans were obtained during breath hold and patients were monitored continuously through single-lead electrocardiography. The scan parameters were programmed to limit radiation exposure to 15 mSv on average. After the procedure, patients were infused with saline (500 mL) to prevent contrast-induced nephropathy and instructed to have their serum creatinine rechecked between 2 and 7 days after the examination.

Using retrospective ECG-gating, reconstruction of at least 10 series synchronized with cardiac cycle (0-90% of R-R time with steps of 10%) was obtained. Trans-axial images were reconstructed using a slice thickness of 0.625 mm and 0.625 increments. The data were then transferred to a dedicated workstation (Advantage Workstation 4.3, GE Healthcare, Milwaukee, WI, USA) for post-processing. We use multiplanar reconstruction of the thoracic aorta in each ECG-gated series and a specific program for the automatic recognition of the contrasted vessel lumen for evaluating diameter, circumference and area of the thoracic aorta in the different phases of the cardiac cycle, using manual correction when necessary.

Four relevant anatomical levels were selected for the evaluation of aortic shape changes. These four levels were: 1 cm proximal to the origin of left subclavian artery (level A), 1 cm (level B), 3 cm (level C) and 10 cm distal to left subclavian artery (level D), as shown in Figure 1. The measurements were done by two observers: they performed the segmentation twice for calculation of intra-observer inter-observer repeatability.

After segmentation of the aortic lumen in each cardiac phase, diameter and area changes over the cardiac cycle were measured. Diameter and cross-sectional area changes were considered the difference between minimum and maximum size during cardiac cycle: these measurements were obtained in a reconstructed plane perpendicular to the aortic centerline. All the measurements were performed between the outer walls of the aorta (adventitia to adeventitia) at any level.

Additionally, data were assessed for the presence of diabetes, hypertension, smoking and age, dividing study population into two groups: those younger than 55 y.o. and those older.

DATA ANALYSIS

Statistical analysis was perfomed using the software SPSS 11.5 (SPSS Inc, Chicago, IL, USA) and GraphPad PRISM version 4.0 (San Diego, CA, USA).

All data on diameter and cross-sectional area are presented as mean ± standard deviation (SD) and categoric variables are expressed as number and percentage. To test normal distribution, the Kologomorow-Smirnov test was used. To analyze statistical differences between minimum and maximum diameters and areas during R-R interval at each level in each patient, paired sample t-test was applied. To evaluate role of different cardiovascular risk factors on diameters/area variations, Student T-test for unpaired data was used. A p-value $\leq$ 0.05 was considered statistically significant. The intra-observer and inter-observer repeatability was analyzed with Bland and Altman's comparing method, chosen because it was considered the most suitable and, since it is already been used in similar studies, it allows a quick comparison [5-8, 11].

RESULTS

All the measurements were performed by two observers: the intra- and inter-observer variability analyses, evaluated with Bland and Altman's comparing method, demonstrated good repeatability of measurements, as shown in Figure 2.

MEAN AORTIC DIAMETER

The results are shown in Table 2. The mean aortic diameters demonstrated statistically significant change ($p \leq 0.05$) during the cardiac cycle at each anatomical landmark.

At level A, mean systolic aortic diameter was 29 ± 3.7 mm (range 23-36.4) and mean diastolic was 27.1 ± 2.9 mm (range 22-33). Level B demonstrated a mean systolic measurement of 26.6 ± 3.3 mm (range 20-34.8) and mean diastolic of 25.5 ± 3.07 mm (range 18.3-32.2). Mean systolic diameter at level C was 30.7 ± 7.3 mm (range 21.4-46.1) and during diastole was 30 ± 7.1 mm (range 20.8-44.8). At level D, during systole, mean diameter was 31.4 ± 7.2 mm (range 21.6-44) and diastolic measurement was 30 ± 5.8 mm (range 20.5-41.5). These data correspond to mean change of 5.5% 1 cm proximal to origin of left subclavian artery (level A, range 0-10.3; SD 3.3, with absolute change of 1.6 ± 1.03 mm), 5.2% 1 cm distal to left subclavian artery (level B, range 8-8.8; SD 2.8, with absolute difference of 1.4 ± 0.7 mm), 5.1% at level C (range 1.7-8.6;

SD 2.06, absolute change 1.6 ± 0.7 mm) and 5.8% at level D (range 0-18.1; SD 5.7, absolute difference 2 ± 2.3 mm) during cardiac cycle.

According to Bland and Altman's analysis, the intra-observer diameter measurements comparison revealed a mean bias of 0.19 mm while the inter-observer diameter measurements mean bias was 0.08 mm, indicating good repeatability of measurements, as shown in Figure 2.

MEAN AORTIC AREA

The results are shown in Table 2. The mean aortic area changes were statistically significant ($p \leq 0.05$) during the cardiac cycle at each anatomical landmark.

Level A showed a mean systolic aortic area of 678.7 ± 156.8 mm^2 (range 484.2-897.6), while the mean diastolic measurement was 622.8 ± 150.5 mm^2 (range 442.5-886.4). At level B the mean systolic area was 551.7 ± 139.3 mm^2 (range 372.5-871) and the mean diastolic was 501.9 ± 114 mm^2 (range 361.4-736.6). Mean systolic area at level C was 713.3 ± 294.4 mm^2 (range 390.6-1326) and during diastole was 523.8 ± 129.1 mm^2 (range 361.4-736.6). Level D, during systole, demonstrated a mean area of 758 ± 261.9 mm^2 (range 427.3-1154.7) and mean diastolic area of 660.8 ± 222 mm^2 (range 387.7-1094.3). Considering relative area changes during cardiac cycle, al level A mean change was 8.3%

(range 0.6-16.9; SD 5.6, absolute value 56 ± 44.7 mm^2), 8.4% at level B (range 1.1-15.4; SD 4.9, with absolute change of 49.9 ± 35.9 mm^2), 19.6% 3 cm distal to the left subclavian artery (range 3-65; SD 20.8, with absolute difference of 189.4 ± 274 mm^2) and 11.7% at level D (range 1.8-29.2; SD 9.7, absolute difference 97.2 ± 105 mm^2).

According to Bland and Altman's analysis, the intra-observer area measurements comparison revealed a mean bias of 4.07 mm^2 while the inter-observer area measurements mean bias was 1.91 mm^2, demonstrating good repeatability of measurements, as shown in Figure 2.

CARDIOVASCULAR RISK FACTORS EVALUATION

Results are showed in Tables 3 and 4.

According to patients age, considering them as 2 groups, those aged ≤ 55 years and those ≥ 56, no statistical difference was observed, neither in diameter nor in aortic changes. The only significant data was the aortic percentage area change at level D, being 19.4 ± 11% the change rate in patients ≤ 55 y.o. and 7.9 ± 6.8 % in those ≥ 56 y.o.

Considering diabetes, there were significant differences at level D, both for diameter and area change. In diabetic patients, at level D, the absolute diameter change was 3.7 ± 3 mm and the percentage change was 10.4 ± 6.8%. In

non-diabetic patients these values were 0.9 ± 0.7 mm and 2.9 ± 2% respectively, reaching a p-value of 0.05 for absolute diameter change and 0.03 for percentage change. The percentage area change differences reached a p-value of 0.04, being 21.5 ± 12.8% the percentage area change in diabetics and 8.5 ± 6.4% in non-diabetics.

For hypertension, there were two important findings, both at level A and level D. At proximal point, in hypertensive patients there was a mean aortic diameter modification of 1.1 ± 0.9 mm and a percentage change of 3.8 ± 3.3%, while in non-hypertensive patients the same measurements revealed 2.2 ± 0.8 mm of mean diameter and 7.8 ± 2% of percentage change, obtaining a p-value of 0.01. At level D mean diameter change was 0.7 ± 0.4 mm in hypertensives and 3.6 ± 2.8 mm in non-hypertensives, with a p-value of 0.02. At this level, percentage diameter change was 2.8 ± 1.9% in hypertensives and 9.5 ± 6.7% in non-hypertensives, reaching a p-value of 0.03.

In patients that were tobacco smokers, a borderline significance was evident at level C and D for aortic area change. At level C there was mean aortic area change of 29.6 ± 12.5 mm^2 in smokers and 303.7 ± 317.9 mm^2 in non-smokers (p 0.06) with a percentage area change respectively of 6.2 ± 2.7% and 29.2 ± 23% (p 0.04). At level D, mean area modification was 30.1 ± 14.5 mm^2 in smokers group and 145.1±116.9 mm^2 in the other (p 0.04) while percentage area change was 6.2 ± 3.9% in smokers and 15.7 ± 10.9% in non-smokers (p 0.06).

DISCUSSION

The present feasibility study was intended to evaluate aortic shape changes in order to characterize type A dissection in a time-resolved method, obtaining morphological and functional information at the same time. This might be useful to achieve possible indicators of the course of disease.

Our results, even though obtained from a small sample size, show that there is a correlation between aortic distensibility and cardiovascular risk factors and that this impact is different at different anatomical levels. These data confirm other ones already shown in literature, increasing functional knowledge and focusing on risk factors never analyzed before (such as diabetes and smoking).

With the development and application of dynamic imaging techniques such as ECG-triggered CTA and MRA, it has become possible to study the aortic motion and distention during the cardiac cycle [5-6]. Several research studies showed significant aortic distention at important landmarks in the abdominal, ascending and descending thoracic aorta [5-8].

Van Herwaarden JA et al. [5] studied aortic motion and distention using ECG-triggered MRA, showing that in patients with atherosclerotic aneurysm disease, the aortic dimensions at the level of and proximal to the aneurysm neck change during the cardiac cycle.

Muhs BE et al. [6] used dynamic CTA to demonstrate changes in thoracic aortic diameter in patient with abdominal aortic aneurysm during each heart

cycle, with excellent temporal and spatial resolution. The native aorta exhibits significant pulsation with each heart cycle, and this may have serious consequences for endograft efficacy and durability.

Van Prehn J and al. [7] evaluated pulsatility and motion along the ascending aorta using ECG-triggered CTA. They demonstrated that the dynamics of the ascending aorta and the arch vessel, considering 3-dimentional motion, are impressive. These results must be considered for future ascending arch branched and fenestrated thoracic endograft design, because they may impair ultimate clinical success.

In 2009, the same group [8], utilized dynamic CTA on pre- and post-operative thoracic endovascular aneurysm repair (TEVAR) patients, finding significant distention of the thoracic aortic arch and descending thoracic aorta during the cardiac cycle, before and after TEVAR.

In other papers, similar observations were made using different techniques, such as M-mode ultrasound and intravascular ultrasound (IVUS) [9-10].

Focusing on cardiovascular risk factors, our data show that smoking has an influence on aortic stiffness at level C and D (even if at this level the statistical significance is borderline). At more proximal levels (A and B) smoking

shows no impact. This reflects and in part confirms that tobacco smoking causes endothelial dysfunction decreasing flow-mediated vasodilatation [12].

In our patient subset, diabetes has a role on aortic wall motion at distal level (point D), but no significance is reached at levels A, B and C. Further data might reinforce this finding, suggesting a different ultrastructural action of glucose at different levels of thoracic aorta, increasing oxidant stress and impairing endothelium-dependent relaxation. This finding might justify a more aggressive anti-diabetic therapy in patients who previously underwent surgical aortic repair with "borderline" descending aorta lesions, in order to prevent ultrastructural damage.

Our measurements confirm that hypertension is one of the most important risk factors for aortic stiffness, as shown in several study [13-14], suggesting a major impact on proximal level (point A). Further data are need to understand if aortic stiffness might be due to stability of proximal thoracic aorta near the previous surgical anastomosis and if pharmacological treatment might have a role in normalizing this finding. Considering our patients medications, the outcomes could suggest a role of beta-blockers in limiting aortic plasticity. Besides, this finding might underline a role of hypertension in determining distal progression of dissection. A closer CT-follow up and a more aggressive anti-hypertensive treatment could be indicated in hypertensive patients to prevent future aortic lesions.

Furthermore, our data, surprisingly, do not reveal any significant correlation between aortic wall motion and age, being the results not significantly different in two age groups. These data differ from those present in the literature and might be due to the small sample size [13, 15-16]. Metafratzi et al. [13], in a RMN-study, showed that aortic distensibility decreases with age and is correlated with various diseases, such as hypertension and atherosclerosis. Ganten M et al. [15] showed an age-dependent decrease of aortic wall elasticity using ECG-CTA. More recently, Li N et al. [16] evaluated 56 healthy patients using dynamic CTA and the age-dependent decrease of elasticity for the thoracic aorta without known vascular disease was detected, as natural process of aging of the aorta.

Other research studies have demonstrated a positive correlation between aortic stiffness and other pathological features, as hypertension [14], end-stage renal disease [17] and coronary artery disease [18]. Decreased distensibility of the aorta might be a factor to predict wall structural alteration due to cardiovascular risk factors (such as atherosclerotic or diabetic) before they become morphologically apparent. Moreover, distensibility of the aorta could be useful in the grading of vascular disease. Therefore, it is important to measure it non-invasively.

More used modalities for studying aorta are CTA or MRA with 3-dimensional reconstruction. Regardless of modality, the resulting images are static images, while human aorta exists in a dynamic environment. Contraction of

the myocardium followed by the ventricular ejection leads to a pulsatile alteration of the aortic shape that withstands over the thoracic aorta. Aortic compliance and cardiac pulsatility naturally result in conformational changes during the cardiac cycle [19].

Several techniques have been suggested to measure vascular elastic properties. These include pulse-wave velocity measurement employing either MR-velocity analysis [11, 20] or Doppler ultrasound (US) [21], methods that monitor the change of vessel cross-sectional area between systole and diastole. Among different proposed techniques, US is a simple and convenient method, but it is operator dependent and suffers from the difficulty of imaging all the parts of the aorta in a single view. Furthermore, the visualization during US can be influenced by the adjacent structures, for example by bowel gas. On the other hand, MR can be more objective than US and more useful in evaluation of vessel wall motion during cardiac cycle [19, 22], but the availability of MR system is limited and the acquisition of several pulse sequences increases the scan time. Also, the monitoring of instable patients can be difficult. Lastly, the spatial resolution of MRI is currently inferior to that of CT. Therefore, although it causes radiation exposure, CTA is still the preferred method to screen aortic pathologies. With ECG-triggered CTA, original patient data can be reconstructed retrospectively during diastole, systole, or anywhere in between and functional

assessment can be obtained without additional radiation exposure or further examinations.

CONCLUSIONS

The purpose of this study was to utilize dynamic CTA to evaluate aortic diameter and cross-sectional area changes during the cardiac cycle at important thoracic aorta anatomic landmarks in patients who previously underwent ascending aorta repair because of type A dissection, and correlate aortic wall motion with several cardiovascular risk factors. This is important to reach an improved understanding of elastic properties of the thoracic aorta in order to give patients a tailored follow up.

Our results demonstrate that smoking, diabetes and hypertension reduce aortic distensibility and that previous surgical repair does not interfere with vessel wall motion.

Besides, our data and other studies in the literature show that with CT distensibility measurements, morphological and functional information could be acquired in one scan. We are currently developing the resources required for dynamic volumetric assessment of the thoracic aorta in order to achieve further evidences.

We acknowledge that our results are preliminary due to a small sample size, but they permit to increase functional knowledge of vessel wall. Aortic distensibility might be a factor to predict wall structural alteration due to cardiovascular risk factors (such as atherosclerosis, smoke or diabetes) before they become morphologically apparent and could be useful in the grading of vascular disease. The correlation between aortic distensibility and clinical

features of each patient could lead to a different timing of surveillance, specifically tailored and designed for each subject. Furthermore, considering possible alterations in aortic stiffness, a more aggressive therapy for treatment of cardiovascular risk factors might be evaluated in future studies and possibly indicated.

Further studies are required to improve insight into the aortic elastic properties and to verify whether a larger patient population would make the results more significant.

TABLES

CLINICAL CHARACTERISTICS	n° (TOT 18 pts)	%
Male/Female	14/4	78/22
Diabetes	7	38.9
Hypertension	10	55.6
Smoking	6	33.3
MEAN AGE 64 ± 12 y.o. (range 47-81)		
Age ≤ 55 yo	6	33.3
Age ≥ 56 yo	12	66.7
Sinus Rhythm	18	100
Dyslipidemia	2	11.1
Previous Heart Surgery	2	11.1
COPD	0	0
Extracardiac Arteriopathy	0	0
CAD	3	16.7
AORTIC SURGERY for Type-A DISSECTION		
Bentall-DeBono technique	11	61
Ascending aorta repair + CABG	3	16.7
Ascending Aorta + Aortic Arch Repair	2	11.1
Ascendine aorta repair	2	11.1

TABLE 1: Clinical characteristics of study population at follow up and emergent surgical repair at first presentation (TOT: total; pts: patients; COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Grafting).

	LEVEL A	LEVEL B	LEVEL C	LEVEL D
SYSTOLIC DIAMETER mm (mean ± SD) [range]	29 ± 3,7 [23 – 36,4]	26,6 ± 3,3 [20 – 34,8]	30,7 ± 7,3 [21,4 – 46,1]	31,4 ± 7,2 [21,6 – 44]
DIASTOLIC DIAMETER mm (mean ± SD) [range]	27,1 ± 2,9 [22 – 33]	25,5 ± 3,07 [18,3 – 32,2]	30 ± 7,1 [20,8 – 44,8]	30 ± 5,8 [20,5 – 41,5]
ABSOLUTE DIAMETER CHANGE mm (mean ± SD) [range]	1,6 ± 1,03 [0 – 3,5]	1,4 ± 0,7 [0 – 2,6]	1,6 ± 0,7 [0,6 – 2,9]	2 ± 2,3 [0 – 7,7]
% DIAMETER CHANGE (mean ± SD) [range]	5,5 ± 3,3 [0 – 10,3]	5,2 ± 2,8 [8 – 8,8]	5,1 ± 2,06 [1,7 – 8,6]	5,8 ± 5,7 [0 – 18,1]
P	***P < 0,05***	***P < 0,05***	***P < 0,05***	***P < 0,05***
SYSTOLIC AREA mm^2 (mean ± SD) [range]	678,7 ± 156,8 [484,2 – 897,6]	551,7 ± 139,3 [372,5 – 871]	713,3 ± 294,4 [390,6 – 1326]	758 ± 261,9 [427,3 – 1154,7]
DIASTOLIC AREA mm^2 (mean ± SD) [range]	622,8 ± 150,5 [442,5 – 886,4]	501,9 ± 114 [361,4 – 736,6]	523,8 ± 129,1 [361,4 – 736,6]	660,8 ± 222 [387,7 – 1094,3]
ABSOLUTE AREA CHANGE mm^2 (mean ± SD) [range]	56 ± 44,7 [5,3 – 151,5]	49,9 ± 35,9 [4,2 – 134,4]	189,4 ± 274 [11,8 – 861,8]	97,2 ± 105 [12,4 – 337,3]
% AREA CHANGE (mean ± SD) [range]	8,3 ± 5,6 [0,6 – 16,9]	8,4 ± 4,9 [1,1 – 15,4]	19,6 ± 20,8 [3 – 65]	11,7 ± 9,7 [1,8 – 29,2]
P	***P < 0,05***	***P < 0,05***	***P < 0,05***	***P < 0,05***

TABLE 2: Systolic and diastolic measurements mean absolute changes and percentage changes at different thoracic aorta anatomic landmarks (SD: standard deviation; %: percentage).

mean ± DS	AGE ≤ 55	AGE ≥ 56	*p*	DIAB	n-DIAB	*p*
Abs. DIAM. CH. A (mm)	1.7 ± 0.3	1.6 ± 1.3	*n.s.*	1.8 ± 0.5	1.5 ± 1.3	*n.s.*
PERC. DIAM. CH. A (%)	5 ± 3.9	6.3 ± 1.1	*n.s.*	6.7 ± 1.6	4.7 ± 3.9	*n.s.*
Abs. AREA CH. A (mm^2)	65.2 ± 27	51.9 ± 52.6	*n.s.*	48.1 ± 23.6	58.5 ± 50.8	*n.s.*
PERC. AREA CH. A (%)	11.5 ± 4.4	6.7 ± 5.7	*n.s.*	9.1 ± 4.6	8 ± 6.2	*n.s.*
Abs. DIAM. CH. B (mm)	1.2 ± 0.9	1.8 ± 0.7	*n.s.*	1.5 ± 0.6	1.3 ± 0.8	*n.s.*
PERC. DIAM. CH. B (%)	4.6 ± 3.3	5.4 ± 2.6	*n.s.*	5.6 ± 2.2	4.9 ± 3.2	*n.s.*
Abs. AREA CH. B (mm^2)	53.2 ± 27.5	48.2 ± 41.1	*n.s.*	36.4 ± 12.4	54.4 ± 40.5	*n.s.*
PERC. AREA CH. B (%)	10.3 ± 5	7.5 ± 4.8	*n.s.*	6.7 ± 1.4	9 ± 5.5	*n.s.*
Abs. DIAM. CH. C (mm)	1.4 ± 0.4	1.7 ± 0.8	*n.s.*	1.6 ± 0.5	1.6 ± 0.8	*n.s.*
PERC. DIAM. CH. C (%)	4.4 ± 2.3	5.5 ± 2	*n.s.*	4.6 ± 2.1	5.4 ± 2	*n.s.*
Abs. AREA CH. C (mm^2)	395.6±419.1	86.4 ± 79.1	*n.s.*	507.9±433.8	83.3±74.1	*n.s.*
PERC. AREA CH. C (%)	34.9 ± 30.7	12 ± 8.6	*n.s.*	42.1 ± 33.7	12.1 ± 7.7	*n.s.*
Abs. DIAM. CH. D (mm)	3.8 ± 3.4	1.1 ± 0.6	*n.s.*	***3.7 ± 3***	***0.9 ± 0.7***	***0.05***
PERC. DIAM. CH. D (%)	10.3 ± 8.1	3.6 ± 2	*n.s.*	***10.4 ± 6.8***	***2.9 ± 2***	***0.03***
Abs. AREA CH. D (mm^2)	170±150.4	60.8±55.7	*n.s.*	209.7±156.7	59.7 ± 52	*n.s.*
PERC. AREA CH. D (%)	***19.4 ± 11***	***7.9 ± 6.8***	***0.05***	***21.5 ± 12.8***	***8.5 ± 6.4***	***0.04***

Table 3: Relation between aortic diameter and area changes and cardiovascular risk factors (DS=Standard Deviation; Abs.=absolute; PERC=percentage; DIAM=diameter; CH=change; DIAB=diabetic patients; n-DIAB=non-diabetic patients; n.s.=not significant).

mean ± DS	HT	n-HT	*P*	smoking	n-smoking	*p*
Abs. DIAM. CH. A (mm)	***1.1 ± 0.9***	***2.2 ± 0.8***	***0.01***	1.1 ± 0.7	1.8 ± 1.1	*n.s.*
PERC. DIAM. CH. A (%)	***3.8 ± 3.3***	***7.8 ± 2***	***0.01***	4.1 ± 2.8	6.1 ± 3.4	*n.s.*
Abs. AREA CH. A (mm^2)	36.1 ± 33.8	75.8 ± 48.1	*n.s.*	44.9 ± 34.4	63.9 ± 52	*n.s.*
PERC. AREA CH. A (%)	5.8 ± 5.9	10.7 ± 4.5	*n.s.*	7.5 ± 6.1	9 ± 5.7	*n.s.*
Abs. DIAM. CH. B (mm)	1.4 ± 0.7	1.3 ± 0.8	*n.s.*	1.4 ± 0.9	1.4 ± 0.7	*n.s.*
PERC. DIAM. CH. B (%)	5.5 ± 3	4.7 ± 2.6	*n.s.*	5.5 ± 3.8	5 ± 2.3	*n.s.*
Abs. AREA CH. B (mm^2)	48.2 ± 33	55.5 ± 41.7	*n.s.*	43.8 ± 34.9	54.2 ± 38.7	*n.s.*
PERC. AREA CH. B (%)	9.2 ± 5.9	7.6 ± 4	*n.s.*	8.3 ± 6.3	8.5 ± 4.1	*n.s.*
Abs. DIAM. CH. C (mm)	1.4 ± 0.6	1.8 ± 0.8	*n.s.*	1.2 ± 0.5	1.7 ± 0.7	*n.s.*
PERC. DIAM. CH. C (%)	5.2 ± 1.9	5 ± 2.4	*n.s.*	4.8 ± 1.9	5.2 ± 2.2	*n.s.*
Abs. AREA CH. C (mm^2)	53.9 ± 39.4	325.1±345.7	*n.s.*	***29.6 ± 12.5***	***303.7±317.9***	***0.06***
PERC. AREA CH. C (%)	10.3 ± 6.1	29 ± 26.5	*n.s.*	***6.2 ± 2.7***	***29.2 ± 23***	***0.04***
Abs. DIAM. CH. D (mm)	***0.7 ± 0.4***	***3.6 ± 2.8***	***0.02***	0.9 ± 0.6	2.6 ± 2.7	*n.s.*
PERC. DIAM. CH. D (%)	***2.8 ± 1.9***	***9.5 ± 6.7***	***0.03***	3.5 ± 2.4	7 ± 6.6	*n.s.*
Abs. AREA CH. D (mm^2)	64.3 ± 61.7	130.1±133.6	*n.s.*	***30.1 ± 14.5***	***145.1±116.9***	***0.04***
PERC. AREA CH. D (%)	9.9 ± 7.4	13.6 ± 12	*n.s.*	***6.2 ± 3.9***	***15.7 ± 10.9***	***0.06***

TABLE 4: Relation between aortic diameter and area changes and cardiovascular risk factors (DS=Standard Deviation; Abs.=absolute; PERC=percentage; DIAM=diameter; CH=change; HT=Hypertensive patients; n-HT=non-hypertensive patients; n-smoking=non-smokers; n.s.=not significant).

FIGURES

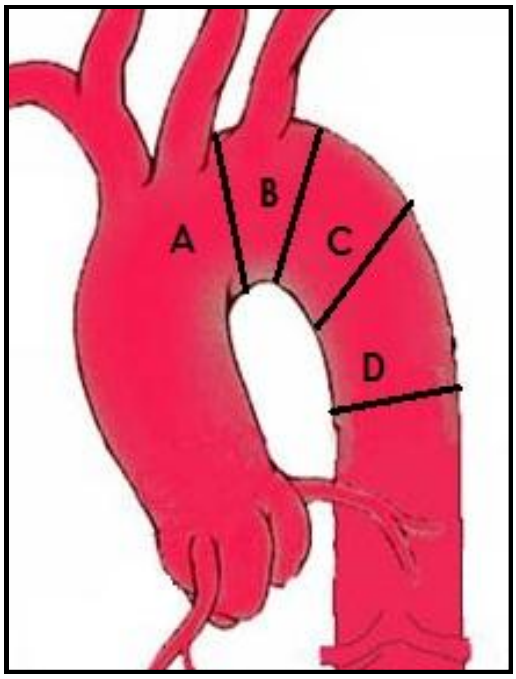

FIGURE 1: Anatomical levels: 1 cm proximal to left subclavian artery (level A), 1 cm (level B), 3 cm (level C) and 10 cm distal to left subclavian artery (level D).

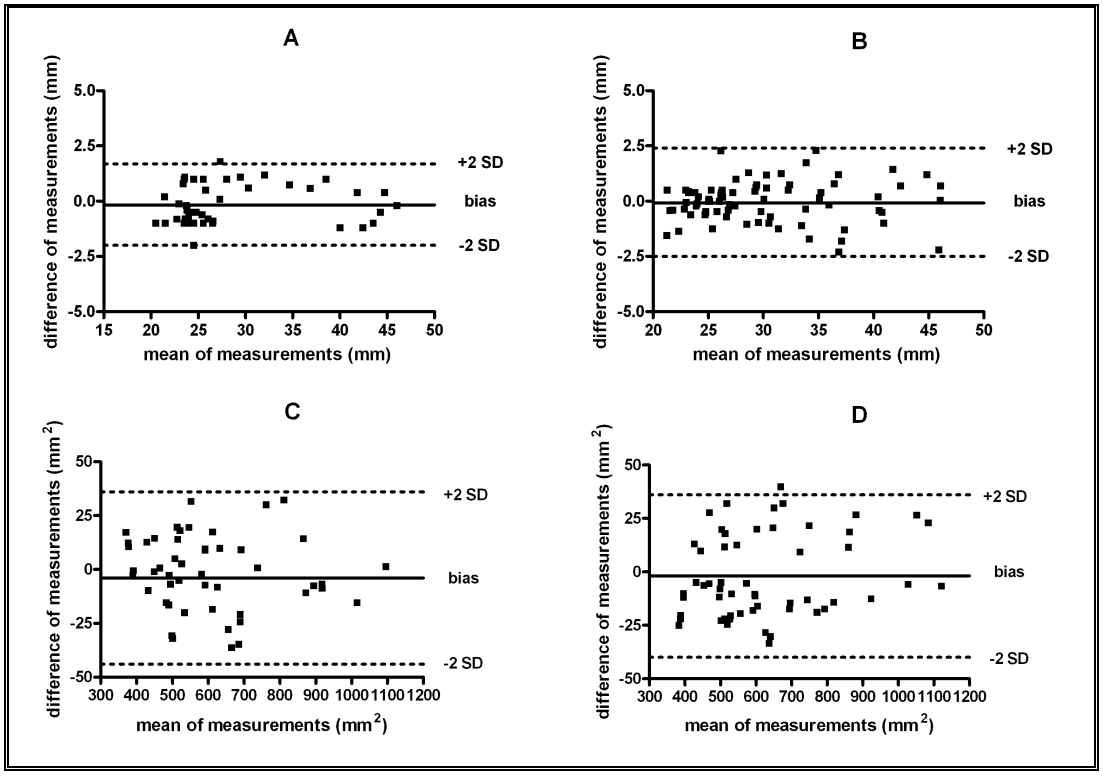

FIGURE 2: the INTRA-observer (**A**) diameter measurements comparison revealed a mean bias of 0.19 mm (range from -1.95 to 1.56 as 95% limits of agreement). The INTER-observer (**B**) variability of mean diameter measurements had a mean bias of 0.08 mm (range from -2.5 to 2.38 as 95% limits of agreement). The INTRA-observer (**C**) area measurements evaluation showed a mean bias of 4.07 mm^2 (range from -44.25 to 36.12 as 95% limits of agreement). Lastly the INTER-observer (**D**) variability of mean area had a mean bias of 1.91 mm^2 (range from -40.03 to 36.22 as 95% limits of agreement). Differences of pair are plotted against the mean of measurements.

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