Published in final edited form as:

Am J Cardiol. 2018 October 15; 122(8): 1429–1436. doi:10.1016/j.amjcard.2018.07.006.

Frequency of Ventricular Arrhythmias and Other Rhythm Abnormalities in Children and Young Adults With the Marfan Syndrome

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Abstract

Individuals with the Marfan syndrome (MFS) are at risk for sudden death. The contribution of arrhythmias is unclear. This study examines the prevalence of arrhythmias in children with the MFS and their relationship to clinical/echocardiographic factors. Data from the Pediatric Heart Network randomized trial of atenolol vs. losartan in MFS were analyzed (6 months–25 years old, aortic root (AR) diameter z-score > 3.0, no prior aortic surgery/dissection). Baseline 24-hour ambulatory ECG monitoring was performed. Significant ventricular ectopy (VE) and supraventricular ectopy (SVE) were defined as ≥ 10 VE or SVE/hour, or the presence of high-grade ectopy. 3-year composite clinical outcome of death, aortic dissection, or AR replacement was analyzed. There were 274 analyzable monitors on unique patients from 11 centers. 20 subjects (7%) had significant VE, 13 (5%) significant SVE; of these, 2 (1%) had both. None had sustained ventricular or supraventricular tachycardia. VE was independently associated with increasing

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The authors have no conflicts of interests or financial disclosures pertaining to this manuscript.

number of major Ghent criteria (odds ratio [OR]=2.13/each additional criterion, $p=0.03$) and greater left ventricular end-diastolic dimension z-score (OR=1.47/each 1 unit increase in z-score, $p=0.01$). SVE was independently associated with greater aortic sinotubular junction diameter z-score (OR=1.56/each 1 unit increase in z-score, $p=0.03$). The composite clinical outcome (14 events) was not related to VE or SVE ($p=0.3$), but was independently related to heart rate variability (higher triangular index). In conclusion, in this cohort, VE and SVE were rare. VE was related to larger BSA-adjusted left ventricular size. Routine ambulatory ECG monitoring may be useful for risk stratification in select MFS patients.

Keywords

Marfan; arrhythmia

Introduction

The Marfan syndrome (MFS) is a connective tissue disorder with an incidence of 2–3 per 10,000 individuals. Caused by mutations in the *FBNI* gene, MFS is a multisystem disorder that affects the cardiovascular, skeletal, and ocular systems. The most life-threatening sequelae of MFS include aortic aneurysm and aortic dissection. The independent contribution of rhythm disturbances to morbidity and mortality in MFS is unclear, with limited data suggesting a small but measurable risk for mortality from arrhythmia¹. The usefulness of 24-hour ambulatory electrocardiographic (ECG) monitoring in assessing the risk for malignant arrhythmias and sudden death has been demonstrated in patients with congenital heart disease^{2–4}. There are limited data on the use of screening ambulatory ECG monitors in those with MFS. Overall, the literature on the arrhythmic burden in pediatric patients with MFS is sparse^{1, 5, 6}. Gaining a better understanding of the arrhythmic potential of Marfan patients will allow us to better manage patients who present with supraventricular or ventricular arrhythmia. The aim of this study was to identify clinical and echocardiographic predictors of ventricular ectopy and other rhythm abnormalities in a well-characterized cohort of children and young adults with Marfan syndrome.

Methods

This was a retrospective analysis of baseline data collected in a cohort of subjects enrolled in the prospective Pediatric Heart Network (PHN) Marfan trial from 2007–2011: “Trial of beta blocker therapy (atenolol) vs angiotensin II receptor blocker therapy (losartan) in individuals with Marfan syndrome.” The study design including inclusion and exclusion criteria⁷, baseline patient characteristics⁸, and baseline echocardiographic characteristics⁹ has been reported in detail. Study subjects ($n = 608$) met the original Ghent diagnostic criteria for MFS,¹⁰ which were in common use at the time of study design. At enrollment, they ranged in age from 6 months to 25 years, had baseline aortic root diameter z-scores > 3.0 , and had no prior aortic surgery or dissection. Young adults were defined as males ≥ 16 years, females ≥ 15 years⁷. The study was approved by the respective Institutional Review Boards at all participating centers.

24-hr ambulatory ECG monitoring was performed on all subjects at baseline, prior to study medication initiation. The 24-hr ambulatory ECG monitors were previously analyzed for average heart rate to assess the efficacy of beta-blockade. They were reanalyzed for this report (Trillium Software, Forest Medical LLC, East Syracuse NYC) to assess supraventricular and ventricular ectopy, supraventricular or ventricular tachycardia (SVT, VT), and heart rate variability (HRV). Similar to Yetman *et al.*¹, significant ventricular ectopy (VE) the primary outcome and was defined as >10 premature beats per hour, or higher grade VE (with coupling intervals >120bpm) appearing as ventricular couplets, triplets, non-sustained VT, sustained VT (>30 seconds), and ventricular fibrillation. Significant supraventricular ectopy (SVE) was defined as >10 premature beats per hour, or higher grade ectopy (with coupling intervals >120 bpm) appearing as atrial pairs, non-sustained SVT, and sustained SVT (>30 seconds). HRV parameters included the standard deviation of beat-to-beat (NN) intervals (SDNN), root mean square of successive differences (RMSSD), and the triangular index (TRII)¹¹. These outcomes were correlated with baseline clinical characteristics including age, weight, height, arm span, arm span to height ratio, and upper to lower segment ratio at randomization, race, number of original major Ghent criteria met (aortic dilation, ectopia lentis, *FBNI* mutation or family member meeting criteria independently, dural ectasia, and/or meeting at least 4 of 8 specific skeletal manifestations¹⁰), presence of an *FBNI* mutation, and pertinent family and past medical history⁸. Baseline echocardiographic measurements were performed at a core laboratory for left ventricular size and function, aortic dimensions and stiffness indices, and presence of tricuspid or mitral prolapse/regurgitation⁹. The composite clinical outcome was met if a patient died, had aortic dissection and/or had aortic root surgery during the 3-year follow-up.

Lastly, at the time of enrollment, subjects underwent a structured interview on frequency and severity of symptoms. Symptoms, specifically palpitations, syncope, dizziness, and chest pain, were then evaluated to determine their relationship to VE and SVE.

Baseline clinical and echocardiographic characteristics of subjects with and without ectopy were compared using a Fisher exact test for categorical variables and either the unpaired t test or Wilcoxon rank sum test for continuous variables. Logistic regression was used to identify predictors of the VE and SVE outcomes. Factors with univariate $p < 0.20$ were candidate predictors for the multivariable logistic regression model selection; $p < 0.05$ was required for retention in the final model. The distributions of time to the composite clinical outcome for the two groups (presence of significant VE or SVE) were compared using the log-rank test. The association between HRV and time to the composite outcome was examined with Cox proportional hazards regression, with age as a covariate. Aortic stiffness indices were indexed by the square root of the R-R interval, which yielded a measure invariant to heart rate (HR). Results are reported without correction for multiple outcomes.

Results

The baseline 24-hr ambulatory ECG monitors of 274 subjects were available to review from 11 study centers in the PHN. The average age of the subjects in our cohort was 11 ± 6 years, which was similar to the 334 subjects who did not have monitors to review due to missing or non-analyzable data. Baseline demographics and echocardiographic findings in our cohort,

as presented in Table 1, were also similar between the two groups. Two patients had a history of arrhythmias requiring antiarrhythmic therapy prior to enrollment. One spontaneously resolved 11 years prior to enrollment, and the other had a successful ablation for SVT performed 3 years prior to enrollment. Both were off antiarrhythmic therapy at the time of enrollment. Neither had VE or SVE on their baseline 24-hr ambulatory monitors.

Twenty subjects (7%) had significant VE, and 13 (5%) had significant SVE. Of these, two patients (1%) had both. Of the patients with significant VE, only 2 had a ventricular ectopic burden above 10% (19% and 21%). There was no VT or SVT noted in any of our subjects. Differences in clinical and echocardiographic characteristics among those with and without significant VE and SVE are summarized in Table 1.

There was no difference in age or gender in those with or without VE, although those with VE met a larger number of major Ghent criteria at the time of their enrollment ($p=0.03$). The presence of mitral regurgitation (MR) did not correlate with VE, although among subjects who had mitral regurgitation, VE was associated with a higher degree of MR (60% among those with mild or more MR vs 24% among those with trivial MR, $p=0.005$). Mitral valve prolapse was not associated with VE (53% vs 34%, $p=0.27$). Left ventricular (LV) size and function did not have a significant association with VE in the univariate analysis, except that those with ectopy tended to have slightly higher LV mass z-scores (by M-mode), although still within normal limits (z-score $+0.02\pm1.51$ vs -0.71 ± 1.16 , $p=0.01$). There was no difference in aortic dimensions or stiffness indices in those with or without significant VE.

There was no difference in gender in those with or without SVE, but the proportion of SVE increased with age ($p=0.03$). Subjects with SVE were more likely to have a prior history of beta-blocker therapy (85% vs 54%, $p=0.04$). There was no difference in mitral valve function or LV indices in those with or without significant SVE. Subjects with SVE had more dilation of their aortic valve annulus (z-score $+2.4\pm1.5$ vs 1.6 ± 1.3 , $p=0.03$) and sinotubular junction (z-score $+2.8\pm0.4$ vs 2.0 ± 1.2 , $p=0.03$). However, there was no difference in aortic root or ascending aorta z-scores. Aortic stiffness measures were associated with significant SVE; those with SVE had higher aortic root elastic modulus ($p=0.02$), HR-adjusted aortic root stiffness index ($p=0.04$), ascending aorta elastic modulus ($p=0.01$), and HR-adjusted ascending aorta stiffness index ($p=0.02$).

In an age-adjusted multivariable model (Table 2), VE was independently associated with an increasing number of major Ghent criteria (odds ratio [OR] 2.1 per each additional criterion met, $p=0.03$). There was an increased risk of VE with a higher left ventricular end-diastolic dimension z-score (OR=1.5 per each 1 unit increase in z-score, $p=0.01$). SVE was independently associated with greater aortic sinotubular junction diameter z-score (OR=1.6 per each 1 unit increase in z-score, $p=0.03$). Among patients with AR elastic modulus > 618 mmHg and an aortic sinotubular junction diameter z-score at or above 3, the prevalence of SVE was 25%.

Over 3 years, no subjects died, 2 had aortic root dissection requiring surgical intervention, and 13 underwent aortic root surgery for significant dilation. The composite outcome was more common in young adults (8 in 55 subjects) than in children (7 in 219 subjects). The

two subjects with aortic root dissection had significant VE, no SVE. The 13 who underwent aortic root surgery (with no dissection) had neither VE nor SVE. Neither the presence of VE or SVE correlated to the composite outcome. Using a Kaplan-Meier analysis, the presence of significant VE was not associated with a shorter time to the composite clinical outcome ($p=0.27$). No subject with significant SVE experienced any of the clinical outcomes.

Heart rate variability, in general, increased with age (Figure 1). Given this association and the higher incidence of clinical outcomes in older subjects, an age-adjusted analysis was performed to evaluate the relationship of HRV and the composite clinical outcome. The composite clinical outcome was not associated with SDNN or RMSSD. However, a larger TRII was independently associated with a higher risk for the composite clinical outcome (age-adjusted hazard ratio 1.22 per 5-unit increase, 95% CI 1.01, 1.47, $p = 0.04$). There was no change in these findings when adjusting for prior beta-blocker use. Eleven of the 14 clinical events occurred in the upper tertile of TRII. Figure 2 displays the unadjusted Kaplan-Meier estimates of time to clinical outcome by tertile of TRII (log rank $p=0.004$).

Finally, in terms of symptoms, palpitations were more common when SVE was present vs absent (46% vs. 14%, $p=0.006$) but were not associated with VE ($p=0.7$). Syncope was not associated with either (Table 3).

Discussion

The presence of significant VE or SVE was rare in this cohort of children and young adults with the Marfan syndrome. The increased risk of VE with a higher LVEDD z-score is similar to that found in Yetman *et al.*, despite the differences in the Marfan cohorts, with Yetman's cohort covering a wider (and older) age range (birth to 52 years) and including patients with prior aortic surgery (8%). While all of our subjects had AR z-score >3.0 , none had prior aortic surgery. All of these differences, along with Yetman's longer follow-up (median 10 years), may explain the higher mortality rate (4%) in their study. Subjects in our study with significant VE also met more major Ghent criteria at baseline. The number of major Ghent criteria is a crude surrogate for phenotypic severity of MFS. Longer follow-up in this young cohort of patients would be useful to determine whether a higher number of Ghent criteria predicts an increased risk of sudden death or malignant arrhythmia over time. Of note, while the subjects in the PHN trial met the original Ghent criteria in use at the time of trial development, a retrospective analysis found that the vast majority of subjects (603/608) also met the revised criteria currently in use^{8, 12}.

It is often difficult to ascertain whether VE is the cause of LV dilation, or if the LV dilation results in increased ectopy. Although the threshold is different in each patient, in general, a daily ectopic burden of over 10% is needed before LV dilation and dysfunction occur¹³. As such, it appears unlikely that the VE in our cohort caused the larger LVs compared to those without VE. Rather, the presence of significant ectopy is most likely secondary to larger LV size. An increase in VE and arrhythmia has been well documented in patients with LV dilation and heart failure¹⁴. Further study is required to determine if the larger LV size is related to the intrinsic cardiomyopathy present in MFS and its underlying genotype^{15, 16}. As there were no deaths in our study, we are unable to comment on whether a higher ectopy

burden or more dilated left ventricle leads to increased mortality. Long term follow-up may provide clarity as to whether significant VE and/or LV dilation increases the risk of sudden death. In terms of SVE, one would expect that SVE might be related to MR and subsequent atrial dilation. However, in our cohort, SVE was unrelated to MR, and instead correlated with dilation of the sinotubular junction, as well as higher aortic root elastic modulus. Increased arterial stiffness has been associated with atrial fibrillation¹⁷, although there are conflicting results¹⁸. It is possible that aortic stiffness reflects LV diastolic function, which in turn influences left atrial size and function, but these were not evaluated in our cohort. We offer no clear hypothesis as to why sinotubular (and not aortic root or ascending aortic) dilation correlates with SVE. Further studies are needed.

Hoffman *et al.* examined numerous HRV measures in MFS, and found that the RMSSD in 24-hr ECG monitors was related to their composite outcome (sudden cardiac death, sustained VT/VF, or arrhythmogenic syncope) in a univariate, but not multivariable, analysis⁶. Schaeffer *et al.*¹⁹ found that HRV was not affected in their cohort of MFS, although they noted that heart rate turbulence (the change in heart rate after a PVC, and a marker of autonomic function) was a risk factor for arrhythmia and sudden death. There are various ways to analyze HRV – the TRII is a geometric calculation that is less affected by sudden changes in the beat-to-beat interval caused by rare extrasystoles or artifact, and is beneficial when analyzing longer recordings such as a 24-hr ambulatory ECG monitor^{11, 20}. The TRII more accurately reflects lower frequency changes in heart rate and is thought to be reflective of a patient's sympathetic rather than parasympathetic tone. Lower HRV by TRII is associated with increased mortality and arrhythmic events^{21–23}. To our knowledge, supranormal HRV has not been previously associated with an increased cardiovascular risk. It is unclear why higher HRV in our study correlated with a higher risk for aortic dissection and surgery, a novel finding. One hypothesis is that the greater oscillation in heart rate and increased sympathetic tone may have increased the wall stress on the aorta, increasing the risk of dilation and dissection. Conversely, we found that the association was attenuated after accounting for age. Because our results indicate that age may be a confounding factor in this association, further study is warranted to confirm the relationship between HRV and aortic outcomes.

Finally, the use of symptoms to determine the presence of significant ectopy was limited in our cohort. Patient-reported palpitations only correlated to significant SVE. Importantly, dizziness and syncope in our study were not associated with ectopy or the composite outcome of death, aortic dissection, or aortic surgery. This is in contrast to the setting of congenital heart disease, where syncope is a significant risk factor for malignant arrhythmias and sudden death^{24, 25}. Patients reporting palpitations warrant assessment with 24-hr ambulatory ECG monitors given the relationship to significant SVE, but its utility in asymptomatic patients with MFS is unclear. A 24-hr ECG monitor during adolescence, especially in those with LV dilation, may be warranted¹. This may also serve as a useful baseline for patients as they get older or undergo cardiac surgery, which may place them at higher risk for significant arrhythmia.

The results of this study should be interpreted in light of its limitations. This is a young cohort of MFS subjects who at baseline had not undergone surgery. The definitions for

significant SVE and VE in our study are consistent with those used in Yetman *et al.*¹, but we acknowledge that isolated SVE and VE can be a normal finding in young subjects. There were no 12-lead ECGs available for review, thus we were unable to correlate our findings with depolarization or repolarization abnormalities. The prevalence rates were low for VE, SVE, and the composite clinical outcome, limiting the statistical power. The percentage of variation explained by the VE and SVE risk factors identified was also low, suggesting that there are other unexamined variables that explain the occurrence of ectopy. A large number of comparisons was conducted, and some findings may be due to chance. Finally not all of the 24-hr ambulatory ECG monitors were available to analyze from the original Marfan trial.

In summary, baseline echocardiographic characteristics are helpful in guiding long-term management in patients with MFS. In our study, the overall incidence of VE and SVE was low; individuals with larger LVs had a higher burden of VE, while those with stiffer aortas were at increased risk for SVE. Close monitoring with 24-hour ambulatory ECGs may be warranted in these patients, as well as those with a history of palpitations. The relationship between an elevated HRV and aortic outcomes is a provocative finding that requires further investigation.

Acknowledgments

This research was funded by a grant from the Marfan Foundation.

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Figure 1:
Scatterplots of heart rate variability by age at randomization.

TRII T1:	89	87	85	46
TRII T2:	90	89	88	40
TRII T3:	95	91	85	40

Figure 2:
Time to composite endpoint by triangular index (TRII) tertile, N= 274, 15 events. The highest TRII tertile had the highest risk to reach the composite outcome.

Table 1:

Baseline Characteristics

Variable	Overall (n=274)			Significant Ventricular Ectopy			Significant Supraventricular Ectopy		
	N	Value*		Yes (n=20)	N	Value*	Yes (n=13)	N	Value*
Age at randomization (years)	274	10.8 ± 5.9		20	254	10.7 ± 6.0	13	261	10.7 ± 6.0
15–25 years old [‡]	274	55 (20%)		20	254	49 (19%)	13	261	53 (20%)
Male	274	171 (62%)		20	254	160 (63%)	13	261	160 (61%)
White	274	234 (85%)		20	254	218 (86%)	13	261	223 (85%)
Black		20 (7%)		0 (0%)		20 (8%)			18 (7%)
Asian		8 (3%)		2 (10%)		6 (2%)			8 (3%)
Other		12 (4%)		2 (10%)		10 (4%)			12 (5%)
Major Ghent criteria	274			20	254		13	261	
	2	119 (43%)		5 (25%)		114 (45%)	0.03 [‡]		114 (44%)
	3	116 (42%)		9 (45%)		107 (42%)			111 (43%)
	4	38 (14%)		6 (30%)		32 (13%)			35 (13%)
	5 (max)	1 (0.4%)		0 (0%)		1 (0.4%)			1 (0.4%)
Family history of Marfan Syndrome	263	159 (60%)		20	243	146 (60%)	13	250	154 (62%)
Family history of aortic dissection	274	38 (14%)		20	254	33 (13%)	13	261	35 (13%)
Family history of aortic surgery	274	82 (30%)		20	254	74 (29%)	13	261	78 (30%)
Prior cardiac surgery	274	7 (3%)		20	254	7 (3%)	13	261	7 (3%)
Weight (kg)	274	40.4 ± 22.2		20	254	39.7 ± 21.2	13	261	40.0 ± 22.4
Height (cm)	274	149.9 ± 32.0		20	254	149.1 ± 32.4	13	261	148.9 ± 32.2
BMI (kg/m ²)	274	16.5 ± 3.6		20	254	16.4 ± 3.2	13	261	16.5 ± 3.7
Aortic valve annulus max diameter z-score	268	1.65 ± 1.27		19	249	1.65 ± 1.28	13	255	1.61 ± 1.25
Aortic root maximum diameter z-score	274	4.32 ± 1.19		20	254	4.33 ± 1.20	13	261	4.31 ± 1.19
Aortic sinotubular junction max diameter z-score	255	2.08 ± 1.20		19	236	2.08 ± 1.18	13	242	2.04 ± 1.17
Ascending aortic max diameter z-score	255	0.97 ± 1.02		18	237	0.99 ± 1.03	12	243	0.96 ± 1.03
Presence of aortic regurgitation	273	34 (12%)		19	254	32 (13%)	13	260	31 (12%)
Among subjects with aortic regurgitation	34			2	32		3	31	
							0.51		1.00

Variable	Overall (n=274)			Significant Ventricular Ectopy			Significant Supraventricular Ectopy						
	N	Value*	N	Value*	N	Value	Yes (n=13)	N	Value	P-value	N	Value	P-value
Trivial		21 (62%)		2 (100%)		19 (59%)		2 (67%)				19 (61%)	
Mild or more		13 (38%)		0 (0%)		13 (41%)		1 (33%)				12 (39%)	
Presence of mitral regurgitation	271	172 (64%)	18	15 (83%)	253	157 (62%)	0.08	13	11 (85%)		258	161 (62%)	0.14
Among subjects with mitral regurgitation	172		15		157		0.005	11			161		1.00
Trivial		126 (73%)		6 (40%)		120 (76%)		8 (73%)				118 (73%)	
Mild or more		46 (27%)		9 (60%)		37 (24%)		3 (27%)				43 (27%)	
Mitral valve prolapse	270		19		251		0.27	13			257		0.42
None		112 (42%)		6 (33%)		106 (42%)		4 (31%)				108 (42%)	
Borderline		64 (24%)		3 (16%)		61 (24%)		2 (15%)				62 (24%)	
Present		94 (35%)		10 (53%)		84 (34%)		7 (54%)				87 (34%)	
LV end-diastolic volume z-score	245	-0.31 ± 1.07	16	-0.09 ± 1.34	229	-0.33 ± 1.05	0.39	11	0.37 ± 1.60		234	-0.34 ± 1.03	0.17
LV end-systolic volume z-score	245	-0.47 ± 1.20	16	-0.31 ± 1.50	229	-0.48 ± 1.18	0.57	12	-0.28 ± 1.31		233	-0.48 ± 1.20	0.57
LV ejection fraction	246	64.9% ± 6.0%	17	64.6% ± 6.6%	229	64.9% ± 6.0%	0.81	11	64.9% ± 6.2%		235	64.9% ± 6.0%	0.99
LV mass z-score	242	-0.18 ± 1.15	15	0.15 ± 1.37	227	-0.20 ± 1.13	0.26	11	0.19 ± 1.25		231	-0.19 ± 1.14	0.29
LV mass/volume ratio (g/mL)	243	0.91 ± 0.14	16	0.93 ± 0.18	227	0.90 ± 0.14	0.54	11	0.88 ± 0.19		232	0.91 ± 0.14	0.58
LV end-diastolic dimension z-score	262	0.82 ± 1.40	18	1.65 ± 1.90	244	0.76 ± 1.35	0.07	13	0.94 ± 1.66		249	0.81 ± 1.39	0.76
LV end-systolic dimension z-score	262	0.41 ± 1.31	18	1.01 ± 1.80	244	0.36 ± 1.26	0.15	13	0.40 ± 0.92		249	0.41 ± 1.33	0.99
LV mass z-score (M-mode)	261	-0.66 ± 1.20	18	0.02 ± 1.51	243	-0.71 ± 1.16	0.01	13	-0.42 ± 1.67		248	-0.67 ± 1.17	0.60
LV shortening fraction	263	36.9% ± 4.7%	19	36.8% ± 5.3%	244	37.0% ± 4.6%	0.89	13	36.9% ± 4.3%		250	36.9% ± 4.7%	0.96
LV diastolic septal thickness z-score	262	-1.14 ± 0.98	18	-0.96 ± 1.04	244	-1.16 ± 0.97	0.43	13	-0.95 ± 0.89		249	-1.15 ± 0.98	0.48
LV diastolic post. wall thickness z-score	259	-1.31 ± 0.98	18	-1.08 ± 1.26	241	-1.33 ± 0.96	0.29	13	-1.04 ± 1.45		246	-1.32 ± 0.96	0.50
Ascending aortic elastic modulus (mmHg)	240	314 (228, 438)	17	318 (206, 537)	223	313 (232, 434)	0.75	12	435 (339, 657)		228	310 (225, 429)	0.01
Heart rate adjusted ascending aortic stiffness index	240	3.6 (2.7, 5.0)	17	3.7 (2.6, 4.9)	223	3.6 (2.7, 5.1)	0.99	12	5.5 (3.8, 7.4)		228	3.6 (2.7, 4.9)	0.02
Aortic root elastic modulus (mmHg)	270	656 (408, 971)	19	763 (514, 917)	251	647 (402, 981)	0.30	13	922 (723, 1034)		257	618 (402, 912)	0.02
Prior medication													
β-blocker	274	151 (55%)	20	14 (70%)	254	137 (54%)	0.24	13	11 (85%)		261	140 (54%)	0.04
ACE inhibitor	274	6 (2%)	20	1 (5%)	254	5 (2%)	0.37	13	1 (8%)		261	5 (2%)	0.26
Calcium-channel Blocker	274	3 (1%)	20	0 (0%)	254	3 (1%)	1.00	13	0 (0%)		261	3 (1%)	1.00
Other antihypertensive	274	13 (5%)	20	3 (15%)	254	10 (4%)	0.06	13	2 (15%)		261	11 (4%)	0.12

Variable	Overall (n=274)				Significant Ventricular Ectopy				Significant Supraventricular Ectopy			
	N		Value*		Yes (n=20)		No (n=254)		Yes (n=13)		No (n=261)	
	N	Value*	N	Value*	N	Value*	N	Value*	N	Value*	N	Value*
Heart rate adjusted aortic root stiffness	270	7.3 (5.0, 11.6)	19	7.6 (6.1, 11.1)	251	7.3 (5.0, 11.6)	0.55	13	9.9 (8.0, 13.1)	257	7.3 (5.0, 11.3)	0.04

* Value is mean±standard deviation, median (interquartile range), or frequency (percentage)

† Mantel-Haenszel test for linear trend

‡ Male 16–25 years, female 15–25 years

LV= left ventricular; ACE=angiotensin-converting enzyme

Table 2:

Multivariable Analysis: Ventricular and Supraventricular Ectopy

Ventricular Ectopy (n=262, 18 patients with significant VE)				Supraventricular Ectopy (n=252, 13 patients with significant SVE)			
	Odds Ratio	95% CI	P-value		Odds Ratio	95% CI	P-value
Number of major Ghent Criteria	2.13 (for each additional Ghent criterion)	1.1, 4.2	0.03	Aortic Sinotubular Junction Max Diameter z-score	1.56 (per each 1 unit increase in z-score)	1.05, 2.32	0.03
LV end-diastolic dimension z-score	1.47 (per each 1 unit increase in z-score)	1.09, 1.99	0.01	Aortic Root Elastic Modulus > 618 (median)	4.88	0.95, 25.2	0.06
Age at randomization (years)	1.02	0.93, 1.11	0.71	Age at randomization (years)	1.05	0.95, 1.17	0.33

Table 3:

Subject symptoms at time of enrollment

Variable	Significant Ventricular Arrhythmias			Significant Supraventricular Arrhythmias		
	Yes (n=20)	No (n=254)	P-value	Yes (n=13)	No (n=261)	P-value
Palpitations	2 (10%)	39 (15%)	0.75	6 (46%)	35 (14%)	0.006
Syncope	1 (5%)	7 (3%)	0.46	1 (8%)	7 (3%)	0.33
Dizziness	4 (20%)	58 (23%)	1.00	4 (31%)	58 (22%)	0.50
Chest Pain	3 (15%)	50 (20%)	0.77	4 (31%)	49 (19%)	0.29
Number of symptoms [*]	3 (0.5, 4.5)	3.5 (1,7)	0.92	5 (0, 8)	3 (1, 6)	0.69

^{*} max possible number of symptoms was 26