UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

FACULTY OF GENERAL MEDICINE

NATURAL EVOLUTION OF THE AORTA

PhD THESIS ABSTRACT

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BACKGROUND

PERSONAL CONTRIBUTION

KEYWORDS

Aorta, aging, luminal diameter, correlation, echocardiography, pathology.

BACKGROUND

INTRODUCTION

Nowadays, when life expectancy has shown a spectacular upsurge, cardiovascular diseases have become the leading cause of death in industrialized countries, despite unprecedented advances in diagnosis and treatment of these disorders. Age is unarguably associated with high risk for cardiovascular events and recent population studies estimated that in Europe, in 2025, the number of elderly will reach 197.9 million by 11% and 78.5% higher than during 2010 or 1975.

Aortic aneurysms are an important cause of mortality and morbidity with an incidence rate of approximately 10.4 per 100,000 persons/year. Frequency is similar for both sexes showing a progressive increase with age and diagnosis of this condition is increasing due to improved screening methods and imaging techniques. The peculiarity of this pathology is very high risk of mortality associated with unrecognized or untreated aneurysms and understanding that most small deviations from normal morphology will not lead to dramatic consequences.

Today, technological progress provides access to a variety of imaging methods that allow examination of the aorta, and selection of the optimal method for evaluation and monitoring is challenging for clinicians, decision being based on specificity, sensitivity of testing and also on cost-effectiveness.

Transthoracic echocardiography (TTE) is the method of choice for initial evaluation of the aorta, being a non- invasive technique, easy to apply that does not involve radiation. Comparison of aortic diameter values obtained by TTE to those offered by complex, expensive methods considered the gold standard is difficult because measurement technique and timings are not standardized and the resulted differences may have clinical implications.

PERSONAL CONTRIBUTIONS

MOTIVATION AND OBJECTIVES

The essentially reason for this study was the desire to analyze the natural history of proximal thoracic aorta in a population without cardiac disease and the relationship between diameters and anthropometric parameters (gender, age, height, weight).

Subsidiary, absence from literature of normal reference values for thoracic aorta diameters obtained by two dimensional (2D)-TTE using inner- inner -edge to edge measurement technique, as recommended in current guidelines, was another argument for present study. Nomograms thus obtained would correspond to those achieved from complex imaging techniques, facilitating both comparison of results and patient monitoring.

The angle of insertion of the aorta into the left ventricle represent an important geometric parameter and was investigated in a small study, three decades ago, when it was proposed that changes of aortic-ventricular coupling contributes to the genesis of hemodynamic disturbances. In this study I proposed a reanalysis of this parameter with high performance ultrasound machines, offering the premises for further hemodynamic investigations by providing normal ranges.

By demonstrating increased feasibility of two-dimensional echocardiographic of aortic assessment and showing that results obtained with this method overlap those obtained by complex methods is an important aspect, as aortic values derived from CT and MRI are based mainly on the inner edge convention, and in the current era of multimodality assessment, comparison between different methods of imaging is mandatory in attempting to facilitate communicability, data exchange, and patient monitoring among different labs.

The **objectives** studied in this thesis are as following:

- Obtaining reference values for proximal thoracic aortic diameters measured by the conventional method TTE -2D and inner edge-to inner edge technique;
- Analysis of the relationship between aortic diameters and different anthropometric predictors to identify the predictor with the largest influence on proximal thoracic aorta diameter;
- Evaluation of the effect of aging on the aorta using a multidisciplinary approach, echocardiographic and pathological, by analyzing the evolution of aortic diameter per decade of age and gender;
- Comparing and analyzing the correlation between the results of the two studies;

- Obtaining a formula for allometric and ratiometric prediction of aorta diameters by identifying constants for gender and anthropometric indices;
- The analysis of the angle of insertion of the aorta into the left ventricle;
- Analysis of two-dimensional TTE feasibility and reproducibility in evaluating proximal thoracic aorta morphology.

MATERIALS AND METHODS

To achieve the previous objectives we conducted a complex descriptive project, multidisciplinary, multicentric. Aortic morphology was analyzed by two different methods, echocardiographic and pathologic.

Study A – ***echocardiographic*** - was retrospective, involving a number of 500 healthy subjects which were assessed by TTE at Monzino Cardiology Center, Italy, between the years 2007-2012. Cardiac examination was performed with latest generation ultrasound machines equipped with transducers suitable for two-dimensional TTE. According to the internal protocol of the laboratory, each echocardiographic examination was archived and still and moving images were stored in DICOM format (Digital Imaging and Communications in Medicine). After selecting suitable subjects, the images for each patient were retrieved from the PAC system (Picture Archiving and Communication) and processed offline using software Medimatic (Medimatic , Genova , Italy) dedicated to analyzing images stored in digital format.

The echocardiographic study consisted of measuring proximal thoracic aorta at five levels (aortic annulus, aortic root, sinotubular junction, ascending aorta, aortic arch) using two-dimensional measuring convention "inner -edge" which implies assessment of internal aortic lumen and excluding vascular walls.

The relationships between aortic measurements and subject characteristics were investigated using bivariate linear regression. Independent associations between aging and aortic measurements were studied using multivariate linear regression, applying both ratiometric and allometric methods. To assess reproducibility, the main investigator repeated the analysis after a period of 2 weeks. A second independent observer, blinded to principal observer's results, performed the measurements in a randomly chosen subgroup of 50 subjects. Interobserver and intraobserver variability were studied as intraclass correlation coefficients.

The **Study B** – ***morphopathologic*** - was prospectively performed in Pathology and Cytology Service Emergency County Hospital of Craiova between years 2012-2013. The study included analysis of vascular tissue samples obtained from 91 subjects who died of different causes and were autopsied. Aortic samples were harvested from four sites: ascending aorta,

aortic arch, distal thoracic aorta and abdominal aorta. The study was designed to support the results of the echocardiographic study regarding influence of age on the aorta. To assess the internal dimension (luminal) of the arteries a program designed in MATLAB programming environment (Mathworks) was developed and used. According to the program, each artery was traced manually and the image was calibrated using a provided ruler positioned within the picture.

Statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL) and Microsoft Excel module of the software package Microsoft Office XP Professional Excel Package. P values <.05 were considered significant.

RESULTS

STUDY A-ECHOCARDIOGRAPHIC

Echocardiographic study results are divided into several subchapters addressing population distribution by gender, age and anthropometric data, echocardiographic profile and diagnosis, reference values for proximal thoracic aorta diameters and aortic - septal insertion angle, the influence of anthropometric indices, feasibility and reproducibility of imaging methods. The multivariate analysis results including anthropometric constants, the prediction formulas and expected progression of different studied parameters are also exposed in details.

Study A consisted of a homogeneous group in terms of gender and age distribution. As expected, anthropometric indices (height, weight, body surface area) showed higher values in male subjects.

The reference values for proximal thoracic aorta

From the statistical analysis it was observed that men expressed higher absolute ***aortic annulus*** size (19 - 25 mm, CI 95%) than women (17 - 22 mm, CI 95%). Average diameters indexed to body surface area were 11.7 ± 1.0 mm/m^2 and 11.6 ±1.0 mm/m^2 for woman respectively man.

Average absolute values for ***aortic root*** was 28.0 ± 2.9 mm for females and 31.8 ± 3.2 mm for males and 17.0 ± 1.9 while average indexed diameters 17.0±1.9 mm/m^2 for females and 16.6 ± 1.8 mm/m^2 for males.

Sinotubular junction followed the same trend as previously analyzed parameters, expressing highest values for males (males 22-32 mm, 19-28 mm females, CI 95%). Averaged absolute values for the female group was 24.1 ± 2.6 mm and 26.8 ± 2.9 mm for male subjects while indexed values were 14.7 ± 1.7 mm/m^2 respectively 13.9 ± 1.8 mm/m^2.

Reference range for ***ascending aorta*** in female subjects was 23-33 mm and 25-36 mm for men, with a confidence interval of 95 %, and the average absolute values for females were 27.9 ± 3.3 mm and 30.1 ± 3.3 mm for males. Average indexed values were 16.9 ± 2.3 mm/m^2 for women and 15.7 ± 1.8 mm/m^2 for man.

Aortic arch expressed mean absolute values of 19.6 ± 2.4 mm for female subjects and 21.4 ± 2.4 mm for males and the reference range calculated for women was 16-24 mm and 17-25 mm for males, with a confidence interval of 95 %. In the analysis normalized for body surface area result was 11.9 ± 1.5 mm/m2 for the sample of women and 11.2 ± 1.4 mm / m 2 for men.

Aortic - septal angle expressed smaller absolute and indexed values in the male group (absolute values of 123 ± 14 degrees for males and 129 ± 13 degrees for females). Regarding the indexed values, average values for males were 65 ± 10 degrees and 78 ± 10 degrees for women. All values obtained were statistically significant with $p < 0.05$.

Evolution of the aorta and influence of anthropometric indices

By analyzing influence of anthropometric indices on aortic growth we observed that age is the best predictor for all aortic diameters except aortic annulus which apparently does not increase in size after reaching adulthood. Height was the weakest predictor for all diameters and weight and body surface area showed similar correlation values . The aortic - septal angle, proved to be influenced only by age that causes a reduction in size.

Prediction formula

Multivariate statistical analysis showed that aortic annulus expresses a natural progression of 0.2 mm / decade of age, 0.4 mm with 10 kg weight gain and 0.4 mm with 10 cm height gain while aortic root showed a significant growth with age, with a natural progression expectation of 1 mm per decade of age, 0.56 mm with 10 kg weight gain and 0.66 mm with 10 cm height gain.

For the sinotubular junction we predicted an increase in diameter of 0.74 mm per decade of age, 0.69 mm with each 10 kg and 0.66 mm for every 10 cm added to height.

Ascending aorta showed the most significant natural progression with age indicating a growth of 1.09 mm per decade of age, 0.66 mm with each 10 kg increase in weight and 0.02 mm with every 10 cm added to the height.

Meanwhile, each decade of age was associated with an increase of the aortic arch by 0.75 mm, each 10 kg weight gain added 0.67 mm and every 10 cm height gain added 0.60 mm the aortic arch size.

All values obtained were highly statistically significant with $p < 0.001$.

Feasibility and reproducibility

Reproducibility analysis showed good to excellent accordance between repeated measurements, for all aortic segments and the aortic-septal angle.

Feasibility of measurement was 100 % for the aortic annulus, aortic root, sinotubular junction and ascending aorta, 99 % for the angle of insertion of the aorta from the left ventricle and 83% for the aortic arch. In the population that aortic arch could not be assess proportion of men was double the proportion of women

STUDY B - MORPHOPATHOLOGICAL

In study B, the gender distribution of the sample population demonstrated predominance of males with a general report M / F of 1.53 while female population showed a slightly higher average age than the males. All measured diameters expressed positive linear correlation with age ($p < 0.05$). Ascending aorta demonstrated to be the most influenced by age while abdominal aorta showed modest progress with age. Men demonstrated higher mean values of aortic diameters than women.

CONCLUSIONS

In the context of constant higher anthropometric indices in men was a noticeable difference between the absolute values of aortic diameters and normalized to body surface area values was observed, in the sense that while the absolute values determined in males were higher than those determined in women after normalization the ratio reversed .

This study demonstrates that normalization for body surface area and weight provides overlapping data while indexing for height is not recommended because of the minimum influence of this parameter on the evolution of aortic dimensions .

The evolution of aortic-septal angle values is influenced only by age, the sharpening phenomenon with age being more pronounced in men.

Estimated progression for each decade of age presented high dispersion, ranging from 0.02 mm for the aortic annulus and reaching 1.03 mm for the ascending aorta, which showed the most pronounced growth with age.

The present study has provided a new clinical accurate tool that allows direct comparison of determined aortic diameters with estimated diameters thus avoiding comparison with diagrams that provide a wide range of values.

Changes in aortic diameters at the various sites of determination were similar in both genders, in both studies, the lowest values being recorded in the aortic annulus and the largest in the ascending aorta.

Statistical analysis indicated that the best predictor for all aortic segments is the age, except for the aortic annulus, which apparently expresses minimum diameter changes after reaching adulthood.

Comparative evaluation between measurements in vivo and morphological measurements on tissue sample of the average values of aortic diameter revealed similar information concerning evolution with age, gender and site of determination with the specification that the values derived from morphology measurements were consistently lower possibly due to the fact that the measurements were taken after formalin fixation of the tissue specimen.

According to the imagistic study which was supported by determinations made directly on human, two dimesional transthoracic echocardiography is a feasible, reproducible method that allows accurate evaluation of proximal thoracic aortic diameters.