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**Study Protocol**

## Study Protocol

# 3D speckle tracking for evaluation of dilative ascending aorta biomechanics: sensitive markers for ascending aorta longitudinal strain predict aortic root dilation rate

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## Abstract

Ascending aortic aneurysm is a predisposing condition for rupture and a risk factor for dissection. In autopsy studies, the prevalence of aortic dissection ranges from 0.2% to 0.8%, whereas in most population-based studies, the incidence of aortic dissection ranges from 0.61 to 7.2/100 000 persons. The surgical option, or endovascular treatment, remains the only effective treatment. Very often, the aorta ruptures at echocardiographic or CT values lower than those indicated by the guidelines for performing an operation. Therefore, research efforts are aimed at discovering new markers for earlier diagnoses to intervene preventively on dilated aortas at risk of rupture. The protocol of our study involves the evaluation of the longitudinal deformation of the dilated ascending aortas that must undergo surgery and their histological data. The objective would be to identify whether the altered distensibility of the aorta upon echocardiographic control is confirmed by histological data in terms of stiffness or other pathophysiological aspects. This would allow the identification of new markers for the early diagnosis of aortas at increased risk of rupture, even if they do not reach the diameters indicated by the guidelines. Patients over 18 years of age, diagnosed with ascending aortic aneurysm with simultaneous aortic valve disease, will be considered for the study. They will be analyzed by intraoperative transesophageal echocardiography with speckle tracking echocardiography during five heart beats using 2D and 3D images. The study will define the 3-segment ascending aorta (aortic ring, aortic root and proximal ascending aorta) and the four quadrants of the ascending aorta (internal curvature, anterior wall, external curvature and posterior wall). A short-axis view at the level of maximum dilation, a long-axis view of the ascending aorta and a histological examination of the aorta. Data will be collected on demographics, clinical data, screening, family history, adherence to study methods, intraoperative details, intraoperative histology and the type of surgery performed. The results of our study will be published in a peer-reviewed journal, and the abstracts will be presented at national or international conferences.

## INTRODUCTION

Ascending aortic aneurysm is a predisposing condition for rupture and a risk factor for dissection. Due to the increased risk of acute aortic syndromes, surgical repair is recommended for patients with ascending aortic aneurysm, according to guidelines, when the diameter exceeds 55 mm [1]. Because they are most often asymptomatic, aortic aneurysms can cause sudden death from rupture of the aorta [2]. In autopsy studies, the prevalence of aortic dissection varies from 0.2% to 0.8%, while in the majority of the population series, the incidence of aortic dissection varies from 0.61 to 7.2/100 000 people. From a therapeutic point of view, there are currently no pharmacological treatments for dilated aortas; therefore, the surgical option or endovascular treatment remains the only effective cure [3]. At the moment, the pathogenetic mechanisms are partly unknown due to the high heterogeneity of the pathophysiological aspects. For this reason, surgical treatment, which may affect the ascending aorta or aortic root, is recommended in patients with ascending aortic aneurysm. Echocardiographic speckle tracking is gaining increasing interest in analyzing the mechanical behavior of the ascending aorta. Combining echocardiography with histological and immunohistochemical tests will provide a better understanding of the biomechanical behavior of the ascending aorta [4], which may help predict aortic complications in high-risk patients and therefore plan their management [5]. In fact, a late diagnosis can expose the patient to a prognosis of thoracic aortic aneurysm (TAA) and acute aortic syndromes, in particular aortic dissection, that becomes extremely unfavorable to the occurrence of serious complications, such as rupture or the presence of multiple organs with clinical signs of

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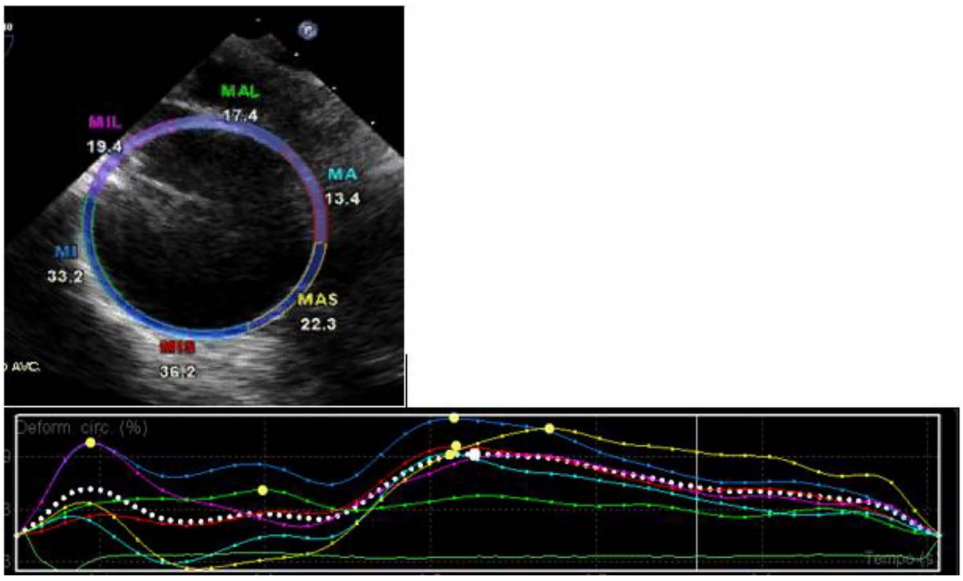


**Figure 1:** Intraoperative TEE

malperfusion. Open surgery is the first choice for aneurysm repair. It is a chronic disease characterized by a permanent localized dilation of the aorta in which an adverse remodeling of the aortic wall occurs and can subsequently progress, predisposing to potentially lethal consequences, such as aortic rupture, which has a very high mortality rate of over 80% and causes 150 000–200 000 deaths every year worldwide [6]. Aortic aneurysms are generally classified as aneurysms that form in the ascending tract, descending thoracic arch or aorta or abdominal aortic aneurysms (AAA). Distinct pathological mechanisms are considered in aneurysms of the thoracic tract and in the abdominal tract. Data in the literature consider several risk factors for aortic aneurysms, including age, smoking, hypertension, hyperlipidemia, male sex, white race and a positive family history [7]. Aortic rupture must not only be a consequence of the increase in the diameter of the aneurysm but also derives from specific alterations, which involve the progressive expansion and weakening of the three layers of the aorta: intima, media and adventitia. Numerous pathological processes contribute, such as breakdown of the extracellular matrix (ECM), inflammation, phenotypic change of vascular smooth muscle cells (SMCs), oxidative stress and neovascularization [8]. These mechanisms can initiate the degradation of elastic fibers and alterations in collagen composition, compromising both the structural part and the flexibility of the aortic wall [9]. Although various studies have established which pathological mechanisms of aortic aneurysms are included, there are currently no effective drugs to treat aortic aneurysm growth or rupture [10].

## MATERIAL AND METHODS

Patients affected by ascending aortic aneurysms undergo intraoperative transesophageal echocardiography and speckle tracking echocardiography during five heartbeats using 2D and 3D images (Fig. 1). To define 3-segment ascending aorta (aortic annulus, aortic root and proximal ascending aorta) and four quadrants of ascending aorta (inner curvature, anterior wall, outer curvature and posterior wall). To view on the short axis the level of maximum dilatation, the long axis views the ascending aorta. Monitoring blood pressure and heart rate. Coupling echo images with histological exams (Fig. 2).

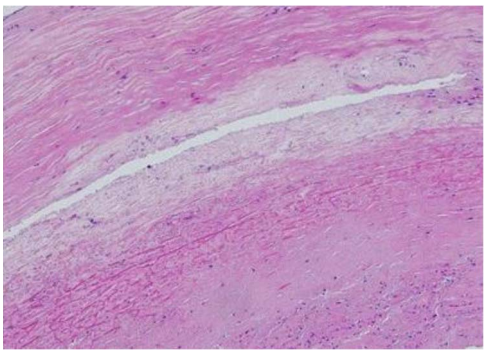

**Figure 2:** Hystological analysis

## RESULTS

Hundred patients undergoing ascending aorta surgery at the Cardiac Surgery Division of the Tor Vergata Hospital will be enrolled. In all cases, a preoperative echocardiography evaluation with strain quantification will be performed (peak ascending aorta strain PaAS, stiffness index, distensibility, diameter and elasticity). All the ascending aorta specimens will be sent for histological and immunohistochemical evaluation. A correlation between strain quantification and histological and immunohistochemical biomarkers will be performed.

Primary aim: to evaluate the correlation of the echocardiographic data of the dilated aortas with the histological data; and secondary aim to define whether, once the normal diameter parameters are exceeded, there is a loss of elasticity and therefore a predisposition to develop acute aortic syndromes.

Secondary aim: diagnostic and prognostic role of strain.

### Eligibility criteria

Inclusion criteria age ≥ 18 years, aortic aneurysm ≥45 mm, aortic aneurysm ≥45 mm with aortic valve disease, provide informed consent.

Exclusion criteria: acute aortic syndromes, connective tissue diseases, contemporary coronary artery disease or mitral and tricuspid disease, do not provide informed consent, data collection tool and sample size.

### Outcome measurement discussion

Primary outcome: velocity of aortic growth, acute aortic dissection.

Secondary outcome: mortality.

### Data analysis

Continuous variables will be expressed as mean ± standard deviation and categorical variables as numbers (percentage). Differences between groups for continuous parameters will be assessed by the student's *t*-test or $\chi^2$ test. A Cox analysis will be performed to assess the capability of aortic biomechanical parameters to predict aortic events and aortic root growth. SPSS was used for all analyses.

### Ethics

Participants shall be informed of the reasons and nature of the study. Informed consent shall be sought, and participants will be informed they can withdraw from the study at any moment.

## LIMITATIONS

### Selection bias

Our study involves performing operator-dependent examinations, therefore making us vulnerable to selection bias at different stages of the registry data collection process. Selection biases reflect the biases present in conducting a clinical practice in the context described. Upon registration in the registry, patients are notified by completing an authorization to be present in the registry within the practice and providing the relevant patient information. Patients' ability to engage in this process may be limited by the anatomical characteristics of the cardiac structures or the need for emergency interventions. Patients requiring coronary bypass or mitral valve surgery are excluded. While these records are subsequently excluded from the dataset, all other presentations (patients may present with multiple problems) that meet the clinical criteria for inclusion are automatically enrolled in the registry, minimizing the risk of criterion-based selection bias in diagnostic or other clinical criteria.

### Classification bias

The real-time requirement for data collection prior to the initial consultation for patients new to the practice presents challenges with respect to both information and classification biases. The registry depends on baseline information to establish a minimum dataset sufficient to place a record in the relevant patient cohort (e.g. changes in surgical strategy, concomitant valvular disease). Reference information can be highly variable in its completeness and accuracy. Patient cohort prioritization was used to mitigate classification bias for the cohort of interest. However, future work may examine the potential benefits of this study, depending on the outcome of the findings and the limitations of bias.

### Information bias

As with any clinical study, our proposal relies on transforming clinical notes and attachments into tabulated data for processing, labeling and consolidation within a registry database. While full access to notes must go through guarantor authorization for all participating surgical practices, the structure and level of detail of the notes and observations may vary. Future work aims to integrate any data from other institutions to automatically apply the agreed coding rules to the raw text; however, the challenge of linguistic harmonization among contributors remains ongoing.

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## CONFLICT OF INTEREST STATEMENT

None declared.

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This research received no external funding.

## AUTHOR CONTRIBUTIONS

D.B. contributed to the clinical problem and study question. D.B., P.N., C.B. and C.P. developed the methods, wrote the manuscript and provided project management. C.A. contributed to the clinical problem, wrote the manuscript, and provided project management. V.A., P.P., A.F., R.S. and C.A. contributed to the clinical problem and provided project management. D.B., P.N. and C.P. they wrote the manuscript. A.O. contributed to the clinical problem, contributed to the study question, developed the methods and wrote the manuscript. M.G.S. and S.T. contributed to the study application, developed the methods and wrote the manuscript. P.N. and C.A. developed the methods.

## DISSEMINATION

We intend to publish our study in a peer review journal. We might present it too at national or international conferences.

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