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Noninvasive Predictors of Ventricular Arrhythmias in Patients With Tetralogy of Fallot Undergoing Pulmonary Valve Replacement

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ABSTRACT

OBJECTIVES This study sought to test the hypothesis that a vectorcardiographic parameter, the QRS vector magnitude (QRSVm), can risk stratify those patients at risk for sustained spontaneous ventricular arrhythmias (VAs) or ventricular arrhythmia inducibility (VAI) in a large cohort of patients with tetralogy of Fallot (TOF).

BACKGROUND Patients with TOF have an increased risk of VAs, but predicting those at risk can often be challenging.

METHODS Blinded retrospective analyses of 177 TOF patients undergoing pulmonary valve replacement (PVR) between 1997 and 2015 were performed. VAI was evaluated by programmed electrical stimulation in 48 patients. QRS intervals and QRSVm voltage measurements were assessed from resting 12-lead electrocardiograms, and risk of VA was determined. Clinical characteristics, including imaging and cardiac catheterizations, were used for other modality comparisons.

RESULTS Sustained spontaneous VA occurred in 12 patients and inducible VA in 18 patients. Age and QRSVm were significant univariate predictors of VA. QRSVm was the only independent predictor of VAI ($p < 0.001$). Using a root mean square QRS value of 1.24 mV, the positive and negative predictive values were 47.9% and 97.8%, respectively, for spontaneous sustained VA. For VAI, using a QRSVm cutoff of 1.31 mV, positive and negative predictive values were 63.0% and 95.3%, respectively.

CONCLUSIONS In TOF patients undergoing PVR, older age was associated with increased spontaneous VA risk. Lower QRSVm predicted spontaneous VA or VAI risk with high negative predictive values. QRSVm is the only independent predictor of VAI. These clinical features may help further risk stratify TOF patients requiring therapies to prevent sudden death. (J Am Coll Cardiol EP 2017;3:162–70) © 2017 by the American College of Cardiology Foundation.

Patients with tetralogy of Fallot (TOF) have a significant burden of arrhythmias postoperatively, reported to be as high as 43.3% in some series (1). The clinical history remains important but may be insufficient for predicting the risk of ventricular arrhythmias (VAs). Invasive risk stratification via programmed electrical stimulation (PES) in TOF patients has been shown to have diagnostic and prognostic value (2). Noninvasive measures of the right ventricle (RV), such as QRS duration (QRSd), QRS fragmentation, increased RV volumes, as well as right ventricular ejection fraction (RVEF) and left ventricular

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ejection fraction (LVEF), have demonstrated association with increased risk of arrhythmias (3-7).

Vectorcardiographic principles provide additional clinical information to the 12-lead electrocardiogram (ECG) and have yielded further diagnostic (8-10) and prognostic (10-15) value to the ECG in the traditional 12-lead configuration. In a small cohort of adult TOF patients, increased risk of sustained spontaneous VA and inducible ventricular arrhythmia has been demonstrated by a measure of QRS dispersion called the QRS vector magnitude (QRSVm, or magnitude of the 3-dimensional QRS vector), with improved predictive value over QRSd or spatial QRS-T angle. The predictive value of QRSVm was independent of magnetic resonance imaging (MRI) RV volume, gadolinium enhancement, or hemodynamics measured via cardiac catheterization (16).

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QRSVm denotes the magnitude of the maximum 3-dimensional QRS vector and is calculated as the root mean square of the QRS wave in 3-dimentional space. It is calculated from the equation:

$$\sqrt{\left\{(QRS maximum\ lead\ II)^2 + (QRS maximum\ lead\ V6)^2 + (-0.5 \cdot QRS maximum\ lead\ V2)^2\right\}}$$

We hypothesized that QRSVm, based on a sinus rhythm ECG recorded just before a TOF patient undergoes pulmonary valve replacement (PVR), will predict risk of spontaneous VA as well as risk of inducible VA during PES in a large cohort of TOF patients. We chose to evaluate QRSVm on ECGs at the time of PVR because of several clinical considerations: 1) the risk of VA and ventricular arrhythmia inducibility (VAI) is high during this time; 2) other clinical parameters (cardiac catheterizations and MRIs) are usually measured during this period so that correlations can be made; and 3) predicting VA or VAI risks before PVR may allow for changes in management at the time of PVR, such as cryoablation during open surgery or consideration of further risk stratification such as electrophysiological (EP) studies around the time of PVR.

PATIENTS AND METHODS

STUDY POPULATION. This study was approved by the institutional review board at the University of Colorado.

A blinded retrospective analysis was performed on available electrocardiograms and associated imaging data from 362 TOF patients from 1977 to 2015 at the University of Colorado Hospital systems (including the Children's Hospital of Colorado). This group included 177 TOF patients who were undergoing PVR via transcatheter insertion utilizing Melody valves (Medtronic, Minneapolis, Minnesota) or via cardiac surgery. Patients were excluded if they did not undergo a procedure for PVR or if they did not have an interpretable ECG with adequate baseline measurement recorded within the 6 months before PVR. Patients also were excluded if a diagnosis of TOF or TOF-like physiology was not certain or if they had left-sided obstruction at the time of PVR. ECG assessment near the time of PVR was chosen because cryoablation during this period might be able to prevent recurrence of arrhythmia (7).

Patients who had sustained spontaneous VA burden (seen by ECG, Holter, exercise stress test, pacemaker, or telemetry monitoring) were identified. Sustained spontaneous VA was defined as ≥30 s of VA or a VA that was associated with hemodynamic instability. For these patients, the arrhythmia had to have occurred within the 6 months before or 6 months after PVR, and their last sinus rhythm ECG before arrhythmia identification/treatment and before PVR was used for evaluation. Thus, at the time of ECG assessment, no patients were taking ion-channel inhibiting medications, had not undergone ablations, and had no new medical devices placed.

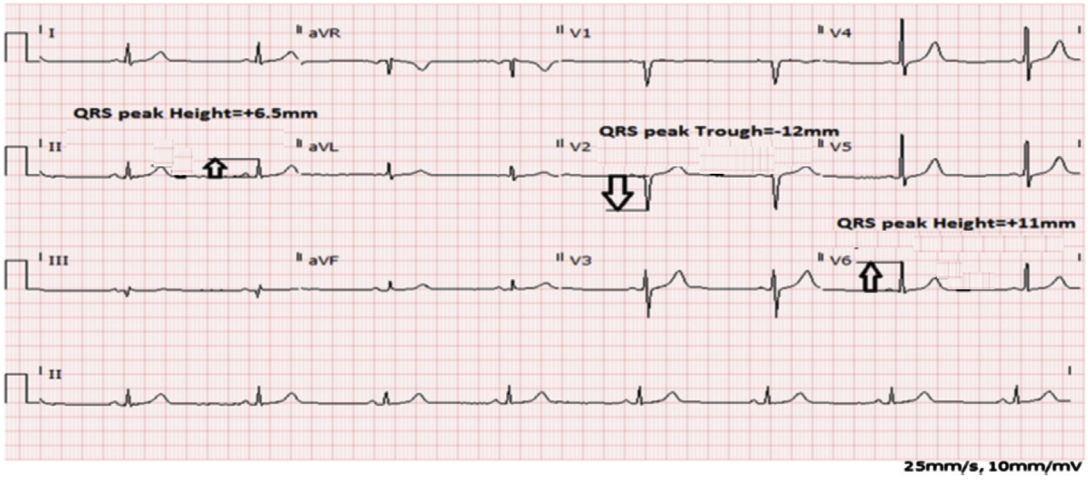
Comparisons were made between those patients with spontaneous sustained VA versus all patients without VA, including those undergoing PES (N = 177); for those with either VA or induced sustained VA (VAI) versus no VA or VAI; and for only those undergoing PES (n = 48), comparisons were made between those who had inducible sustained VA (VAI) versus those without VAI.

EP STUDIES AND ECGs. Some patients had undergone EP studies before PVR. Inducibility was evaluated from EP studies using PES, as previously described (2). Briefly, PES was performed at 2 drive trains and at 2 sites, with up to triple extrastimuli and decrementing to ventricular effective refractory period or 180 ms. If a patient was noninducible, the protocol was repeated on isoproterenol. Inducibility was defined as any VA (monomorphic VA, polymorphic VA, or ventricular fibrillation [VF]) that

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
ECG = electrocardiogram
EP = electrophysiology
IQR = interquartile range
LVEDP = left ventricular end-diastolic pressure
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
MRI = magnetic resonance imaging
OR = odds ratio
PES = programmed electrical stimulation
PVR = pulmonary valve replacement
QRSd = QRS duration
QRSVm = QRS vector magnitude
ROC = receiver-operating characteristic
RV = right ventricle
RVEDP = right ventricular end-diastolic pressure
RVEDV = right ventricular end-diastolic volume
RVEF = right ventricular ejection fraction
TOF = tetralogy of Fallot
VA = ventricular arrhythmia
VAI = ventricular arrhythmia inducibility
VF = ventricular fibrillation
VT = ventricular tachycardia

FIGURE 1 Calculation of QRSVm From a 12-Lead ECG



QRSVm = SQRT[QRSX^2 + QRSY^2 + QRSZ^2] = SQRT[11 mm^2 + 6.5 mm^2 + (-0.5 · -12 mm)^2] = 14.1 mm = 1.41 mV. ECG = electrocardiogram; QRSVm = QRS vector magnitude.

lasted ≥30 seconds or was hemodynamically unstable requiring pace termination or defibrillation.

Sinus rhythm ECGs (GE, Milwaukee, Wisconsin, or Phillips, Andover, Massachusetts) were recorded at 25 mm/s speed with 10 mm/mV for limb and precordial leads. ECGs were analyzed within 6 months of PVR. Measurements of QRSVm (Figure 1) and QRSd intervals were performed. QRSVm was performed blinded by 1 author (D.C.) on the full-scale view (10 mm/mV) PDF file of the ECG using electronic calipers. Intraobserver and interobserver variability as described in the Statistical Analysis section were measured by 2 authors (D.C., N.S.). QRSd was reported on the ECG device. Pre-operative and post-operative differences were assessed based on the pre-operative ECGs and the post-operative ECGs recorded within 1 month of PVR.

TABLE 1 Clinical Characteristics of Patients With Sustained Spontaneous VAs Versus All Others (Including Those Undergoing PES) at the Time of PVR

	VA (n = 12)	No VA (n = 165)	p Value
Age (yrs)	28.0 (19.0–51.3)	15.0 (8.0–29.0)	0.006
Male (%)	6 (50.0%)	87 (52.6%)	0.855
Transcatheter Melody PVR	1 (8.3%)	21 (12.7%)	1.000
Repeat PVR	1 (8.3%)	12 (7.3%)	1.000
Spatial QRS-T angle (°)	93.5 (43.6–120.7)	104.4 (66.1–132.9)	0.503
QRSVm (mV)	1.05 (0.82–1.15)	1.51 (1.16–2.22)	<0.001
QRS duration (ms)	158.0 (133.0–169.0)	146.0 (128.0–164.0)	0.271
Pulmonary regurgitation fraction (%)	37.3 ± 11.6	44.1 ± 13.3	0.423
MRIs performed	4 (33.3%)	63 (38.2%)	0.770
MRI RV volume (ml/m^2)	156.6 ± 35.0	170.3 ± 34.7	0.499
MRI LV volume (ml/m^2)	95.4 ± 5.0	79.5 ± 16.9	0.056
RV ejection fraction (%)	43.0 ± 17.9	41.8 ± 8.6	0.906
LV ejection fraction (%)	50.3 ± 5.7	52.8 ± 6.8	0.453
Cardiac catheterizations	3 (25.0%)	67 (40.6%)	0.369
RV end-diastolic pressure (mm Hg)	9.0 ± 1.0	10.5 ± 3.8	0.093
LV end-diastolic pressure (mm Hg)	12.5 ± 1.5	11.0 ± 4.5	0.114
Gadolinium enhancement (+)	4 (100.0%)	30 (68.2%)	0.444

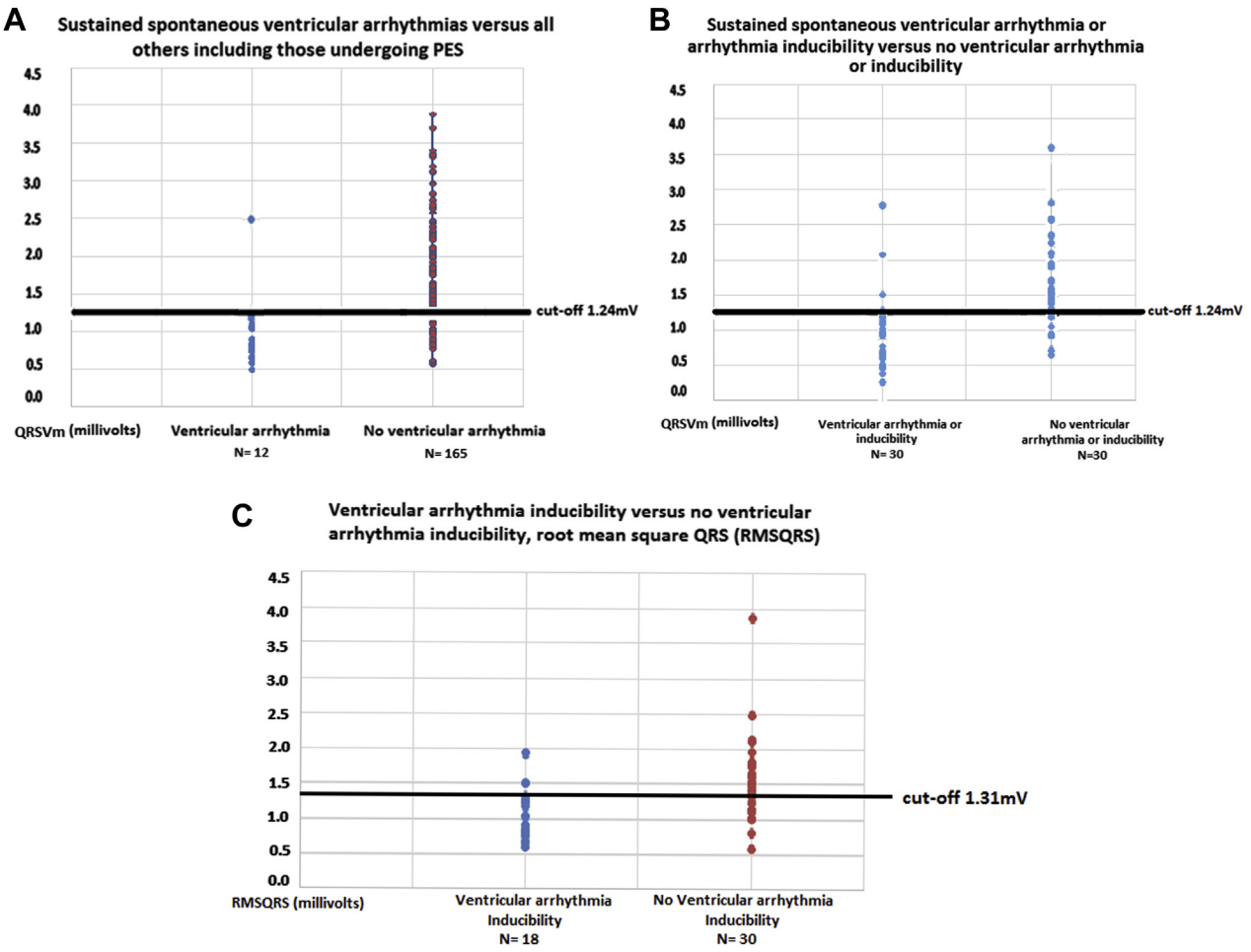
Values are median (interquartile range), n (%), or mean ± SD.

LV = left ventricle; MRI = magnetic resonance imaging; PES = programmed electrical stimulation; PVR = pulmonary valve replacement; QRSVm = QRS vector magnitude; RV = right ventricle; VA = ventricular arrhythmia.

MRI AND CARDIAC CATHETERIZATIONS. MRI data within 6 months of the patient's PVR were included in data analysis. MRI measurements of left ventricular and RV volumes were indexed to body surface area. Presence of gadolinium enhancement, as well as RVEF, LVEF, and pulmonary regurgitant fractions, also were assessed. Hemodynamic measurements from cardiac catheterization were included if they were recorded within 6 months of PVR. Cardiac catheterization data included left-sided phasic and mean pressures as well as oxygen saturation data.

STATISTICAL ANALYSIS. Data were assessed for normality using Shapiro-Wilk testing. Non-normally distributed continuous data are presented as median and interquartile range (IQR) (first and third quartiles). Normally distributed data are presented as mean ± SD. Student *t* test, Mann-Whitney *U* test, and contingency table testing were used to identify significant differences between groups. A value of $p < 0.05$ was considered significant. Odds ratios (ORs) were

FIGURE 2 QRS Vector Magnitude



(A) QRSVm for TOF patients with and those without spontaneous VAs (including patients undergoing PES). **(B)** QRSVm for TOF patients with spontaneous VAs versus all others without spontaneous VA, including those undergoing PES. **(C)** QRSVm for TOF patients with and those without ventricular arrhythmia inducibility.
PES = programmed electrical stimulation; QRSVm = QRS vector magnitude; TOF = tetralogy of Fallot; VA = ventricular arrhythmia.

calculated to estimate risk for parameters identified as significantly different by comparative analysis.

Univariate analysis was performed to identify predictors associated with VAs or VAI. Multivariate analysis was performed using logistic regression analysis to identify independent risk factors for VAs or VAI. Selection of variables for inclusion in the multivariate analysis was made using a stepwise approach (p removal = 0.10).

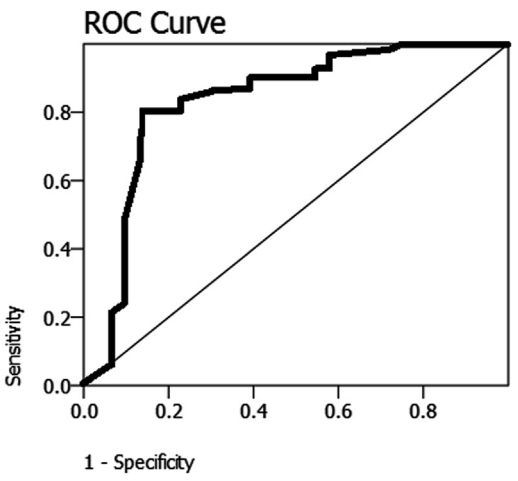
Receiver-operating characteristic (ROC) curves were generated to determine optimal cutoff values for variables, particularly QRSVm, in the prediction of VAs during the follow-up period. The curve point with the highest sum of sensitivity and specificity was labeled as the optimal cutoff point and was used in OR, sensitivity, and specificity analyses.

Pearson and Spearman 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 2 of the authors (D.C., N.S.). Data analysis was performed using SPSS (IBM, Chicago, Illinois).

RESULTS

PATIENT DEMOGRAPHICS. One hundred seventy-seven patients met the inclusion criteria (median age 13 years; IQR: 8 to 29 years). The cohort was 52.0% male. Nineteen Melody valves were inserted percutaneously, and 158 open-heart surgeries were

FIGURE 3 Area Under the ROC Curve for QRSVm for TOF Patients With Spontaneous Sustained VAs Versus No VAs (Including Those Undergoing PES)



Area under the curve: 0.81 (95% confidence interval: 0.70 to 0.91). ROC = receiver-operating characteristic; other abbreviations as in Figure 2.

TABLE 2 Univariate and Multivariate Analyses for Spontaneous VA (n = 12) Versus All Other Patients (Including Those Undergoing PES (n = 165)

	Odds Ratio (95% Confidence Interval)	p Value
Univariate		
Age	1.04 (1.01–1.08)	0.012
Male	0.87 (0.28–2.95)	0.874
Transcatheter Melody PVR	0.65 (0.08–5.35)	0.690
Repeat PVR	1.25 (0.15–10.64)	0.841
Spatial QRS-T angle	0.99 (0.98–1.01)	0.453
QRSVm	0.80 (0.69–0.93)	0.004
QRS duration	1.01 (0.99–1.03)	0.326
Pulmonary regurgitation fraction	0.97 (0.89–1.05)	0.397
MRI RV volume	0.99 (0.96–1.02)	0.448
MRI LV volume	1.13 (1.00–1.29)	0.056
RV ejection fraction	1.01 (0.91–1.13)	0.811
LV ejection fraction	0.95 (0.82–1.10)	0.467
RV end-diastolic pressure	0.87 (0.60–1.27)	0.484
LV end-diastolic pressure	1.09 (0.093–1.28)	0.303
Gadolinium enhancement	N/A	N/A
Multivariate		
Age	1.10 (0.97–1.25)	0.137
QRSVm	0.95 (0.78–1.15)	0.103
MRI LV volume	1.18 (1.00–1.39)	0.053

Abbreviations as in Table 1.

performed to replace the pulmonary valves. Twelve patients (6.8%) had documented sustained VAs. Forty-eight patients (27.1%) had undergone PES studies before PVR. Of those patients, 18 (37.5%) had sustained VAI (12 polymorphic ventricular tachycardia (VT)/VF and 6 monomorphic VT without difference in parameters between these subgroups). Sixty-seven MRIs and 70 cardiac catheterizations were performed before PVR.

RISK OF SPONTANEOUS VAs (INCLUDING PATIENTS UNDERGOING PES TESTING). Age and QRSVm were significantly different in patients with spontaneous sustained VA (n = 12) compared to all patients without spontaneous VA, including those patients undergoing PES, regardless of whether they had VAI or did not have VAI (n = 165) (Table 1). QRSVm for those patients with spontaneous VA was 1.05 mV (IQR: 0.81 to 1.18 mV), whereas all other patients had a median QRSVm of 1.62 mV (IQR: 1.23 to 2.28 mV). Using a QRSVm cutoff of 1.24 mV (Figure 2A), the positive and negative predictive values were 42.9% and 97.8%, respectively (OR: 33.7; 95% confidence interval [CI]: 8.1 to 141.6). Area under the ROC curve was 0.81 (95% CI: 0.70 to 0.91) (Figure 3). Although age and QRSVm were significant univariate predictors, with multivariate analysis no parameters were significant predictors (Table 2). Syncope may have been an independent predictor of VA; however, it was not included in univariate or multivariate analyses because of the limited number of patients with syncope thus underpowered comparisons.

RISK OF SPONTANEOUS VA OR VAI. Only age and QRSVm significantly differentiated TOF patients with VA or VAI (n = 30) from those without VA or VAI (n = 30). QRSVm significantly differentiated patients with spontaneous VA (median 1.05 mV; IQR: 0.79 to 1.24 mV) compared to those without VA (median 1.50 mV; IQR: 1.10 to 1.80 mV), with $p < 0.001$ (Table 3, Figure 2B). The area under the ROC curve was 0.83 (95% CI: 0.73 to 0.92). The positive and negative predictive values, using a cutoff of 1.24 mV, were 84.9% and 92.6%, respectively. The area under the ROC curve was 0.83 (95% CI: 0.73 to 0.92). Patients with a QRSVm of 1.24 mV had OR OF 70.0 for spontaneous VA or VAI (95% CI: 12.5 to 393.4). Age significantly differentiated VA (median age 34.0 years; IQR: 24.3 to 53.0 years) from no VA (median age 17.0 years; IQR: 13.0 to 22.0 years; $p = 0.002$). QRSVm remained the only independent predictor of VA or VAI ($p = 0.011$) on multivariate analysis (Table 4).

RISK OF INDUCIBLE VA. QRSVm was the only parameter that significantly differentiated ($p < 0.001$) patients with VAI (0.98 mV; IQR: 0.76 to 1.24 mV) from

those without sustained VAI (1.51 mV; IQR: 1.1 to 1.8 mV). For QRSVm, the positive and negative predictive values, using a cutoff of 1.31 mV (Figure 2C), were 63.0% and 95.2%, respectively, with OR of 34.0 for those with VAI (95% CI: 3.9 to 293.3). Age, history of syncope, QRSd, MRI volumes, gadolinium enhancement, and catheter-measured hemodynamics were not significantly different between those with VAI and those without VAI (Table 5). Of those with VAI, there was no difference in characteristics between those who had monomorphic VT versus those who had polymorphic VT (Table 6). QRSVm remained an independent predictor on multivariate analysis when gender ($p = 0.061$) and RVEF ($p = 0.101$) were taken into account ($p = 0.005$) (Table 7).

CORRELATIONS WITH OTHER MEASUREMENTS. QRSVm had significant correlation coefficients when compared to age, QRSd, and left ventricular end-diastolic volume (LVEDV), with r values of -0.420, -0.190, and 0.280, respectfully. QRSd had significant correlation coefficients when compared to age, spatial QRS-T angle, QRSVm, and RVEF at 0.480, 0.350, -0.190, and -0.490, respectively. Repeat PVR was associated with lower RVEF and lower LVEF, with correlation coefficients of -0.40 and -0.30, respectively.

Higher LVEDV was inversely associated with age and right ventricular end-diastolic volume (RVEDV), with correlation coefficients of -0.33 and -0.20, respectfully.

RVEF significantly correlated with repeat PVR, QRSd, RVEDV, and LVEF, with correlation coefficients of -0.370, -0.490, -0.490, and 0.580, respectfully. Left ventricular end-diastolic pressure (LVEDP) significantly correlated with age and right ventricular end-diastolic pressure (RVEDP), with correlation coefficients of 0.420 and 0.530, respectively.

REPEATABILITY OF MEASURES TESTED AND CHANGE OVER TIME. Intraclass correlation coefficients for QRSVm for interobserver and intraobserver variability were 0.94 and 0.92, respectively, for 10% of the sample.

For patients without sustained VA, the difference in QRSVm was a median of 0.15 mV (IQR: -0.06 to 0.37 mV) before PVR versus 0.12 mV (IQR: -0.09 to 0.25 mV) after PVR. There was no significant difference for QRSvm between values taken before PVR and QRSvm values measured within 1 month after PVR.

DISCUSSION

RISK OF SPONTANEOUS VA. Of the clinical characteristics in this TOF cohort, only age and QRSVm were univariate predictors with significant ORs for predicting spontaneous sustained VA. On multivariate analyses, no single parameter was a significant predictor for spontaneous VA when all patients,

TABLE 3 Clinical Characteristics of Patients with Sustained Spontaneous VA or VAI Versus Those Without VA or VAI at the Time of PVR

	VA/VAI (n = 30)	No VA/VAI (n = 30)	p Value
Programmed electrical stimulation	18	30	<0.001
Age (yrs)	34 (24.3-53.0)	17.0 (13.0-22.0)	0.002
Male (%)	15 (50.0%)	16 (53.3%)	0.796
Transcatheter Melody PVR	1 (3.3%)	1 (0.0%)	1.000
Repeat PVR	2 (6.7%)	1 (3.3%)	0.554
Spatial QRS-T angle (°)	100.6 (78.8-126.1)	97.3 (54.6-127.6)	0.342
QRSVm (mV)	1.05 (0.79-1.24)	1.50 (1.10-1.80)	<0.001
QRS duration (ms)	160.0 (146.0-174.5)	158.0 (138.0-180.0)	0.308
Pulmonary regurgitation fraction (%)	44.3 ± 16.8	45.7 ± 11.9	0.885
MRIs performed	12 (40.0%)	15 (50.0%)	0.604
MRI RV volume (ml/m^2)	156.2 ± 26.8	164.5 ± 36.5	0.303
MRI LV volume (ml/m^2)	75.9 ± 36.6	76.7 ± 10.0	0.952
RV ejection fraction (%)	40.9 ± 13.9	46.0 (32.5-53.0)	0.820
LV ejection fraction (%)	51.8 ± 6.3	51.7 ± 6.0	0.965
Cardiac catheterizations performed	13 (43.3%)	15 (50.0%)	0.796
RV end-diastolic pressure (mm Hg)	11.6 ± 3.6	11.5 ± 4.7	0.906
LV end-diastolic pressure (mm Hg)	12.1 ± 1.8	9.3 ± 1.5	0.886
Gadolinium enhancement (+)	10 (83.3%)	9 (75.0%)	0.615

Values are n, median (interquartile range), n (%), or mean ± SD.
VAI = ventricular arrhythmia inducibility; other abbreviations as in Tables 1 and 2.

TABLE 4 Univariate and Multivariate Analyses for Spontaneous VA or VAI (n = 30) Versus No VA or VAI (n = 30)

	Odds Ratio (95% Confidence Interval)	p Value
Univariate		
Age	1.04 (1.00-1.08)	0.034
Male	1.48 (0.53-4.12)	0.456
Transcatheter Melody PVR	0.93 (0.06-15.7)	0.962
Repeat PVR	N/A	N/A
Spatial QRS-T angle	1.00 (0.99-1.02)	0.509
QRSVm	0.84 (0.74-0.95)	0.005
QRS duration	1.01 (0.99-1.03)	0.223
Pulmonary regurgitation fraction	0.99 (0.90-1.09)	0.849
MRI RV volume	0.98 (0.95-1.01)	0.212
MRI LV volume	1.00 (0.96-1.04)	0.891
RV ejection fraction	0.99 (0.90-1.09)	0.836
LV ejection fraction	0.99 (0.84-1.16)	0.861
RV end-diastolic pressure	1.10 (0.85-1.41)	0.466
LV end-diastolic pressure	1.01 (0.71-1.44)	0.959
Gadolinium enhancement	3.06 (0.48-19.7)	0.240
Multivariate		
Age	1.03 (0.99-1.07)	0.123
QRSVm	0.85 (0.74-0.96)	0.011

Abbreviations as in Tables 1 to 3.

TABLE 5 Clinical Characteristics in Patients with Inducible VAI Versus No VAI at the Time of PVR

	Inducible (n = 18)	Not Inducible (n = 30)	p Value
Age (yrs)	19.0 (12.0–34.0)	17.0 (13.0–22.0)	0.449
Male (%)	14 (77.8%)	16 (53.3%)	0.061
Transcatheter Melody PVR	0 (0.0%)	1 (3.3%)	1.000
Repeat PVR	2 (11.1%)	1 (3.3%)	0.644
Spatial QRS-T angle (°)	100.6 (80.0–128.5)	97.3 (54.6–127.6)	0.395
Root mean square QRS (mV)	1.0 (0.8–1.2)	1.5 (1.1–1.8)	<0.001
QRS duration (ms)	161.0 (146.0–176.0)	158.0 (138.0–180.0)	0.420
Pulmonary regurgitation fraction (%)	35.0 (25.0–73.0)	51 (40.0–52.5)	0.783
MRIs performed	14 (46.7%)	15 (50.0%)	1.000
MRI RV volume (ml/m^2)	155.4 ± 17.3	164.5 ± 36.5	0.497
MRI LV volume (ml/m^2)	71.5 ± 26.3	76.7 ± 10.0	0.766
RV ejection fraction (%)	33.0 (32.0–35.0)	46.0 (32.5–53.0)	0.101
LV ejection fraction (%)	71.5 ± 26.3	51.7 ± 6.0	0.666
Catheterizations performed	10 (55.6)	15 (50.0%)	0.772
RV end-diastolic pressure (mm Hg)	12.4 ± 3.8	11.5 ± 4.7	0.614
LV end-diastolic pressure (mm Hg)	11.0 ± 1.6	9.3 ± 1.5	0.166
Gadolinium enhancement (+)	6 (75.0%)	9 (75.0%)	1.000

Values are median (interquartile range), n (%), or mean ± SD. Of the 165 patients, 48 (27.1%) underwent programmed electrical stimulation studies performed before pulmonary valve replacement (PVR). Of these 48, 18 (37.5%) had sustained ventricular arrhythmia inducibility.

Abbreviations as in Tables 1 and 3.

including those undergoing PES, were included in the comparison. However, there was a trend toward significance for LVEDV, age, and QRSVm.

RVEDV by MRI was not helpful in predicting risk of VA. QRSd has had equivocal results in terms of predicting VA in published reports. Similar to previous findings, we found significant correlations between RV volumes and QRSd (1,3). Given the younger mean age of patients in our study, this may be one reason why QRSd and RV volumes were not independent predictors for VA compared to results of previous studies with older patient populations (4,17).

A decrease in the peak magnitude of the QRS complex (as measured by QRSVm) is a measure of increased dispersion of depolarization or less unidirectional absolute depolarization, which may be a potential cause of increased arrhythmogenic risk (14). By measuring a derived 3-dimensional voltage, one is assessing overall summative depolarizing vector forces in the X-, Y-, and Z-directions. As summative vectors begin to disperse in different directions, the overall absolute magnitude in 1 particular direction decreases. Thus, increased dispersion of depolarization, as measured in our study by a lower QRSVm, was found to be associated with an increased risk of spontaneous VA. Similar findings in signal-averaged ECG measurements have been demonstrated in a smaller cohort (17). QRSVm has excellent negative predictor value. If a patient had QRSVm > 1.24 mV, his or her risk for spontaneous VA was very low, regardless of whether the patient had an inducible VA on PES.

In our study, gadolinium enhancement in the RV (including around the outflow tract conduit or patch and outside of the ventricular septal patch) was not associated with an increased risk of VAs. Older age was associated with an arrhythmogenic risk, as previously reported (1,18). Increased LVEDV, although not statistically significant, approached significance (univariate p = 0.053, multivariate p = 0.058). Given the trend toward a significant difference in LVEDV, likely ventricular-to-ventricular interactions likely play a role in patients with TOF and may be related to their arrhythmia burden (19).

As with other arrhythmic syndromes, a history of syncope should raise concern and prompt treatment and evaluation. However, given the low numbers of patients with syncope, we were not able to analyze this parameter in univariate or multivariate analyses. In previous studies, syncope has been shown to be an independent predictor of VAs (1).

RISK OF INDUCIBLE VA. QRSVm was the only independent predictor in either the VAI versus no inducibility comparison group as well as the VA or inducibility versus no arrhythmia or inducibility comparison group. This relationship has been previously reported (14). Induced VAs included polymorphic and monomorphic VT and VF. There were no differences in

TABLE 6 Clinical Characteristics of Patients with VAI, Monomorphic VT Versus Polymorphic VT, at the Time of PVR

Inducible VT Subgroup	Polymorphic (n = 6)	Monomorphic (n = 12)	p Value
Age (yrs)	37.0 (23.5–47.0)	36.0 (32.5–50.0)	0.566
Male (%)	4 (60.0%)	7 (63.4%)	0.750
Transcatheter Melody PVR	0 (0.0%)	0 (0.0%)	1.000
Repeat PVR	1 (16.7%)	0 (0.0%)	0.333
Spatial QRS-T angle (°)	125.3 (85.5–157.0)	104.9 (87.9–115.8)	0.330
Root mean square QRS (mV)	1.2 (0.7–1.3)	0.9 (0.8–1.2)	0.678
QRS duration (ms)	156.0 (146.0–162.0)	172.0 (152.0–180.0)	0.140
Pulmonary regurgitation fraction (%)	24 (16.0–52.0)	31 (12–65)	0.783
MRIs performed	5 (83.3%)	9 (75.0%)	1.000
MRI RV volume (ml/m^2)	161 ± 15.3	152.9 ± 24.2	0.666
MRI LV volume (ml/m^2)	70.0 ± 24.2	72.3 ± 37.1	0.825
RV ejection fraction (%)	32.0 (28.0–53.0)	41.0 (37.5–44.5)	0.552
LV ejection fraction (%)	51.0 (46.0–53.0)	58.0 (56.5–59.5)	0.666
Catheterizations performed	3 (50.0)	7 (58.3%)	1.000
RV end-diastolic pressure (mm Hg)	10.7 ± 3.5	13.1 ± 3.9	0.377
LV end-diastolic pressure (mm Hg)	9.0 ± 1.6	11.0 ± 2.1	0.246
Gadolinium enhancement (+)	2 (50.0%)	4 (100.0%)	0.429

Values are median (interquartile range), n (%), or mean ± SD.

VT = ventricular tachycardia; other abbreviations as in Tables 1 and 3.

TABLE 7 Univariate and Multivariate Analyses for History of VAI Versus No VAI at the Time of PVR

	Odds Ratio (95% Confidence Interval)	p Value
Univariate		
Age	1.029 (0.966–1.097)	0.374
Male	3.06 (0.816–11.494)	0.097
Transcatheter Melody PVR	N/A	N/A
Repeat PVR	N/A	N/A
Spatial QRS-T angle	1.00 (0.989–1.016)	0.776
QRSVm	0.78 (0.648–0.927)	0.005
QRS duration	1.00 (0.982–1.027)	0.698
Pulmonary regurgitation fraction	0.97 (0.89–1.05)	0.436
MRI RV volume	0.99 (0.96–1.02)	0.504
MRI LV volume	0.97 (0.88–1.07)	0.560
RV ejection fraction	0.85 (0.71–1.02)	0.076
LV ejection fraction	1.08 (0.84–1.38)	0.562
RV end-diastolic pressure	1.06 (0.87–1.29)	0.599
LV end-diastolic pressure	2.39 (0.67–8.45)	0.178
Gadolinium enhancement	0.71 (0.04–14.35)	0.826
Multivariate		
Male gender	4.63 (0.98–21.94)	0.054
QRSVm	0.75 (0.62–0.92)	0.005

Abbreviations as in Tables 1 to 3.

QRSVm among the arrhythmic subgroups, but the number of patients was small. The risk of VAI or spontaneous arrhythmia in these groups was independent of QRSd, hemodynamics, RV volume, or presence of gadolinium enhancement. RVEF was not a predictor of VAI, unlike for other diseases of the RV for which RVEF has been found to be a risk predictor (20).

CORRELATIONS OF PARAMETERS MEASURED. Correlation coefficients showed QRSVm to be inversely proportional to age, QRSd, and LVEDV (which was inversely proportional to RVEDV). QRSd showed a significant positive correlation with age, spatial QRS-T angle, and decreased RVEF. It was inversely associated with QRSVm and RV volume. Increasing age was significantly correlated with increased QRSd, decreased QRSVm, RVEF, and LVEF, and increased LVEDP. These may be scar-mediated, as there was no direct correlation with RV volume. Thus, as the patient population became older, they had wider QRSd, lower QRSVm (thus greater time and voltage dispersion of depolarization), lower RVEF/LVEF, and increased LVEDP, likely due to impaired filling via RV-LV interactions. These changes each predispose the patient to an increased arrhythmia risk (5). QRSd was inversely correlated to RVEF and positively correlated to RVEDP; thus, as conduction time increases, fractional output from the RV decreases and end-diastolic pressure remains higher. This finding is similar to that previously reported by Koestenberger et al. (21). In addition, the investigators found a significant positive correlation with QRSd and MRI-measured RV volume. However, our cohort differs from that reported by Koestenberger et al. (21) in that our study population included adults.

Of interest, of all the parameters tested, the highest correlation coefficients were found for LVEDP with RVEDP (0.513) and LVEF with RVEF (0.580). These findings likely indicate ventricular-to-ventricular interactions given the significant and highly positive correlations (18). There were no significant correlations for either RVEDP or LVEDP with QRSVm, indicating that end-diastolic pressures may not be associated with voltage dispersion of depolarization.

STUDY LIMITATIONS. The retrospective nature of this study is a limitation. Furthermore, not all patients with post-repair TOF were evaluated; only those undergoing PVR were studied. MRI and catheterization data were not available for all patients. ECG at one time point may not be reflective of a dynamic disease process. Temporal changes in vectorcardiographic parameters may impact the association with VA risk over longer periods of follow-up. Other limitations include the fact that first and repeat PVR patients were included; that not all patients had undergone VAI testing; that signal-averaged ECG, heart rate variability, and QRS fragmentation were not measured; and that both transcatheter and surgical PVR patients were included, although no significant differences were found between these 2 cohorts of patients.

CONCLUSIONS

Patients with TOF undergoing PVR are at greater risk for VA burden at older ages. Dispersion of depolarization, as measured by QRSVm, was the best ECG predictor of VA burden with a high negative predictive value. Furthermore, it was the only independent predictor of VAI. QRSVm may help noninvasively risk stratify patients with TOF undergoing PVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with TOF have an increased risk of VAs. With current clinical criteria, identifying those at risk for VAs can be challenging. QRSVm is a vectorcardiographic measure of ventricular dispersion of depolarization that can be used to further risk stratify those patients at risk for VAs, particularly those undergoing PVR.

TRANSLATIONAL OUTLOOK: QRSVm is a vectorcardiographic measure of ventricular dispersion of depolarization. Abnormal ventricular dispersion of depolarization may be associated with an increased risk of VAs. By assessing QRSVm, those patients at highest risk for VAs may be identified, but larger prospective studies in other cohort populations are needed before this concept can be translated to clinical practice.

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