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 (BMI) on the dimension of the aortic root. Materials and Methods: Participants were volunteers of African descent who were recruited during and after an organized health fair by the medical students’ body from All Saints University, School of Medicine. 169 participants consisting of 62 males and 107 females with ages ranging from 9 to 84 years agreed to volunteer by signing the consent after which a questionnaire was administered and a preliminary clinical procedure was used to check for blood pressure (BP), blood glucose (BG), and BMI. The measurement of the aortic root was carried out by an experienced single investigator who was not aware of the purpose of measurements, using a DUS-5000 ultrasound machine (Miami, Florida, USA) at a low-frequency micro-convex transducer preset to “adult cardiac” with a default frequency of 4 MHz. Results: Among the participants, 35.03%, 47.80%, and 29.11% had normal BP, BG, and BMI readings, respectively. The Chi-squared analysis identified a significant correlation between the diameter of the aortic annulus (AA) and BMI. Diastolic BP is also correlated with the diameter of the AA. Sinus of Valsalva (SV) showed an unusual correlation with BG as opposed to BP and BMI. Conclusion: The disparity in how a systemic factor individually correlates with the AA and the SV is not clear. The study targets to provide educational concept in this regard.

Keywords: Aortic annulus, aortic root, blood glucose, blood pressure, body mass index, sinus of Valsalva

Résumé

Contexte: La racine aortique est un agrégat de divers composants qui relie le ventricule gauche à l’aorte. Les pathologies les plus prédominantes ont été associées à la dilatation de la racine aortique conduisant à des anévrismes. But: Cette étude est conçue pour mesurer le rôle des morbidités systémiques telles que l’hypertension, le diabète et l’indice de masse corporelle (IMC) sur la dimension de la racine aortique. Matériel et méthodes: Les participants étaient des volontaires d’origine africaine qui ont été recrutés pendant et après une foire organisée par les étudiants de médecine de l’école de médecine All Saints University. 169 participants, soit 62 hommes et 107 femmes âgés de 9 à 84 ans, ont accepté de faire du bénévolat en signant le consentement après l’administration du questionnaire et en utilisant une procédure clinique préliminaire pour vérifier la tension artérielle, la glycémie, et BMI. La mesure de la racine aortique a été effectuée par un chercheur expérimenté qui ne connaissait pas le but des mesures, en utilisant une échographe DUS-5000 (Miami, Floride, USA) à un transducteur micro-convexe basse fréquence préréglé à “adult cardiac” avec une fréquence par défaut de 4 MHz. Résultats: Parmi les participants, 35.03%, 47.80%, et 29.11% avaient respectivement des valeurs normales de BP, BG, et BMI. L’analyse du khi carré a mis en évidence une corrélation significative entre le diamètre de l’anneau aortique (AA) et l’IMC. La pression artérielle diastolique est également corollée avec le diamètre de l’AA. Sinus de Valsalva (SV)
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. The aortic root is a complex structure that allows unidirectional blood flow while maintaining laminar blood flow, minimal resistance, tissue stress, and damage. This coordinated function of the aortic root ensures adequate coronary perfusion and left ventricular function. The aortic root is an aggregate of distinct entities, namely, the aortic valve leaflets, the leaflet attachments, the sinuses of Valsalva (SVs), the interleaflet trigones, the sinotubular junction, and the annulus.

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. 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 SVs. 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 among surgeons as to what the annulus represents. Many surgeons believe that it represents the remnants of the removed valvular leaflets while others describe it as the virtual, circular ring that is defined by the semilunar leaflet attachments. One thing is clear though, the dimension and geometry of the aortic annulus (AA) are very essential in determining the long-term durability of aortic root repair. The annulus is the diameter that is analyzed by the echocardiographer when providing the diameter of the aortic root.

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 nonathletic population. Of these, demographic characteristics are most relevant. These includes age, sex, height and body size, and blood pressure (BP) to some extent. Among the demographic factors, height has been shown to be the most important determinant of the size of the aortic root. Several autopsy reports have associated aortic root size and age and has 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. Although attributed to the relatively average lesser body size, females have been generally accepted to have smaller aortic dimensions. BP, however, has stirred up several debates surrounding its relationship to the size of the aortic root. Pelliccia et al. also revealed 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. 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, possibly due to the intrinsic weakness of the media. Ankylosing spondylitis, a spondyloarthropathy, in 2%-10% of cases has been associated with cardiovascular diseases such as aortic root dilatation, and resulting dilatation is attributed to a sclerosing inflammatory process involving the aortic root. Marfan syndrome, caused by mutations in the gene coding for fibrillin-1 protein, results in structurally weak elastic fibers within the media of the aorta. Some others include emphysema probably due to the increased systemic elastolytic activity, foramen ovale due to an underlying tissue disorder or a mechanistic effect, mucopolysaccharidosis, and syphilitic aortic aneurysm caused by an oblitative endarteritis of the vasa vasorum of the
Hypertension has also been linked with an increased diameter of the aortic root at the supraaortic ridge and proximal aorta, but asymptomatic. The implication of diabetes on the morphology of the aortic root has been associated with a protective role from aortic root dilatation.

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

**MATERIALS AND METHODS**

**Participants**

Participants were attendees at the health fair organized by the American Medical Student Association. 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. 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. One hundred and sixty-nine participants, including 62 males and 107 females with ages ranging from 9 to 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 (subcategorized into eight groups), sex, and lifestyles categorized as sedentary or active. Subsequently, simple clinical procedures were done, such as BP checks which are classified using the standard hypertension classification consisting of normal, prehypertension, stage 1 hypertension, and stage 2 hypertension; BMI; and blood glucose (BG) checks which are categorized into normoglycemia, hypoglycemia, hyperglycemia, and diabetic. The participants categorized as hyperglycemic are those having (i) impaired fasting glucose and (ii) those with a provisional diagnosis of diabetes. The participants categorized as diabetic are those who gave a history of previously confirmed cases of diabetes and were on treatment.

**Selection criteria**

The volunteers included in this study were Dominicans of African descent.

**Ultrasound examination and measurements**

The measurement of the aortic root was carried out by an experienced single investigator using a DUS-5000 ultrasound machine (Manufactured in 2010, Miami, Florida, USA) using a low-frequency micro-convex transducer preset to “adult cardiac” with a default frequency of 4 MHz.

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 participant’s chest wall on the 2nd–4th intercostal space at the left parasternal area looking at the heart in its longitudinal axis (left parasternal view). Using this view, we can 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 two levels: (1) annular region (corresponds echocardiographically to the hinge points of aortic cusps) and (2) the SV.

**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 were done by Chi-squared analysis. Multiple regression analysis was also performed to predict factors that influence the diameter of the SV and AA. Linear prediction graphs were also illustrated to show possible correlations. Statistical hypothesis tests with P < 0.05 were considered statistically significant. Values are presented as mean ± standard deviation or number (%).

**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 age range of 9–84 years, with most individuals belonging to 51–60 years. One of the participants was excluded from the study due to previous heart surgery. Preliminary studies involved the distribution of the participants based on the data from the self-administered questionnaire [Table 1].

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

Simple regression analysis to predict the diameter of the AA from the diastolic BP indicated that it is statistically significant with diameter of the AA, F (1, 59) = 7.71, P < 0.01 (with 95% confidence interval ranging 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].

**Discussion**

SV normally has a diameter of 29–45 mm², though data available have shown that the dimension of the aortic root does not usually exceed 40 mm in healthy controls. Pathologies associated with the SV are usually described as being rare; however, most of the predominant cases are mainly associated with aneurysms. Complications of most conditions associated with SV usually result in the rupture of the SV causing a left-to-right shunt. Although, other ruptures could lead to the right ventricle or right atrium, and on rare occasions could rupture into the interventricular septum. Cases involving rupture into the pericardial space usually lead to sudden death. Aneurysms are usually asymptomatic until they rupture; thus, early diagnosis is essential for life.

| 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)±SD | \( \chi^2 (P) \) | Mean diameter of the aortic annulus (mm)±SD | \( \chi^2 (P) \) |
| --- | --- | --- | --- | --- | --- |
| 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 | |

SD=Standard deviation

| 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)±SD** | **Mean diameter of the aortic annulus (mm)±SD** | **\( P \) (sinus of Valsalva and aortic annulus)** |
| --- | --- | --- | --- |
| Normal BP | 32.61±3.35 | 22.86±2.53 | 0.542 and 0.91 |
| Prehypertensive BP | 33.32±3.70 | 24.55±3.09 | |
| Stage 1 hypertensive BP | 33.15±4.65 | 25.15±3.51 | |
| Stage 2 hypertensive BP | 34.74±3.15 | 25.47±2.55 | |
| Normal BG | 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±0.9 | 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 | |

SD=Standard deviation, BP=Blood pressure, BG=Blood glucose, BMI=Body mass index
preservation as these ruptures have a rapid hemodynamic deterioration, thus making them lethal.\textsuperscript{[34]} The incidence of a number of aortic aneurysms in Western surgical cases has been reported to be 0.14\%-0.23\%, while Asian reports have reported 0.46\%-3.5\%.\textsuperscript{[30]}

Similar to the SV, the AA is a complex three-dimensional structure.\textsuperscript{[35]} 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.\textsuperscript{[36]} Systemic irregularities such as hypertension, diabetes, dyslipidemias, faulty collagen, and obesity, among others, tend to affect the integrity of the aorta; thus, it might be logical to assume that such systemic factors could affect the diameter of the SV and AA.\textsuperscript{[37]} In this study, we have looked at the possible determinants of aortic root dilatation with a focus on the effect of BP, BG, 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 much fewer explanation on the pathophysiology associated with SV and AA.\textsuperscript{[36-39]}

**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.\textsuperscript{[11,40,41]} Similar to the Framingham Heart Study,\textsuperscript{[41]} 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\textsuperscript{[39]} and the male hormonal influence, as sex steroids have demonstrated their ability to regulate the deposition of elastin and collagen fibers \textit{in vitro} as well as the expression of matrix metalloproteinases.\textsuperscript{[42]}

**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.\textsuperscript{[12]} 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.\textsuperscript{[43-47]} Our study showed a similar finding, with a linear increase in the diameters studied but was not statistically supported.

**Effect of blood pressure**

This study like some others that utilized the systolic pressures showed little-to-no significance with the aortic root dimensions. Palmieri \textit{et al.}, in their study, demonstrated that increasing systolic pressure caused progressive enlargements only at the supraaortic ridge and the ascending aorta.\textsuperscript{[39]} However, increasing diastolic pressures caused an increase in all the aortic dimensions with distal segments recording the largest increments.\textsuperscript{[39]} Other studies like the Framingham Heart study directly correlated the diastolic pressure to aortic diameters with systolic and pulse pressures showing an inverse relationship.\textsuperscript{[11,41]} 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. Furthermore, multivariate models have shown that the aortic root diameter is not related to hypertension or the duration of hypertension.\textsuperscript{[39]}

**Effect of body mass index**

Height and weight have been shown to correlate with aortic root diameter.\textsuperscript{[10]} In this study, however, BMI is only correlated with the AA and not the SV, 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 toward the obese group. To support this observation, Palmieri \textit{et al.} previously demonstrated that individuals with dilatation of the SV had lower adipose and fat-free masses as well as BMI.\textsuperscript{[39]}

Clinically, aortic root enlargement has been shown to be independently and strongly associated with aortic regurgitation. Although the Framingham Study could only insignificantly demonstrate the negative link between aortic regurgitation and BMI,\textsuperscript{[48]} this negative relationship between obesity (BMI) and aortic regurgitation was strongly supported by the Strong Heart Study.\textsuperscript{[49]}

The supposed mechanism has been linked to evidence, suggesting the existence of a local vasoregulatory role displayed by perivascular adipose deposits in addition to systemic effects.\textsuperscript{[50]} It was proposed that adipokines released from adipose tissues mediate a local effect; thus, the \textit{“perivascular adipose tissues (PVAT)”} in healthy controls mediate an anticontractile action as seen in medium-sized vessels\textsuperscript{[26]} and small arteries.\textsuperscript{[51]} However, in obese patients, the PVAT dilatory effect is lost as a result of the expression of tumor necrosis factor (TNF)-\(\alpha\) or interleukin 6 which have negative effects on the endothelium and smooth muscles\textsuperscript{[52]} TNF-\(\alpha\) 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,\textsuperscript{[52]} 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 cases might likewise mediate 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 an aortic diameter (aneurysmal or nonaneurysmal). \[54\] 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 behaves in constriciting blood vessels. \[57\] This study, however, showed an unusual association of elevated plasma BG 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 BG 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-\(\alpha\) secreted by the faulty adipose tissue, either by a local or by a systemic mechanism. This response might ultimately result in insulin resistance accompanied by a deranged plasma glucose. However, this hypothesis cannot be validated and further studies will still be required.

**Opinion**

Heart diseases, particularly hypertension, and diabetes mellitus are fast becoming prevalent in the African population. However, cases of morbidities associated with large vessels, particularly the aortic root dilatation (closely associated with regurgitation and aneurysms), appear to be low in the African population. \[58\] The low African prevalence of aortic root dilatation might be attributed to the relatively higher obesity seen in the African population when compared to the Caucasian population. It appears from this study that the relatively increased adiposity in the African population confers a protective constriction on the aortic root. Therefore, it can be conjectured that hypertensive patients with low BMI will be expected to be more prone to aortic dilatations. Thus, clinicians and cardiologists should have a high index of suspicion in this vulnerable group of patients.

**Limitations**

This study might have benefitted much more from a larger population as evidenced by the more positive results generated by similar studies like the Framingham and Strong Heart Studies.

**Conclusion**

The SV and AA are the major components 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 BP, BG, and BMI put in focus, the study showed that hypertension, especially diastolic hypertension, impacts the aortic root linearly, and also showed an unusual correlation of BG to the diameter of the SV for which further studies will be needed. Furthermore, the study reveals a “somewhat protective effect” of an increased BMI on the aortic root. Hence, further studies are still required to fully understanding the aortic root structures in terms of their mechanism and pathology as it relates to BP, BG, and BMI.

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**Conflicts of interest**

There are no conflicts of interest.

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