### Title

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### Authors

Cortez, Daniel
Sharma, Nandita
Imundo, Jason



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ORIGINAL ARTICLE

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# Pediatric noncompaction patients with high spatial QRS-T angles are at increased risk for ventricular tachycardia

Daniel Cortez[1,2,3] | Nandita Sharma[1] | Jason R. Imundo[1]

[1]Electrophysiology/Pediatric Cardiology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania

[2]Clinical Sciences, Lund University, Lund, Sweden

[3]University of Colorado, Aurora, Colorado

**Correspondence**
Daniel Cortez, Electrophysiology/Pediatric Cardiology, Penn State Milton S. Hershey Medical Center, 9 Tiffany Building, Hershey, PA 17033.
Email: dr.danielcortez@gmail.com

## Abstract

**Introduction**: Noncompaction cardiomyopathy (NCCM) patients may develop sustained ventricular arrhythmias (VA). Currently no known electrocardiogram (ECG) parameter has demonstrated predictive value for VA development. The spatial QRS-T angle has demonstrated ability to identify VA in other cardiomyopathy populations.

**Methods**: A total of 39 patients with NCCM, defined by compact to non-compact ratio of >2.3 by magnetic resonance imaging, were assessed. The first ECG taken at time of MRI was assessed utilizing the heart rate, the QRS duration (QRSd), the corrected QT interval (QTc), and the spatial QRS-T angle (SPQRS-T angle, three-dimensional angle between the QRS and T-wave vectors) were assessed.

**Results**: Eight patients developed VA (20.5%). Median time to event was 3 months (95% CI 1.0 to 24.0 months). There were no significant differences between baseline ejection fraction or fractional shortening. Baseline median heart rate, spatial QRS-T angles, and indexed left ventricular end-diastolic volumes were all significantly higher in patients with VA development ($p$-value <0.05). Only heart rate and the SPQRS-T angle had significant univariate hazard ratios (HR) for VA at 1.031/beat per minute (1.001–1.071) and at a cut-off of 147 degrees the SPQRS-T angle gave a hazard ratio of HR of 5.773 (95% CI 1.161 to 28.702). The multivariate hazard ratio was only significant for the SPQRS-T angle, 1.031/degree (1.001–1.066). Survival analysis by Kaplan-Meier yielded a significant difference at a cutoff of 147 degrees.

**Conclusion**: The SPQRS-T angle identified those at risk for VA development. Future studies are warranted with larger populations of noncompaction patients.

KEYWORDS

noncompaction cardiomyopathy, spatial QRS-T angle, ventricular arrhythmias

## 1 | INTRODUCTION

Since its first recognition in eight cases, left ventricular noncompaction has been a continually recognized cardiomyopathy in pediatric patients (Chin, Perloff, Williams, & Mohrmann, 1990). Echocardiography or MRI imaging techniques are generally used for diagnosis with MRI highly sensitive and specific for noncompaction based on a noncompacted/compacted ratio of >2.3 in diastole (Petersen et al., 2005). Noncompaction cardiomyopathy can lead to significant ventricular arrhythmias (VA's) or significant ventricular dysfunction leading to sudden death (Chin et al., 1990; Ichida et al., 1999). Furthermore in pediatric patients with noncompaction cardiomyopathy, bundle branch blocks, lateral, or inferior T-wave inversions or flattening are only sometimes present at asymptomatic presentation (Ichida et al., 1999). Currently, no known electrocardiogram (ECG) parameter has been shown to can predict which patients have ventricular arrhythmias.

A derived-vectorcardiographic parameter, the spatial QRS-T angle (angle between the QRS vector and T-wave vector in

  

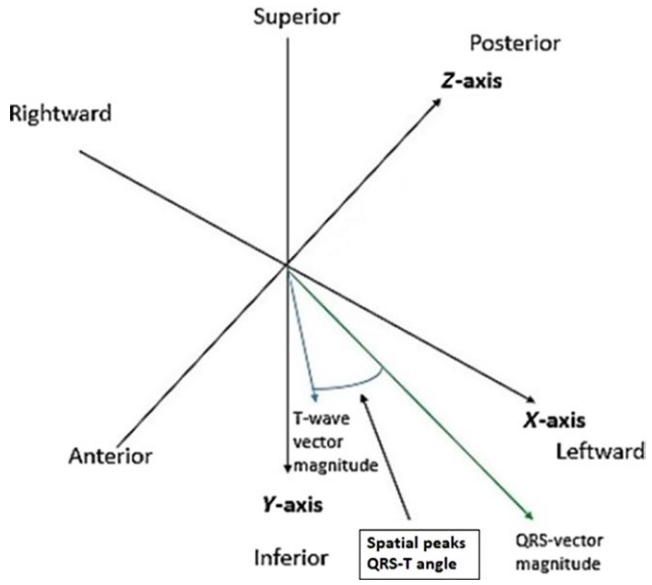


**FIGURE 1** Spatial QRS-T angle and QRS wave vector magnitude

three-dimensional space, Figure 1), has been shown to identify those hypertrophic cardiomyopathy and ischemic cardiomyopathy patients at risk for ventricular arrhythmias (Cortez, Graw, & Mestroni, 2016; Rautaharju et al., 2007; Rautaharju, Kooperberg, Larson, & LaCroix, 2006; Voulgari et al., 2006).

We predict the spatial QRS-T angle can identify pediatric noncompaction patients at risk for ventricular arrhythmias.

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

This study was approved by the Institutional Review Board at the University of Colorado.

A blinded retrospective analysis was performed of 39 patients with history of noncompaction cardiomyopathy from between 2004–2013 at University of Colorado Hospital systems (including the Children's Hospital of Colorado) were reviewed. All 39 patients met inclusion criteria for noncompaction cardiomyopathy as defined by noncompact ratio of >2.3 by magnetic resonance imaging (Petersen et al., 2005). Only patients with interpretable ECG's with adequate baseline measurements and those not on medications to treat heart failure at time of baseline ECG/MRI were included.

Development of sustained ventricular arrhythmias was assessed by telemetry, electrocardiogram, Holter, or event monitoring. Sustained ventricular arrhythmia (VA) is defined as 30 s or greater or those with symptomatic ventricular tachycardia. Comparisons were performed between noncompaction cardiomyopathy patients with eventual VA development versus those who did not develop VA. All included patients had an electrocardiogram (ECG) at baseline and were not taking anti-hypertensives or on beta blockade at baseline ECG analysis. Patients were assessed by ECG at first presentation prior to initiation of inotropic support, beta blockade, afterload reducers or diuretics and prior to diagnosis of noncompaction cardiomyopathy.

### 2.2 | Electrocardiograms

Sinus rhythm ECGs (Phillips, NV, USA) were performed at 25 mm/s speed with 10 mm/mV for limb and precordial leads. ECGs were analyzed at baseline MRI diagnosis of noncompaction. The first ECG taken at time of MRI was assessed utilizing the heart rate, the QRS duration (QRSd), the corrected QT interval (QTc), and the spatial peaks QRS-T angle. The Spatial peaks QRS-T angle is defined as the angle between the maximum depolarization and maximum repolarization vectors in three-dimensional space, as calculated by the Kors' regression-related method via the visual estimation method as previously described (Cortez, Sharma, Devers, Devers, & Schlegel, 2014; Kors, Herpen, Sittig, & Bemmel, 1990). Spatial QRS-T is shown in Figure 1. Calculation of the spatial peaks QRS-T

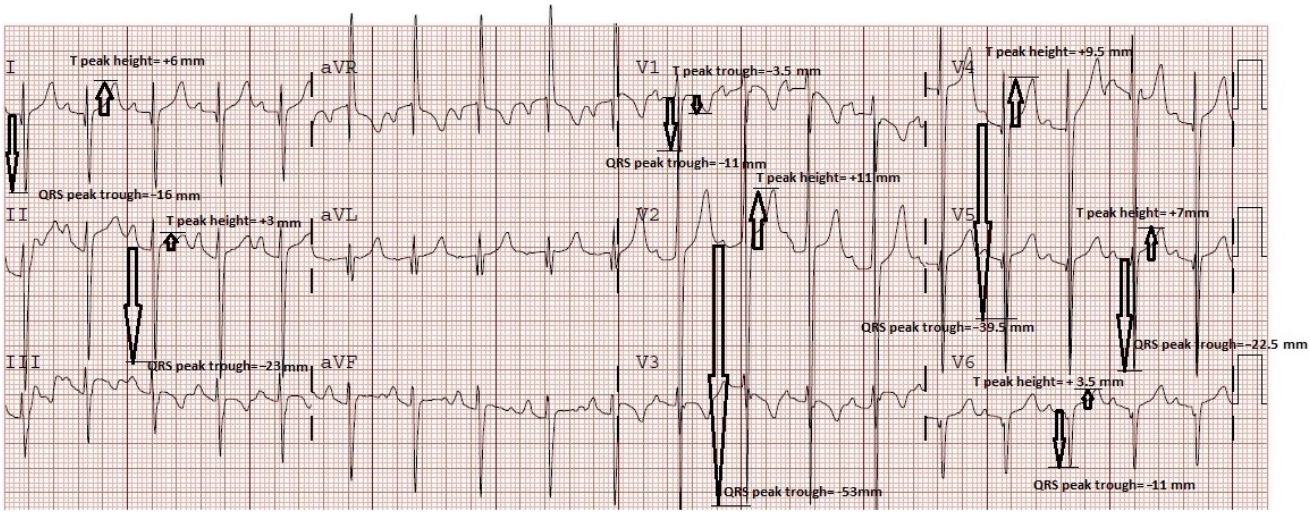


**FIGURE 2** Calculation of spatial QRS-T angle and QRS vector magnitude

angle is shown in Figure 2. All measures were assessed utilizing digital calipers.

### 2.3 | Statistics

Data were assessed for normality using Shapiro-Wilk testing. Non-normally distributed continuous data are presented as median and interquartile ranges (1st and 3rd quartiles), while normally distributed data are presented as mean ± *SD*. Student's *t* test, Mann-Whitney *U* test and contingency table testing were used to identify significant differences between groups. Significant *p*-values were <0.05. Relative risks were calculated to estimate risk for parameters identified as significantly different by comparative analysis. Survival analysis utilizing Kaplan-Meier curves and Cox regression were performed for significant parameters. Pearson's and Spearman's correlation coefficients were used as appropriate for parametric and nonparametric data. Intraobserver and interobserver variability were estimated by intraclass correlation coefficients based on a 10% sample of the population. Repeatability was performed by NS and DC. Data analysis was performed using SPSS (IBM, Chicago, IL, USA).

## 3 | RESULTS

Of 39 total patients, eight of them developed VA (20.5%). Time till VA median follow-up was 3.0 months (IQR 1.0–24.0), while those without development of VA had a median follow-up of 24.0 months (IQR 14.0–36.0 months). Six male patients developed VA, while 12 male patients did not develop VA (38.7%, *p*-value 0.076). No patients with TTN mutation developed VA and three patients (33.3%) who developed VA had the MYH7 mutation, while three of those who did not develop VA had MYH7 mutations (*p*-value 0.187). Please see Table 1 for demographic, MRI, and ECG data.

### 3.1 | ECG predictors

Those who developed VA had a higher baseline heart rate than those who did not develop VA with median heart rate of 147 bpm (138–163 bpm) vs. 139 bpm (IQR 115–144 bpm) (p-value 0.001, Table 1). The AU the ROC was 0.77 (95% CI 0.63 to 0.91), and at a cutoff of 147 bpm, the sensitivity, specificity, positive, and negative predictive values and relative risk was 100.0%, 67.7%, 44.4%, 100.0%, and 3.1 (95% CI 1.9 to 5.2), respectively, as shown in Table 2. The univariate hazard ratio for VA development for heart rate was 1.039 (95% CI 1.001 to 1.079) without significant hazard ratio when the SPQRS-T angle was taken into account (*p*-value 0.122). The QRSd nor the QTc were significant in analyses. (Table 3).

The SPQRS-T angle was higher in those patients with eventual VA development with median SPQRS-T angle of 147 degrees (IQR 138–163 degrees) versus 113 degrees (IQR 107–143 degrees) (*p*-value 0.015, Table 1). The AU the ROC of 0.88 (95% CI 0.70 to 1.00), and at a cutoff of 147 degrees, the sensitivity, specificity, positive, and negative predictive values and relative risk are 75.0%,

**TABLE 1** Baseline characteristics for noncompaction patients with eventual ventricular arrhythmia (VA) development and those without development of VA

| | VA (8) | no VA (30) | p-value |
|---|---|---|---|
| Age (years) | 1.0 (0.8–3.0) | 0.5 (0.2–12.0) | 0.335 |
| Male sex | 6 (35.5%) | 12 (35.5%) | 0.076 |
| Follow-up (months) | 3.0 (1.0–24.0) | 24.0 (14.0–36.0) | **<0.001** |
| Familial recurrence | 4 (50.0%) | 14 (45.2%) | 1.000 |
| TTN | 0 (0.0%) | 3 (10.0%) | 0.083 |
| MYH7 | 3 (33.3%) | 3 (10.0%) | 0.187 |
| LVEDV indexed (ml/m^2) | 207.5 (201.3–209.9) | 187.4 (156.0–195.2) | **0.031** |
| Late enhancement presence | 0 (0.0%) | 3 (9.7%) | 1.000 |
| Ejection fraction (%) | 22.5 (17.0–28.0) | 25.0 (15.9–35.8) | 0.171 |
| Fractional Shortening (%) | 10.0 (9.5–12.0) | 12.0 (11.9–18.0) | 0.057 |
| Lateral T-wave inversions | 8 (100.0%) | 25 (80.6%) | 0.313 |
| Inferior T-wave inversions | 5 (62.5%) | 18 (58.1%) | 1.000 |
| Third degree heart block | 0 (0.0%) | 1 (3.3%) | 1.000 |
| Heart rate (bpm) | 139 (115–144) | 155 (144–165) | **0.001** |
| QRSd (ms) | 68 (64–132) | 76 (70–78) | 0.413 |
| QTc (ms) | 477 (460–499) | 434 (430–477) | 0.057 |
| Spatial peaks QRS-T angle (degrees) | 147 (138–163) | 113 (107–143) | **0.015** |
| QRS vector magnitude (milli-volts) | 2.89 (1.36–3.00) | 1.73 (1.22–2.51) | 0.392 |

*Note*. TTN: Titan mutation; MYH7: myosin heavy chain mutation; LVEDVi: indexed left ventricular end-diastolic volume; QRSd: QRS duration; QTc: corrected QT interval.
Bold indicates significant *p*-value <0.05.

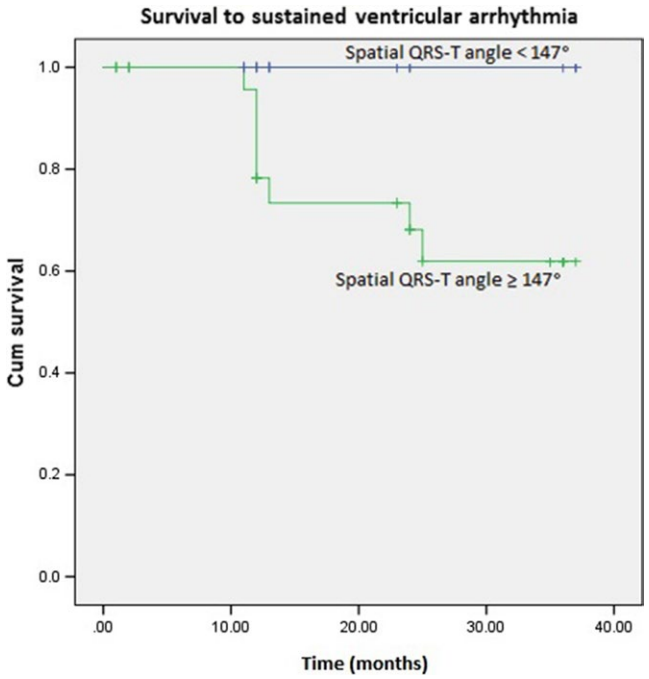


**FIGURE 3** Spatial peaks QRS-T angle survival curve based on a cutoff of 147 degrees, *p*-value 0.039

80.7%, 50.0%, 92.6%, and 3.9 (95% CI 1.7 to 8.8), respectively, as shown in Table 2. The univariate hazard ratio for ECMO need based on the SPQRS-T angle was 1.041 (95% CI 1.005 to 1.078) with univariate hazard ratio of 5.773 (95% CI 1.161 to 28.702) based on a cutoff of 147 degrees (Table 3). The spatial QRS-T angle was the only independent predictor with a significant hazard ratio of 1.031 (95% CI 1.001 to 1.074) and a Kaplan-Meier survival curve showed significant survival difference at a cutoff of 147 degrees (Figure 3).

### 3.2 | MRI predictors

LVEDVi was significantly larger in those noncompaction patients with development of VA at 207.5 ml/m$^2$ (95% CI 201.3 to 209.9 ml/m$^2$) compared to those without VA development at 187.4 ml/m$^2$ (95% CI 156.0 to 195.2 ml/m$^2$, *p*-value 0.031). The AU the ROC of 0.88 (95% CI 0.70 to 1.00), and at a cutoff of 207 ml/m$^2$, the sensitivity, specificity, positive, and negative predictive values and relative risk are 62.5%, 100.0%, 100.0%, 91.2%, and 31.1 (95% CI 2.4 to 642.6), respectively, as shown in Table 2. The univariate hazard ratio for ECMO need based on LVEDVi was not significant at 1.080 (95% CI 0.982 to 1.188). Multivariate testing was not performed on LVEDVi. Fractional shortening nor gadolinium enhancement were significant predictors of ventricular arrhythmia development.

### 3.3 | Correlations

Heart rate correlated significantly with the SPQRS-T angle (0.478), LVEDVi (0.551), and negatively correlated with age (−0.529). The SPQRS-T angle also correlated with LVEDVi (0.435), but otherwise did not significantly correlate with any of the other measurements. The QTc significantly correlated with age (0.575).

### 3.4 | Repeatability

Intraclass correlation coefficients for intraobserver and interobserver variability were 0.91 and 0.95.

## 4 | DISCUSSION

Overall, the importance of this study demonstrates that heart rate and SPQRS-T angle were significant predictors of ventricular arrhythmia development in pediatric patients with noncompaction cardiomyopathy. LVEDVi did significantly separate those with VA from those without VA development, but when looking at time dependency did not give a significant hazard ratio. The baseline ECG at presentation was more helpful than the baseline MRI for identification of eventual ventricular arrhythmia development in our cohort of patients.

### 4.1 | Heart rate

Heart rate cutoff of 147 bpm gave a relative risk of 3.1 for development of ventricular arrhythmia. Of course, given our patient population studied there is likely great variability in the patients' heart rates-based multiple variables related to the patients' age and clinical situation; thus, one is to view this cutoff value with caution.

### 4.2 | SPQRS-T angle

Similar to adults with nonischemic cardiomyopathy (i.e., hypertrophic cardiomyopathy), the SPQRS-T angle had predictive value for identifying patients at risk for ventricular arrhythmias (Cortez et al., 2016). In our noncompaction cardiomyopathy cohort, the age

**TABLE 2** Cutoff values, sensitivity, specificity, positive and negative predictive values (PPV, NPV), area under the receiver operating characteristic curve (AU ROC) and relative risk (RR) with 95% confidence intervals (95% CI) for age, indexed left ventricular end-diastolic volume (LVEDVi, milliliters per meter squared), fractional shortening (FS, %), heart rate (beats per minute), corrected QT interval (QTc, ms), and spatial peaks QRS-T angle (SPQRS-T angle, degrees)

| | Cutoff | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AU ROC (95% CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| LVEDVi | 208 ml/m$^2$ | 62.5 | 100.0 | 100.0 | 91.2 | 0.88 (0.70–1.00) | 31.1 (2.4–642.6) |
| Heart rate | 143 bpm | 100.0 | 67.7 | 44.4 | 100.0 | 0.77 (0.63–0.91) | 3.1 (1.9–5.2) |
| SPQRS-T angle | 144.9 deg | 75.0 | 80.7 | 50.0 | 92.6 | 0.81 (0.55–0.98) | 3.9 (1.7–8.8) |

**TABLE 3** Univariate and multivariate predictors of eventual ventricular arrhythmia development including age, indexed left ventricular end-diastolic volume (LVEDVi), fractional shortening, heart rate, and spatial peaks QRS-T angle (SPQRS-T angle)

| | Univariate Hazard ratio | p-value |
|---|---|---|
| LVEDVi | 1.080 (0.982–1.188) | 0.114 |
| Heart rate/bpm | 1.039 (1.001–1.079) | 0.049 |
| SPQRS-T angle/degree | 1.041 (1.005–1.078) | 0.026 |
| SPQRS-T angle 147 degrees | 5.773 (1.161–28.702) | 0.019 |
| | **Multivariate Hazard ratio** | **p-value** |
| Heart rate | 1.029 (0.992–1.068) | 0.122 |
| SPQRS-T angle | 1.031 (1.001–1.066) | 0.049 |

studied was much younger. The spatial QRS-T angle itself is a marker of depolarization–repolarization discordance. In adults, the SPQRS-T angle has been shown to correlate with reduced left ventricular ejection fraction, and left ventricular dilation, whereas in our study correlation with LVEDVi was the only significant MRI correlate to the SPQRS-T angle in our younger study population (Shi, Ferrier, Sasse, Harding, & Larsen, 2014). Given the QRSd, QTc, and T-wave inversions in particular leads did not have predictive value for ventricular arrhythmia development in our cohort, it demonstrates that both depolarization and repolarization duration (and T-wave inversion) do not necessarily show independent risk assessment.. However, when the angle between the maximum depolarization and repolarization vectors, as measured by the SPQRS-T angle, progression to VA was independently predicted in this study, based on baseline ECG at presentation. Although a significant relationship to heart rate was noted, development of VA was still independent of heart rate when assessed by the SPQRS-T angle.

### 4.3 | MRI measures

Baseline fractional shortening and gadolinium enhancement were not useful measures for determining risk of VA in noncompaction. In a similar set of pediatric patients, LV dilation at baseline did not identify those at risk for sudden death or ventricular arrhythmia but 2 of the 3 did have low ejection fractions at baseline (Ichida et al., 1999). The aforementioned study, did have longer follow-up, and a similar baseline age group (1 week to 15 years), however, with slightly smaller number of patients and slightly different end-point studied (Ichida et al., 1999).

### 4.4 | Limitations

The size of the noncompaction cardiomyopathy cohort is a strong limitation. The study performed was a retrospective case–control study and thus limited the availability of longer follow-up. It also limited the ability to identify other causes of elevated heart rates such as agitation when the ECG was performed, which is important given the young age of the patients. As the Frank lead vectorcardiogram was not readily available, estimation of the QRS-T angle based on the Kors' regression was also a limitation of this study, although this regression has proven to be a close approximation of the Frank lead vectorcardiogram (Cortez et al., 2014).

## 5 | CONCLUSION

Only the spatial peaks QRS-T angle had significant independent predictive value in this cohort for identifying noncompaction patients at risk for ventricular arrhythmias. The LVEDVi and heart rate had high negative predictive values for development of significant VA as well, but did not have independent predictive value. Larger prospective studies are warranted with longer-term follow-up.

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None.

## CONFLICT OF INTEREST

No conflict of interest present.

## ORCID

*Daniel Cortez* http://orcid.org/0000-0001-9874-0733

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