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Utility of Genetic Testing in Elite Volleyball Players with Aortic Root Dilation

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Abstract

Basketball and volleyball attract individuals with a characteristic biophysical profile, mimicking features of Marfan Syndrome (MFS). Consequently, identification of these abnormalities can be lifesaving.

Purpose—To determine how physical examination, echocardiography, and genetic screening can identify elite volleyball players with a previously undiagnosed aortopathy.

Methods—We have performed cardiac screening on 90 US Volleyball National Team members and identified four individuals with dilated sinuses of Valsalva. This case series reports on three individuals who underwent a comprehensive genetics evaluation, including gene sequencing.

Results—Cardiac screening combined with genetic testing can identify previously undiagnosed tall athletes with an aortopathy, in the absence of non-cardiac findings of a connective tissue disorder. Subject #1 had a revised Ghent systems (RGS) score of 2 and a normal aortopathy gene panel. Subject #2 had a RGS score of 1 and genetic testing revealed a *de novo* disease causing mutation in the gene encoding fibrillin-1 (*FBNI*). Subject #3 had a RGS score of 4.0 and had a normal aortopathy gene panel.

Conclusions—Despite variable clinical features of MFS, dilated sinuses of Valsalva were found in 4.9% of the athletes. A disease-causing mutation in the *FBNI* gene was identified in Subject #2, who had the lowest RGS but the largest aortic root measurement. Subjects #1 and #3, with the highest RGS, had a normal aortopathy gene panel. Our findings provide further evidence suggesting that a cardiac evaluation, including a screening echocardiogram, should be performed on all elite tall adult athletes independent of other physical findings. Genetic testing should be considered for athletes with dilated sinuses of Valsalva (male >4.2cm, female >3.4cm), regardless of other extra-cardiac findings.

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Keywords

Tall athletes; Marfan syndrome; Volleyball; sinuses of Valsalva; Fibrillin-1

Introduction

The past two decades have brought important advances in the understanding of athlete's heart. In addition to the changes in chamber size and ventricular wall thickness, the changes and differences in the aortas of elite athletes are now better known. Recent studies suggest there are enough data on tall athletes to define their upper limit of normal aortic root size. Certain sports, including volleyball and basketball, select for individuals with a characteristic biophysical profile (exceptionally tall and thin, long arm span) such that when combined with cardiovascular abnormalities may be indicative of an underlying connective tissue disorder like Marfan Syndrome (MFS)(10). Despite the lack of overt clinical features, these individuals may be at increased risk for having an aortopathy due to an underlying connective tissue disorder.

Several recent studies have suggested that an aortic root dimension of > 4.0 cm in men and > 3.4 cm in women is abnormal, independent of height (6-7,9-10). A recent cross sectional analysis revealed that the prevalence of aortic root dilation was as high as 8% in volleyball players compared to only 1% in elite athletes from all sports (1,3,7,9,10). Most recently, a study on 526 professional basketball players from the National Basketball Association helped to establish new normative values for this group of athletes, in which their average height is 6'7"(5). In this study, the largest aortic root diameter was 4.2 cm, suggesting that an aortic root dimension exceeding 4.2cm is likely indicative of an aortopathy.

Over the last 5 years the United States National Volleyball team has implemented a cardiac screening program that has included 90 male and female athletes. All members undergo a baseline history, physical and echocardiogram, with serial follow-up indicated based on the initial findings. We recently reported our findings on the first 70 athletes that underwent screenings. In that study, three male athletes had an aortic sinus diameter 4 cm, (4, 4.2, and 4.3 cm).

One female athlete had an aortic sinus diameter > 3.4 cm (3.6cm). There were no other intra-cardiac or arterial abnormalities among these four athletes, and specifically all had a trileaflet aortic valve. Twenty-four of the 70 athletes (34%) had at least one characteristic of MFS on physical exam based on Ghent criteria, but none had more than 2 characteristics. Sixteen athletes (23%) had an upper body/lower body ratio < 0.85 and 4 of 70 (6%) had armspan/height ratios > 1.05 , indicating the inherent selection for this body type in elite volleyball players. The clinical significance of these findings, and whether or not these individuals had an underlying aortopathy, was unclear.

Since that study we have identified one additional male with a sinuses of Valsalva dimension > 4.2 cm. Based on the recent study by Engel, et. al (5), we performed genetic testing on two of the three males found to have a sinus of Valsalva measurement of at least 4.2cm, and on the one female with a measurement of > 3.4 cm, i.e., the individuals with the largest aortic

root measurements among the 90 players that have undergone assessments. We report our findings and discuss their significance with respect to clinical implications and future screening approaches.

Methods

Informed consent was obtained from each of the subjects, and the Institutional Review Board of the University of California San Diego approved the study as a community service project. Histories, physical examinations and follow-up echocardiograms were performed on three subjects with a dilated sinus of Valsalva, as we have described previously (7). Measurements of the sinuses of Valsalva were performed as described by Devereux et al. (10) (see document, Supplemental Digital Content 1, Supplemental Methods). A clinical genetics evaluation by a board-certified clinical geneticist, including generation of a revised Ghent systems score (7) as well as genetic testing, were performed on the three of the subjects. Genetic testing was performed by Ambry Genetics (Aliso Viejo, California) using a 22 gene aortopathy panel (TAADNext panel: ACTA2, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB1/2, CBS, COL5A1, and TGFB3).

Results

Three subjects (two males and one female) who were found to have dilation of the sinuses of Valsalva underwent genetic evaluation. Their findings are listed in Table 1. One additional male had a sinus of Valsalva measurement of 4.3cm, but declined having a genetic evaluation. He had no other clinical features of Marfan syndrome.

Subject #1

Subject #1 is a 27-year-old member male with a past medical history of labral surgery and a stress fracture of L1 with epidural injection. There was no previous history of cardiac problems, ectopia lentis, or pneumothoraces. There was no known family history of connective tissue disorders, aortic aneurysms or aortic dissections. Paternal height is 206cm and maternal height is 180cm.

His initial echocardiogram demonstrated a sinuses of Valsalva dimension of 4.3 cm. There was no valve prolapse or regurgitation. His height is 205.7cm, weight 90.311 kg, and BMI 21.34 kg/m². Positive findings on physical exam included a mild pectus excavatum and striae atrophicae on his back. The remainder of the physical exam was normal, giving a revised Ghent criteria system score of 3. A repeat echocardiogram a year after his initial study revealed a possible increase of 1mm in his sinuses of Valsalva measurement. Genetic testing using the aortopathy panel (TAADNext*) was performed by Ambry Genetics, and was negative for all 22 genes in the panel.

Subject #2

Subject #2 is a 24-year-old male with a past medical history notable for myopia and an appendectomy. There was no previous history of cardiac problems, ectopia lentis, or

pneumothoraces. There was no known family history for connective tissue disorders, aortic aneurysms or aortic dissections. Paternal height is 188cm and maternal height is 170cm.

An initial screening echocardiogram demonstrated a sinuses of Valsalva dimension of 4.5cm. His height is 204.5 cm, weight 89.5 kg, and BMI 21.4 kg/m². His physical findings are notable only for striae. The remainder of the physical exam was normal, giving a revised Ghent system score of 1. Repeat echocardiograms performed over the next two years demonstrated 1-2mm increase in his sinuses of Valsalva dimension (Figure 1), respectively. There was no valve prolapse or regurgitation.

Genetic testing using the aortopathy panel revealed a sequence variant in the Fibrillin-1 gene(c.1846G>C; Chr15: 48797336; p.Glu616Gln), which substitutes a highly conserved residue in an epidermal growth factor-like (EGF-like) domain. His parents were tested and did not carry the variant, indicating a likely *de novo* disease-causing mutation.

Subject #3

Subject #3 is a 27-year-old female with a history of mild scoliosis, stress fracture at L5-S1, osteoarthritis and tendonitis of the left knee with arthroscopic repair in 2009. There was no previous history of cardiac problems, ectopia lentis, or pneumothoraces. There was no known family history for connective tissue disorders, aortic aneurysms or aortic dissections. Paternal height is 182.8 cm, and maternal height is 170.18 cm.

A screening echocardiogram demonstrated a sinuses of Valsalva measurement of 3.6cm without any significant valve prolapse or regurgitation. Her height was 189.4 cm, weight 78.9kg, and BMI 21.7 kg/m². Her physical findings were notable for a positive wrist and negative thumb sign, positive striae, pes planus, an upper to lower segment ratio of 0.83, and mild thoracolumbar scoliosis. The remainder of the physical exam was normal, giving a revised Ghent system score of 4.0 (one point for wrist sign, one point pes planus, one point for scoliosis, and one point for skin striae). Repeat echocardiograms over the ensuing four years demonstrated a possible 1mm increase in her sinuses of Valsalva dimension.

Genetic testing revealed a heterozygous sequence variant in the TGFB3 gene (p.S55N), a known polymorphism occurring in at least 1-2% of the African population. Her biological parents were tested and both were also found to be heterozygous carriers of the same sequence variant. Screening echocardiograms were then performed on her parents. Her mother and father had a normal echocardiogram, including normal aortic root dimensions.

Discussion

In this study, we identified four out of 90 subjects with a dilated sinus of Valsalva, based on previously published normative data for tall athletes (6,7,9,10) and most recently for NBA players(5). In our cohort, three males had a sinuses of Valsalva measurement exceeding 4.2cm, and two of them underwent a complete genetics evaluation. In both cases, serial echocardiograms over a two-year period demonstrated possible slight progression. Subject #1 was found to have several mild features of MFS (Ghent score of 3), while Subject #2 had minimal stigmata of Marfan syndrome (Ghent score 1), yet targeted gene sequencing

revealed a likely *de novo* disease-causing mutation in the FBN1 gene. Based on the revised Ghent criteria he meets the diagnostic criteria for having Marfan syndrome. Current recommendations from the American Heart Association and the American College of Cardiology (Task Force 7) state that patients with aortic disease or who have a condition associated with development of aortic disease should only participate in “low-intensity, noncompetitive exercise” (2). In line with these recommendations and the results of our assessments, subjects #1 and 2 have retired from competitive volleyball and are under close medical care. Subject #1 is being followed medically and with serial echocardiograms. Subject #2 has been started on Losartan and is contemplating having elective aortic root replacement surgery in the near future. Subject #3 had several extra-cardiac features of Marfan syndrome (Ghent score=4.0). Her initial sinuses of Valsalva measurement is 3.6cm, just at the upper limit of normal, with a possible 1mm increase over the ensuing four years (9). Based on her current echocardiographic findings and negative gene test results she is continuing to participate in competitive volleyball but with elimination of high resistance weightlifting, with close medical monitoring including serial echocardiograms.

Our findings underscore the importance of determining which clinical parameters should be assessed in tall athletes and what should be considered abnormal. Most importantly, we identified one athlete (subject #2) with significant aortic root dilation in the absence of other significant findings of Marfan syndrome that nonetheless very likely has an aortopathy caused by a *de novo* Fibrillin-1 gene mutation. Based on this study and previously published studies, elite tall adult athletes, independent of other physical findings of a connective tissue disorder, should be considered for undergoing a comprehensive cardiac evaluation including a history, physical and a screening echocardiogram. Furthermore, genetic testing should be considered for males with sinuses of Valsalva dimensions >4.2cm, and females >3.4cm, which can help confirm the diagnosis of an aortopathy even in the absence of other non-cardiac findings of a connective tissue disorder. However, a negative aortopathy gene panel does not rule out the possibility of a genetic etiology, since not all genetic causes have been identified, and such athletes require close medical follow-up.

In conclusion, our results suggest that clinical screening combined with genetic testing in elite volleyball players can lead to the identification of individuals with previously undiagnosed aortopathies who are at risk for life-threatening aortic dissections, as in the tragic case of Flo Hyman who was a top member of the US Olympic volleyball team that died from an acute aortic dissection during international competition, and was diagnosed with Marfan syndrome postmortem (11).

In the future, longer serial follow-up times and more comprehensive genetic testing should aid in the identification of tall athletes with an aortopathy, and help guide recommendations for screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Facial and upper extremity images of Subject #2 (above). Echocardiographic parasternal long axis view (below), demonstrating marked dilation of the aortic root.

Table 1

Summary of cardiovascular profile and genetic findings of three subjects found on screening to have dilated sinuses of Valsalva.

#	Sex	Age	Ht (cm)	Wt (kg)	Extra-cardiac [^]	Sinuses of Valsalva(cm) [*]	Other cardiac	Gene panel
1	M	27	205.7	90.3	Mild pectus, striae (2)	4.3 (+3.04)	Normal	Negative
2	M	24	204.5	89.5	Striae (1)	4.5 (+4.22)	Normal	Fibrillin-1 mutation
3	F	25	189.4	78.9	Mild Scoliosis, positive thumb sign, striae, pes planus, decreased upper to lower segment ratio (4.5)	3.6 (+1.94)	Normal	TGFB3 polymorphism

[^] Revised Ghent systemic score is shown in parentheses

^{*} Measured in centimeters. Z-score is shown in parentheses (see supplemental methods for details).