Original Article

Correlating Possible Predisposing Demographics and Systemic Conditions with the Aortic Root

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Abstract

Background: The aortic root is an aggregate of various components that connects the left ventricle to the aorta. The most predominant pathologies have been associated with the dilation of the aortic root leading to aneurysms. **Aim:** This study is designed to measure the role of systemic morbidities such as hypertension, diabetes, and body-mass-index has on the dimension of the aortic root. **Materials and methods:** Participants were volunteers who were recruited during and after an organized health fair by the Medical Students' body from …, School of Medicine, …. 169 participants, 62 males, 107 females with ages ranging from 9-84 years agreed to participate by signing the consent after which a questionnaire was administered and a preliminary clinical procedure was used to check for blood pressure, blood glucose, and body mass index. The measurement of the aortic root was carried out by an experienced single investigator using a DUS 5000 ultrasound machine (Miami, Florida, USA) using a low-frequency micro-convex transducer preset to "adult cardiac" with a default frequency of 4MHz. **Results and Discussion:** Among the participants, 35.03%, 47.80%, and 29.11% had normal blood pressure, blood glucose, and BMI readings, respectively. The chi-squared analysis identified a significant correlation between the diameter of the aortic annulus and body mass index. Diastolic blood pressure also correlated with the diameter of the aortic annulus. Sinus of Valsalva showed no correlation with blood pressure, blood glucose, and body mass index. **Conclusion:** The disparity in how systemic factor individually correlates with the aortic annulus and the sinus of Valsalva is not clear. The study targets to provide educational concept in this regard.

Keywords: Blood pressure; Blood glucose; Sinus of Valsalva; Aortic annulus; Aortic root; Body mass index

Introduction

Anatomy of the aortic root

The aortic root is the bridge between the left ventricle and the ascending aorta. It forms the outflow tract from the left ventricle that supports the aortic valve leaflets [1]. The aortic root is a complex structure that allows unidirectional blood flow while maintaining laminar blood flow, minimal resistance, tissue stress and damage [2]. This coordinated function of the aortic root ensures adequate coronary perfusion and left ventricular function [3,4]. The aortic root is an aggregate of distinct entities [Figure 1], namely: the aortic valve leaflets, the leaflet attachments, the sinuses of Valsalva (SV), the inter-leaflet trigones, the Sinotubular junction and the annulus [2,5]. [Figure 1].

The aortic valve has three leaflets that form the physical boundary between the left ventricle and aorta. The presence of three leaflets ensures that there is low resistance valvular opening. Valvular dysfunction can occur if there is an alteration of the size and height of the leaflets [5]. The leaflet is attached to the aortic root wall in a crown shaped manner termed the "annulus". There are three bulges on the aortic wall and this is collectively called the sinuses of Valsalva [6,7]. The Sinotubular junction separates the aortic root from the ascending aorta. Dilatation of the Sinotubular junction can lead to aortic valve insufficiency.

There has been variation amongst surgeons as to what the annulus represents. Many surgeons believe it represents the remnants of the removed valvular leaflets, [8] while others describe it as the virtual, circular ring that is defined by the semi-lunar leaflet attachments [2]. One thing is clear though, the dimension and

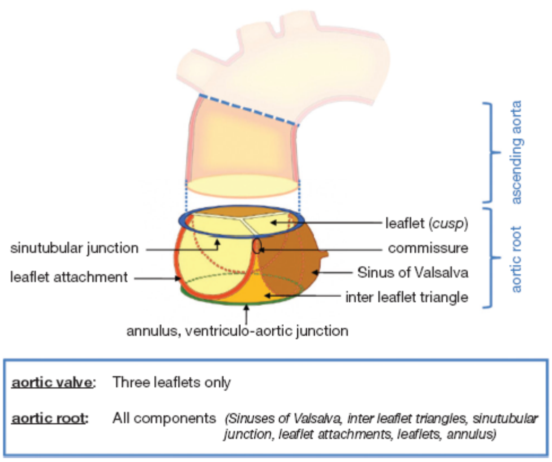

Figure 1: Proposed classification for the aortic root components [2,6].

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geometry of the aortic annulus are essential in determining the long term durability of aortic root repair [2]. The annulus is the diameter that is analyzed by the echocardiographer when providing the diameter of the aortic [1].

Physiological determinants and mechanisms of aortic root dilatation

There are factors that have been shown to have some impact on the dimensions of the aortic root in the healthy and the non-athletic population. Of these, demographic characteristics happen to be most relevant. These include; age, sex, height and body size and blood pressure to some extent [9]. Among the demographic factors, height has been shown to be the most important determinant of the size of the aortic root [10]. Several autopsy reports have associated aortic root size and age [11]. and have been hypothesized to be as a result of increasing collagen in the wall of the aorta with increasing age. This results in stiffness and progressive vessel enlargement while responding to mechanical stress. Though attributed to the relatively average lesser body size, females have been generally accepted to have smaller aortic dimensions [12]. Blood pressure, however, has stirred up several debates surrounding its relationship to the size of the aortic root [13,14]. Pelliccia et al. [9]., also demonstrated that the aortic root dimensions of healthy athletes are in the 99th percentile which corresponds to the upper limits of physiological remodeling of the aortic root and this has been attributed to be the adaptation to chronic exercise.

Pathological determinants

There are several disease processes and pathologies that have also been linked to dilatation of the aortic root resulting in a dysfunctional aortic valve with a net valvular insufficiency. Formerly in North America, aortic root dilatation was observed to be the most important cause of aortic valve insufficiency [15]. Some pathologies predisposing to aortic root dilatation include; bicuspid aortic valve, the most common congenital cardiac defect, frequently linked to aortic dilatation and cystic medial necrosis, [16] possibly due to the intrinsic weakness of the media [17]. Ankylosing Spondylitis, a spondyloarthropathy, in 2-10% of cases has been associated with cardiovascular diseases [18] such as aortic root dilatation, and resulting dilatation is attributed to a sclerosing inflammatory process involving the aortic root [19]. Marfan's syndrome, caused by mutations in the gene coding for the fibrillin-1 protein [20] results in structurally weak elastic fibers within the media of the aorta. Some others include, emphysema probably due to the increased systemic elastolytic activity, [19] foramen ovale, due to an underlying tissue disorder or a mechanistic effect [21]. Mucopolysaccharidosis [22] and Syphilitic aortic aneurysm caused by an obliterative endarteritis of the vasa vasorum of the aorta [19]. Hypertension has also been linked with an increased diameter of the aortic root at the supra-aortic ridge and proximal aorta, but asymptomatic [23]. The implication of diabetes on the morphology of the aortic root has been associated with a protective role from aortic root dilatation [22,24].

This study is aimed at correlating aortic root dimensions to basic demographics and variables captured in a population of Dominicans. Largely, the study hopes to access the impact universal morbidities such as hypertension, diabetes, and body-mass-index have on the dimension of the aortic root.

Materials and Methods

Participants

Participants were attendees at the health fair organized by the American Medical Students Association (AMSA). This health fair is an approved program by both the University governing body and the Ministry of Health; the study was approved by the Research and ethical committee of the All Saints University, School of Medicine. A consent form detailing the procedure to be performed was given to the volunteers and the procedure was further duly explained by student assistants at the fair. 169 participants, 62 males, 107 females with ages ranging from 9-84 years agreed to participate by signing the consent after which a questionnaire was administered.

Preliminary checks

The variables included in the questionnaire were: age (sub-categorized into 8 groups), sex, lifestyles categorized as sedentary or active. Subsequently, simple clinical procedures were done, such as blood pressure checks and classified using the hypertension classification, [25] body-mass-index (BMI), [26]. and blood glucose checks which were categorized into normoglycemia, hypoglycemia, hyperglycemia, and diabetic. The participants categorized as hyperglycemic are those having; i) impaired fasting glucose and ii) those with the provisional diagnosis of Diabetes [27]. The participants categorized as diabetic are those who gave a history of previously confirmed cases of diabetes and were on treatment.

Ultrasound examination and measurements

The measurement of the aortic root was carried out by an experienced single investigator using a DUS 5000 ultrasound machine (Miami, Florida, USA) using a low-frequency micro-convex transducer preset to "adult cardiac" with a default frequency of 4MHz.

The participants were requested to expose their chest to around the 5th intercostal and were given a clean drape to cover themselves in order to make them comfortable and were required to lie supine on the examination bed. During the scan, only the required area was exposed (the left thoracic region up to about the 5th intercostal space). The transducer was applied to the subject's chest wall on the 2nd to the 4th intercostal space left parasternal area looking at the heart in its longitudinal axis (left parasternal view) [12]. Using this view, we are able to visualize and measure the largest diameter of the aortic root. Two-dimensional aortic root measurements were done at the end of diastole at the left parasternal long-axis view at 2 levels: 1) annular region (corresponds echocardiographically to the aortic cusps hinge points); 2) the sinus of Valsalva [28].

Statistical analysis

Statistical analysis was performed by STATA/IC 13.0 for windows (Texas, United States of America). Group comparisons based on the self-administered questionnaire was done by chi-squared analysis. Multiple regression analysis was also performed to predict factors that influence the diameter of the sinus of Valsalva and aortic annulus. Linear prediction graphs were also illustrated to show possible correlations. Statistical hypothesis tests with $p<0.05$ was considered as significant. Values are presented as mean ± standard deviation or number (%).

Table 1: Demographic information and their impact on the diameter of the sinus of the valsalva and aortic annulus.

Baseline characteristics		Frequency % (n)	Mean diameter of the sinus of the Valsalva mm (S.D)	Chi-Squared P-value	Mean diameter of the aortic annulus mm (S.D)	Chi-Squared P-value
Sex	Male	36.69 (62/169)	34.71 (3.75)	0.001	24.88 (2.86)	0.043
	Female	63.31 (107/169)	32.19 (3.59)		23.43 (3.04)	
Lifestyle	Sedentary	36.17 (34/94)	32.67 (3.19)	0.701	24.9 (3.49)	0.281
	Active	63.83 (60/94)	32.81 (3.53)		24.08 (3.19)	

Table 2: Systemic evaluation and their impact on the diameter of the sinus of the valsalva and aortic annulus.

Category by examination	Mean diameter of the sinus of the valsalva mm (S.D)	Mean diameter of the aortic annulus mm (S.D)	P-value (sinus of valsalva and aortic annulus)
Normal B.P	32.61 (3.35)	22.86 (2.53)	0.542 and 0.91
Prehypertensive B.P	33.32 (3.70)	24.55 (3.09)	
Stage 1 hypertensive B.P	33.15 (4.65)	25.15 (3.51)	
Stage 2 hypertensive B.P	34.74 (3.15)	25.47 (2.55)	
Normal B.G	33.04 (3.50)	23.65 (2.27)	0.05 and 0.449
Hypoglycemic	34.41 (3.62)	24.7 (2.68)	
Hyperglycemic (impaired glucose homeostasis and provisional diagnosis of diabetes)	32.93 (3.58)	23.12 (3.27)	
Diabetic	37.30 (1.04)	28.20 (0.57)	
Underweight	34.86 (2.89)	29.10 (0)	0.619 and 0.021
Normal BMI	33.56 (4.05)	24.17 (3.73)	
Overweight	33.12 (3.28)	24.01 (2.78)	
Obese	32.70 (4.14)	23.81 (2.62)	

Results

A total of 169 Dominicans voluntarily participated in the study. They composed of 36.69% (62/169) males and 63.31% (107/169) females. Participants fell into the range of 9 years to 84 years, with most individuals belonging to 51-60 years. One of the participants was excluded from the study due to previous heart surgeries. Preliminary studies involved the distribution of the participants based on the data from the self-administered questionnaire [Table 1].

Further examination of the participants identified 35.03% (55/157), 29.30% (46/157), 26.20% (38/157), and 10.19% (16/157) with normal, pre-hypertensive, stage 1 hypertensive and stage 2 hypertensive blood pressure (B.P), respectively. There were 1.27% (2/157) individuals with hypotensive B.P. Other investigations showed 47.80% (76/159), 5.03% (8/159), 45.28% (72/159), and 1.89% (3/159) participants with normal, hypoglycemic, hyperglycemic (impaired glucose homeostasis and the provisional diagnosis of diabetes) and diabetic blood sugar levels. Evaluation of BMI showed only 29.11% (68/159) within the normal range, while, 3.16% (5/159), 36.71% (58/159), and 31.01% (49/158) were underweight, overweight, and obese, respectively. The impact of blood glucose (B.G), B.P, and BMI on the diameter of the sinus of Valsalva and aortic annulus was also measured [Table 2]. Linear prediction graphs showed how age correlated with the diameter of the sinus of Valsalva and aortic annulus [Figures 2 and 3].

Simple regression analysis to predict the diameter of the aortic annulus from the diastolic B.P indicated that it statistically significantly predicted the diameter of the AA, F (1, 59) = 7.71, p <0.01 (with 95% Confidence Interval from 2% to 15%). Further regression analysis showed no correlate. The sonographic evaluation of the heart of each participant was carried out. Most patients presented with relatively healthy heart tissue with no signs of clinically or radiologically significant pathology [Figure 4].

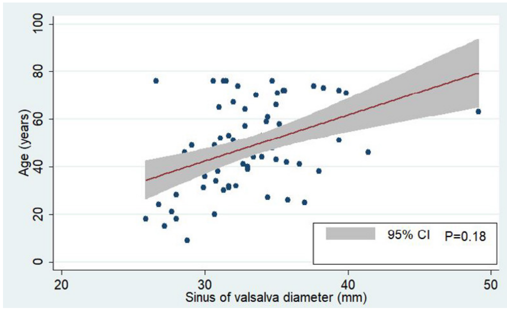

Figure 2: Linear prediction graph between age and the diameter of the sinus of Valsalva (with 95% Confidence Interval from 0.2% to 2.89%).

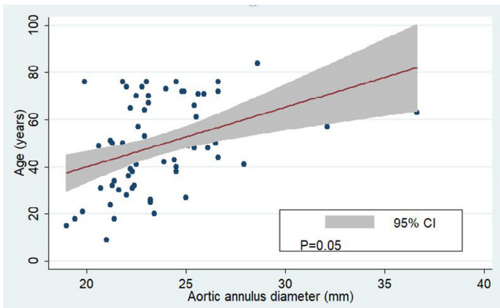

Figure 3: Linear prediction graph between age and the diameter of the aortic annulus (with 95% Confidence Interval from 1.25% to 2.81%).

Figure 4: Ultrasound image of a normal heart.

Discussion

SV normally has a diameter of 29-45 mm [2] though data available has shown that the dimension of the aortic root does not usually exceed 40 mm in healthy subjects [9]. Pathologies associated with the SV are usually described as being rare; however, most of the predominant cases are mainly associated with aneurysms [29]. Complications of most conditions associated with SV usually result in the rupture of the SV causing a left to right shunt [30]. Although, other ruptures could lead into the right ventricle or right atrium, [31] and on rare occasions could rupture into the interventricular septum [32]. Cases involving rupture into the pericardial space usually lead to sudden death [32]. Aneurysms are usually asymptomatic until they rupture, thus early diagnosis is essential for life preservation as these ruptures have a rapid hemodynamic deterioration, thus making them lethal [33]. Incidence on a number of cases in Western surgical cases has reported 0.14 - 0.23%, while Asian reports have reported 0.46% to 3.5% [29].

Similar to the SV, the aortic annulus (AA) is a complex three-dimensional structure [34]. The clinical significance of the AA is its role in the surgical insertion of prosthetic heart valves. The main pathology is associated with faulty valve insertion [35]. Systemic irregularities like hypertension, diabetes, dyslipidemias, faulty collagen, and obesity, among others, tend to affect the integrity of the aorta, thus it might be logical to assume such systemic factors could affect the diameter of the SV and AA [36]. In this study, we have looked at the possible determinants of aortic root dilatation with a focus on the effect of B.P, B.G, and BMI and how their irregularities could pose a threat to the veracity of the SV and AA. Few reports have been recorded on these anatomical locations with a much fewer explanation on the pathophysiology associated with SV and AA [37,38].

Effect of sex

Sex has been demonstrated to have an effect on the aortic root by several studies. In this study, females had smaller aortic root dimensions when compared to males similar to other previous studies [12,39,40]. Similar to the Framingham heart study [40] which recognized a 2.4 mm decrease in the female dimension, we observed a decrease of about 2.5 mm in the SV dimension and about 1.4 mm in the AA. This decrease was attributed to lean body mass of the female [9]. and the male hormonal influence, as sex steroids have demonstrated their ability to regulate the deposition of elastin and collagen fibers in vitro as well as the expression of matrix metallo-proteinases [41].

Effect of age

The aging process impacts the aortic size as a result of thinning and fragmentation of media elastic fibers, collagen deposition in the wall resulting in stiffness as well as the effect of mechanical stress. Previously there had been several debates as to the effect of age on the aortic root diameter with several autopsies showing an age related increase in the aortic root [42-46]. Our study showed a similar finding, with a linear increase in the diameters studied but was not statistically supported.

Effects of blood pressure

This study like some others that utilized the systolic pressures showed little to no significance with the aortic root dimensions. Palmieri et al. [38]. in their study, demonstrated that increasing systolic pressure caused progressive enlargements only at the supra-aortic ridge and the ascending aorta. However, increasing diastolic pressures caused an increase in all the aortic dimensions with distal segments recording the largest increments [38]. Other studies like the Framingham Heart study, directly correlated the diastolic pressure to aortic diameters with systolic and pulse pressures showing an inverse relationship [11,40]. This study, however, only linearly correlated diastolic pressures to the AA and not the SV. This might be due to our comparable limitation in sample size. Also, multivariate models have shown that the aortic root diameter is in no way related to hypertension or the duration of hypertension [38].

Effect of Body Mass Index (BMI)

Height and weight have been shown to correlate with aortic root diameter [10]. In this study, however, BMI only correlated with the aortic annulus and not the sinus of Valsalva and this might be due to our comparably small sample size relative to other larger studies. On the other hand, direct observation of the BMI group means showed that the underweight population had the highest root diameter, which clearly decreased towards the obese group. To support this observation, Palmieri and colleagues [38]. previously demonstrated that subjects with dilatation of the sinus of Valsalva had lower adipose and fat-free masses as well as BMI.

Clinically, aortic root enlargement has been shown to be independently and strongly associated with aortic regurgitation. Though the Framingham study could only insignificantly demonstrate the negative link between aortic regurgitation and BMI [47]. This negative relationship between obesity (BMI) and aortic regurgitation was strongly supported by the Strong Heart Study [48].

The supposed mechanism has been linked to evidence suggesting the existence of a local vasoregulation role displayed by perivascular adipose deposits in addition to systemic effects [49]. In was proposed that adipokines released from adipose tissues mediate a local effect, thus the "perivascular adipose tissues (PVAT)" in healthy subjects mediate an anti-contractile action as seen in medium sized vessels [50] and small arteries [51]. However, in obese patients, the PVAT dilatory effect is lost as a result of the expression of Tumor necrosis factor (TNF)-α or IL-6 which have negative effects on the endothelium and smooth muscles [52]. TNF-α also induces inflammation which is believed to be the genesis of insulin resistance, and with insulin resistance, the vasodilatory effect of insulin on vessels is lost [53]. resulting in a net constriction. Furthermore, several studies have shown a positive relationship between the amount of adipose tissues in the epicardium and the existence and the extent of coronary diseases [53]. Putting the above into account, the assumption, therefore, is that the extensive epicardial adipose tissue seen in obese subjects might likewise be mediating a paracrine vasoconstrictive effect around the aortic root?.

Effect of glucose

Very little report is available on the effect of deranged plasma glucose on the dimension of the aortic root. However, studies have almost without a doubt demonstrated the inverse relationship diabetes has with the aortic diameter (aneurysmal or non-aneurysmal) [54]. This has been attributed to the possible theory that diabetes might inhibit metalloproteinases that are responsible for the degradation of the wall of the aorta with a net wall stress reduction [55,56]. Likewise, studies done on mice showed that diabetic mice express modified proteins (O-GlcNac) that behave in constricting blood vessels [57]. This study, however, showed an unusual association of elevated plasma blood glucose with the SV and not the AA. The reason for this link is unclear considering previous studies. With a careful cross-examination of our study population, we decided to put together a possible cause-effect hypothesis as a result of the very high percentage of overweight/obese population (68%), relative to a good number of the participants with a deranged blood glucose level (47%).

In view of the highly obese population, the hypothesis questions the possibility that the correlation to the SV is an evidence of one of the "initial" inflammatory responses and vasomodulatory (vasodilatory) effects of TNF-α secreted by the faulty adipose tissue, either by a local or systemic mechanism. This response might ultimately result in insulin resistance accompanied by deranged plasma glucose. However, this hypothesis cannot be validated and further studies will still be required.

Conclusion

The SV and AA are a major component of the aorta with vital clinical significance. However, few studies have elucidated on these anatomical positions in terms of their mechanism and pathology. The current study was able to identify if systemic properties affect the diameter (functionality) of these structures. With B.P, B.G, and BMI put in focus, the study located B.G to be the only systemic factor that correlated to the diameter of the SV. The study targets to provide educational concept in this regard. Although, further study is still needed in fully understanding these structures in terms of their mechanism and pathology. Also, further studies could identify why B.P, B.G, and BMI play little role on the diameter of these structures.

Conflict of Interest

The authors declare no conflict of interest.

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