Published in final edited form as:

Am J Cardiol. 2013 May 15; 111(10): 1501–1504. doi:10.1016/j.amjcard.2013.01.308.

Comparison of Electrocardiographic QTc Duration in Patients With Supravalvar Aortic Stenosis With Versus Without Williams Syndrome

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Abstract

Cardiovascular abnormalities in Williams syndrome (WS) are largely attributable to elastin haploinsufficiency resulting from a large deletion of the elastin-containing region on chromosome 7q11.23. The risk of sudden death in patients with WS is 25- to 100-fold greater than that in the general population. The corrected QT (QTc) interval is prolonged in 14% of patients with WS. Patients with nonsyndromic supravalvar aortic stenosis (NSVAS) have elastin mutations resulting in elastin haploinsufficiency and a vascular phenotype nearly identical to that of WS. No previous studies have evaluated the QTc duration in NSVAS. A retrospective review of all electrocardiograms (ECGs) performed on consecutive patients with NSVAS at Arkansas Children's Hospital from January 1, 1985 to January 1, 2012 was completed. ECGs with nonsinus rhythm or unmeasurable intervals were excluded. The ECGs were read by 1 reader who was unaware of previous readings. A QTc interval of ≥ 460 ms was defined as prolonged. The NSVAS cohort was compared to previously published WS and control groups using the mixed model for continuous electrocardiographic variables and the generalized estimating equation for binary indicators for prolonged QTc. The generalized estimating equation used bootstrapping with 1,000 replicates. A total of 300 ECGs (median 6, range 1 to 27) from the 35 identified patients with NSVAS met the inclusion criteria. A total of 482 ECGs from patients with WS and 1,522 ECGs from controls were included. The mean age of the patients with NSVAS at ECG was 7.3 ± 6.9 years; 64% were male. The mean QTc duration was 409 ± 20 ms in the NSVAS group, 418 ± 17 ms in the control group ($p < 0.001$), and 436 ± 27 ms in the WS group ($p < 0.001$ compared to the control group). The prevalence of QTc prolongation was 0.3% in the NSVAS group, 2.0% in the control group ($p < 0.001$), and 14.8% in the WS group ($p < 0.001$ compared to controls). No patients with NSVAS died. In conclusion, cardiac repolarization is normal in patients with NSVAS. Elastin haploinsufficiency does not appear to be the etiology of QTc prolongation in patients with WS. The possible contribution of other genes on 7q11.23 to QTc prolongation in WS should be investigated.

Supravalvar aortic stenosis (SVAS) was first described by Chevers¹ in 1842 as a narrowing at the level of the sinotubular junction of the aorta. It has since been recognized as a diffuse arterial abnormality that occurs in approximately 1:20,000 live births.² SVAS occurs frequently in patients with Williams syndrome (WS)³ and has also been described in

familial cohorts with nonsyndromic SVAS (NSVAS).⁴ WS results from the deletion of approximately 28 genes on chromosome 7q11.23,³ and the deletion of the elastin gene within this region produces the vascular phenotype of SVAS.⁴ Patients with WS have been shown to have an increased risk of sudden cardiac death, and prolongation of the corrected QT (QTc) interval on the electrocardiogram (ECG) occurs in about 14% of patients.⁵ Keating has shown that NSVAS results from mutations in elastin, resulting in elastin haploinsufficiency.⁴ As a result of the elastin haploinsufficiency, patients with NSVAS have a vascular phenotype identical to that seen in patients with WS. No studies have evaluated cardiac repolarization measurements in patients with NSVAS. We sought to determine whether the prevalence of QTc prolongation is increased in patients with NSVAS.

Methods

A retrospective review was undertaken of all patients with NSVAS seen at the Arkansas Children's Hospital from January 1, 1976 to January 1, 2012. The patients with NSVAS were identified using a surgical database of all cardiothoracic surgeries performed at our institution, databases from the echocardiography and cardiac catheterization laboratories, and the database from the cardiology clinic. Syndromic patients were excluded from the present study.

In patients with multiple ECGs, all available ECGs were reviewed. ECGs with nonsinus rhythm (i.e., low right atrial rhythm), bundle branch block, or unmeasurable intervals were excluded. A single reader (H.M.) who was unaware of previous electrocardiographic readings read all the ECGs, and the intervals were measured using standard techniques. The QTc interval was determined using Bazett's formula.⁶ A QTc interval of ≥ 460 ms was defined as prolonged.⁷

All available cardiovascular data from the identified patients were reviewed, including history, physical characteristics, surgical records, and ancillary testing. Ventricular hypertrophy severity (graded as none, mild, moderate, or severe) was determined from the echocardiographic reports. The severity of SVAS documented for each subject was obtained in the same manner. The university's institutional review board approved the present study.

Descriptive statistics were summarized as the mean $\pm$ SD for continuous electrocardiographic variables and as frequencies and percentages for the categorical demographic and electrocardiographic variables. Control and WS comparison group data previously obtained at the Children's Hospital of Philadelphia⁵ were reanalyzed after removal of the ECGs with bundle branch block and compared to that data from the NSVAS group. Comparisons of the QTc intervals among the 3 groups (NSVAS, WS, and control) were performed using the mixed model for continuous electrocardiographic variables and generalized estimating equation for binary indicators for a prolonged QTc interval. The correlations among multiple ECGs from the same patient were taken into account in both the mixed models and the generalized estimating equations by introducing an autoregressive variance covariance structure when fitting the models. Pairwise comparisons between any 2 groups were also conducted according to the fitted models. The density curve of the QTc interval was plotted for each group and compared using the permutation test. The prevalence of a prolonged QTc interval for each group was evaluated using the bootstrap method with 1,000 replicates. Data were analyzed in this portion of the analysis using R, version 2.15.0 (R Development Core Team, Vienna, Austria), and SAS, version 9.3 (SAS Institute, Cary, North Carolina). *p* Values <0.05 indicated statistical significance.

General linear mixed models were used to determine whether an association exists between the qualitative echocardiogram-based measures and the QTc interval. General linear mixed

models allow for differences to be estimated between each severity grade while accounting for any repeated observations in a participant. Qualitative measures included the severity of SVAS and right ventricular hypertrophy and left ventricular hypertrophy; the presence of right ventricular hypertrophy or left ventricular hypertrophy on the echocardiogram (yes or no) was also a qualitative measurement. The association between the echocardiographic and electrocardiographic findings of ventricular hypertrophy was estimated using Fisher's exact test owing to the sparseness of the data. The detailed predictive capacity, as summarized by the sensitivity, specificity, and positive and negative predictive values, was also estimated for the qualitative classification of moderate or severe right and left pulmonary artery stenosis and SVAS by varying cutoffs of the quantitative measurement of the average gradient for each of the arteries. All analyses in this portion of the analysis were completed using Stata, version 12.1 (StataCorp, College Station, Texas).

Results

The baseline demographic and electrocardiographic data from the 3 groups are listed in Table 1. A total of 306 NSVAS ECGs were available from 35 patients, and 300 ECGs from 35 patients met the inclusion criteria. Three ECGs from 1 patient with postoperative bundle branch block and 3 ECGs with low right atrial rhythm were excluded. A total of 482 WS ECGs and 1,522 control ECGs were available; the data from these ECGs have been previously published.⁵ The median number of ECGs for the patients with NSVAS was 6 (range 1 to 27). The mean age at NSVAS ECG was 7.3 ± 6.9 years, and 64% of the patients were male. None of the patients with NSVAS died. The QTc interval range for the NSVAS group was 354 to 462 ms. The distribution of the QTc intervals for all 3 groups is shown in Figure 1. The QTc interval did not correlate with right ventricular hypertrophy ($p = 0.826$) or left ventricular hypertrophy ($p = 0.179$) on the ECG.

Of the 35 patients with NSVAS in the present study, all had echocardiographic data available for review. The mean number of echocardiograms in the NSVAS group was 12.6 ± 8.4 . Right ventricular hypertrophy was present on 104 echocardiograms: 68 mild, 17 moderate, and 19 severe. Left ventricular hypertrophy was present on 111 echocardiograms: 69 mild, 33 moderate, and 9 severe. No correlation was found between either the echocardiographic presence or severity of either right ventricular hypertrophy ($p = 0.469$) or left ventricular hypertrophy ($p = 0.925$) and the QTc interval. The severity of right ventricular hypertrophy on the echocardiogram did not correlate with the presence of right ventricular hypertrophy on the ECG ($p = 0.300$). The severity of SVAS correlated with the echocardiographic severity of left ventricular hypertrophy ($p = 0.023$). No correlation was found between either the echocardiographic presence or severity of SVAS and the QTc interval ($p = 0.926$). The severity of SVAS on the echocardiogram did not correlate with the presence of left ventricular hypertrophy on the ECG ($p = 0.999$). The severity of left ventricular hypertrophy on the echocardiogram correlated positively with the presence of left ventricular hypertrophy on the ECG ($p < 0.001$). No correlation was found between the QRS-T angle on the ECG and the presence of either right ventricular hypertrophy ($p = 0.741$) or left ventricular hypertrophy ($p = 0.608$).

Discussion

The incidence of sudden cardiac death is increased 25- to 100-fold in patients with WS.⁸ The increased prevalence of QTc prolongation in patients with WS might be associated with this increased risk.⁵ Furthermore, the QTc interval on ambulatory ECGs in patients with WS is directly correlated with the prevalence of ventricular ectopic complexes.⁹ These findings have been of significant interest to both providers and families.

Significant cardiovascular abnormalities, primarily arterial stenoses, occur in 80% of patients with WS.¹⁰ The vascular phenotype of patients with WS is recapitulated in NSVAS as a result of elastin haploinsufficiency.⁴ If elastin haploinsufficiency is related to the QTc prolongation in patients with WS, the QTc interval would be expected to be prolonged in patients with NSVAS. The QTc interval was not prolonged in the present cohort of patients with NSVAS. The mean QTc interval in the NSVAS cohort was shorter statistically than that in the control group. This finding suggests that the QTc prolongation seen in WS is not related to elastin haploinsufficiency.

Structural abnormalities, including ventricular hypertrophy¹¹ and coronary artery stenosis with insufficiency,¹² have been shown to be associated with QTc prolongation. In the present cohort, SVAS was correlated with the severity of left ventricular hypertrophy, a finding in keeping findings from previous studies.¹³ Ventricular hypertrophy was common in the study cohort; however, the presence and/or degree did not correlate with the QTc interval on the ECG. Patients with NSVAS and WS are known to have coronary ostial stenosis in 45%¹⁴; however, no patient with SVAS in the present cohort demonstrated evidence of QTc prolongation. These findings suggest that neither ventricular hypertrophy nor coronary ostial stenosis are the causative mechanism of QTc prolongation in patients with WS.

The present results suggest that the deletion of 1 of the approximately 27 genes other than elastin on 7q11.23 in patients with WS might be the etiology of the QTc prolongation seen in patients with WS. Currently, none of the remaining genes on 7q11.23 are known to be involved in cardiac repolarization.⁵ Additional investigation of these remaining genes is needed.

The present study was retrospective. The NSVAS group included only 35 subjects, although 300 ECGs were included. This group of subjects might not be representative of all patients with NSVAS. The NSVAS group was significantly younger and had more males than the control and WS groups. Although the age difference was not likely to be clinically significant, the effect of differences in the gender distribution is uncertain. The original echocardiographic images could not be obtained for all studies, necessitating the use of the reported severities from the echocardiographic reports, which might have resulted in inconsistency in the severity gradations of ventricular hypertrophy. This limitation was likely of minimal significance, given the correlation of left ventricular hypertrophy severity with SVAS severity.

Acknowledgments

Support for this project was in part provided by the University of Arkansas for Medical Science's Translational Science Institute (NCATS/NIH 1 UL1 RR029884).

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Figure 1.
Graph demonstrating normal QTc distribution in patients with NSVAS compared to that in patients with WS.

Table 1

Baseline demographic and electrocardiographic data

Variable	Controls (n = 1,522 ECGs)	NSVAS (n = 300 ECGs)	WS (n = 482 ECGs)	p Value [*]
Males	822 (54%)	192 (64%)	222 (46%)	<0.001
Age (yrs)	9.7 ± 5.8	7.3 ± 6.9	10.0 ± 9.8	0.004
Heart rate (beats/min)	90.0 ± 23	99.1 ± 28	105 ± 24	<0.001
PR interval (ms)	131 ± 22	128 ± 23	123 ± 23	0.19
QRS interval (ms)	81 ± 11	78 ± 12	80 ± 13	0.01
QT interval (ms)	348 ± 38	326 ± 44	337 ± 42	<0.001
Corrected QT interval (ms)	418 ± 17	408 ± 20	436 ± 27	<0.001
Prevalence of prolonged corrected QT interval	2.0%	0.3%	14.8%	<0.001

* Comparison between control and NSVAS study groups.