Echocardiographic and signal averaged ECG indices associated with non-sustained ventricular tachycardia after repair of tetralogy of Fallot

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Abstract
Objective—To identify any possible association between different readily available non-invasive indices and potential malignant ventricular arrhythmias in patients with repaired tetralogy of Fallot.
Design—27 consecutive patients, mean (SD) age 27.3 (11.7) years, were studied 15.7 (6.7) years after corrective surgery for tetralogy of Fallot, using 12 lead ECG, 24 hour Holter recordings, signal averaged ECG, and echocardiography. The following variables were measured: standard QRS duration, filtered QRS duration (fltQRS), low amplitude signal duration, and root mean square voltage of the last 40 ms of the fltQRS (RMS-40), as well as right ventricular systolic pressure, right ventricular ejection fraction, and the ratio of the maximum short axis diameters of the right and left ventricles (RD:LD).
Results—All patients had right bundle branch block, with a mean QRS duration of 137.1 (14.9) ms. There were no patients with sustained arrhythmia. Five patients had runs of non-sustained ventricular tachycardia (group A) and the other 22 patients did not (group B). Univariate analysis showed that fltQRS and RD:LD ratio were significantly associated with non-sustained ventricular tachycardia. In addition, a fltQRS ⩾ 148 ms, low amplitude signal ⩾ 32.5 ms, RMS-40 ⩽ 23 μV, and RD:LD ratio ⩾ 1.05 were cut off points with a high sensitivity for detecting patients with non-sustained ventricular tachycardia.
Conclusions—Abnormal signal averaged ECG and echocardiographic variables are associated with potentially malignant ventricular arrhythmias on the Holter recordings in asymptomatic patients with repaired tetralogy of Fallot.
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Keywords: arrhythmias; tetralogy of Fallot; echocardiography; signal averaged ECG

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Patients with repaired tetralogy of Fallot have a low but definite risk of arrhythmia related sudden cardiac death.[1–5] Several different invasive and non-invasive haemodynamic and electrophysiological variables have been examined to identify high risk patients after corrective surgery.[6–10] Among these, the presence of non-sustained ventricular tachycardia indicates a specific patient subgroup in need of close follow up, and in which antiarrhythmic treatment has been considered.[11] In this study we looked for a possible association between the Holter findings suggesting potentially malignant arrhythmias and different readily available non-invasive indices. We used transthoracic echocardiography and signal averaged electrocardiography—a technique much more sensitive than the 12 lead ECG for detecting slow and inhomogeneous ventricular conductivity[12–14]—in a cohort of adults with repaired tetralogy of Fallot.

Methods

PATIENT POPULATION

Our cohort of adults with repaired tetralogy of Fallot who are being followed up in our department consists of 32 patients. It is known that signal averaged ECG findings can be influenced by different haemodynamic variables,[15] so in order to be sure that they were solely the result of right ventricular haemodynamics, we excluded those cases with large residual ventricular septal defects and depressed left ventricular ejection fraction, as well as cases with a permanent pacemaker or on antiarrhythmic drugs. After these exclusions our study population consisted of 27 patients (mean (SD) age 27.3 (11.7) years, range 13–51 years), who were studied 15.7 (6.7) years after corrective surgery for tetralogy of Fallot. All patients had postoperative right bundle branch block, were in New York Heart Association (NYHA) functional class I or II, and the repair had been done through a right ventriculotomy. Patients had been operated on at different centres. They had had a mean of 4 (2) Holter monitor analyses during their follow up in our institution.

PROCEDURES

The study method consisted of 24 hour ambulatory Holter monitoring, signal averaged ECG, and echocardiogram, all performed within a period of 48 hours.

Holter monitoring
Two channel Oxford Medilog II TM MR45 recorders (Oxford Medical Instruments, Abingdon, Oxfordshire, UK) were used to perform Holter monitoring. Patients were instructed to use the event button of the recorder whenever they felt any precordial distress. The following variables were analysed: mean heart rate, maximum heart rate, minimum heart rate, number of premature ventricular contractions in each hour, number of multiform premature ventricular contractions in 24 hours, occurrence of R on T phenomenon, number of ventricular couplets in 24 hours, and number of

Table 1 Factors examined divided according to whether there was (group A) or was not (group B) non-sustained ventricular tachycardia

Variable	*Group A (n=5)*	*Group B (n=22)*	*p Value*
Age (years)	32.8 (14.5)	26.1 (11.1)	NS
RVP (mm Hg)	55.0 (20.9)	47.9 (21.5)	NS
Standard QRS (ms)	146.0 (21.6)	134.7 (12.5)	NS
fltQRS (ms)	170.6 (25.0	147.8 (15.8)	< 0.05
RMS-40 (μV)	20.8 (1.8)	35.5 (19.5)	NS
LAS (ms)	39.6 (11.1)	26.0 (13.2)	NS
RVEF (%)	34.4 (10.3)	40.6 (7.2)	NS
RD:LD	1.2 (0.2)	0.9 (0.2)	< 0.05

Values are mean (SD).
fltQRS, duration of the filtered QRS of the signal average ECG; LAS, low amplitude < 40 μV signal duration; QRS, duration QRS complex on ECG; RD:LD ratio, short axis maximum right ventricular diameter:short axis maximum left ventricular diameter; RMS-40, root mean square voltage of the last 40 ms of the filtered QRS; RVEF, right ventricular ejection fraction; RVP, right ventricular pressure.

Table 2 Univariate logistic regression analysis of group A patients (presence of non-sustained ventricular tachycardia) v group B patients (absence of non-sustained ventricular tachycardia)

Variable	*Rate ratio*	*95% CI*	*p Value (two tailed)*
Age (years)	1.06	0.91 to 1.25	0.45
RVP (mm Hg)	1.02	0.97 to 1.06	0.50
RVEF (%)	0.91	0.80 to 1.03	0.14
Standard QRS (ms)	1.05	0.98 to 1.13	0.15
fltQRS (ms)	1.07	1.00 to 1.14	0.04*
RMS-40 (μV)	0.92	0.82 to 1.03	0.13
LAS (ms)	1.08	0.99 to 1.18	0.07†
RD:LD	1.05	1.00 to 1.11	0.05*

*p < 0.05 (significant); † < 0.10 (suggestive).
See table 1 for key to abbreviations.

non-sustained or sustained ventricular tachycardia episodes in 24 hours. Ventricular arrhythmias detected on Holter monitoring were graded according to their severity and frequency.

Signal averaged electrocardiography
Signal averaged electrocardiography was performed in a quiet room with the subject in the horizontal position using a Corazonix-Predictor device. Three bipolar orthogonal leads (x, y, z) were used. Detected signals were amplified (1×10^4) and converted to digital form in a frequency sample of 2000/s. Up to 600 cardiac cycles were averaged in order to reduce the noise level below 0.4 μV. Premature ventricular contractions and artefacts were rejected after comparison with a template recognition pattern formed from eight normal cardiac cycles. A bidirectional Butterworth filter with a frequency band of 40–250 Hz was used. A vector magnitude (VM) was formed based on the equation: $VM = (x^2 + y^2 + z^2)$.

The following signal averaged ECG variables were calculated: filtered QRS duration (fltQRS); low amplitude (< 40 μV) signal duration in the terminal portion of the filtered QRS complex; and root mean square voltage of the last 40 ms (RMS-40).

Echocardiography
A transthoracic echocardiogram was performed using a 2.5 MHz transducer interfaced with a Hewlett-Packard Sonos 2500 ultrasound system (Hewlett-Packard inc, Andover, Massachusetts, USA). Studies were recorded at all the standard sites. Flow through the pulmonary valve was inspected for the presence of restriction.[16] Right ventricular systolic pressure was estimated using continuous Doppler tracings at the tricuspid valve. The right ventricular ejection fraction was assessed using automated boundary detection in the apical four chamber view.[17] The maximum short diameter of the right and left ventricles (RD, LD) in the four chamber view was measured and the ratio (RD:LD) estimated. The RD:LD ratio was measured twice by two different observers. The intraobserver and interobserver variability was 3% and 4%, respectively.

GROUPS
The patients were divided into two groups according to the severity of ventricular arrhythmias detected on the ambulatory Holter recording: group A, patients who had runs of non-sustained ventricular tachycardia; group B, patients who did not have such runs.

STATISTICS
Values are given as mean (SD). Univariate logistic regression analysis was performed between the two groups on all the factors assessed. A probability value of $p \leqslant 0.05$ was considered significant. Fisher's exact test was used to compare frequency distributions between groups. Factors that were found to have a significant or suggestive association with the presence of non-sustained ventricular tachycardia were used for stepwise multivariate logistic analysis in order to identify confounding factors.

Receiver operating characteristic (ROC) curves were plotted for every factor that was found from the univariate analysis to be significant or suggestive for the presence of non-sustained ventricular tachycardia. These were inspected for the cut off point that maximised the true positive ratio while maintaining a false positive ratio less than 50%. The estimated cut off points of these factors were used for generation of 2 × 2 contingency tables in order to determine their sensitivity, specificity, and positive and negative predictive value. The SAS package was used for the statistical analyses.

Results
CLINICAL DATA
All patients were well and asymptomatic. None of them had a history of sustained arrhythmia. All had complete right bundle branch block (mean QRS duration 137.1 (14.9) ms) on ECG. None had a QRS duration of ⩾ 180 ms. The mean follow up time after surgery in group A patients was 17.8 (4.21) years, which was not significantly different from group B patients (15.27 (7.25) years, p = 0.464).

UNIVARIATE LOGISTIC REGRESSION ANALYSES
Group A patients had more premature ventricular contractions than group B patients (150/hour *v* 3/hour). Paired premature ventricular contractions and multiform premature ventricular contractions were only observed among group A patients. The runs of non-sustained ventricular tachycardia in group A patients ranged from 5–10 consecutive beats at a rate of 130–160 beats/min.

Table 3 Multiple logistic regression analysis of group A patients (presence of non-sustained ventricular tachycardia) v group B patients (absence of non-sustained ventricular tachycardia)

Variable	*Model 1*	*Model 2*	*Model 3*	*Model 4*
fltQRS	1.07 (1.00 to 1.15)	1.07 (1.00 to 1.15)		1.16 (0.95 to 1.42)
p Value:	0.06	0.06		0.15
LAS	1.09 (0.98 to 1.22)		1.14 (0.99 to 1.14)	1.33 (0.91 to 1.96)
p Value:	0.11		0.08	0.15
RD:LD		1.06 (1.00 to 1.14)	1.08 (1.00 to 1.16)	1.19 (0.94 to 1.52)
p Value		0.07	0.05	0.14

Values are odds ratios (95% confidence interval).
See text for description of models.
See table 1 for key to abbreviations.

Table 4 Estimated values for sensitivity, specificity, and positive and negative predictive value for the cut off points

	Sensitivity (%)	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
fltQRS ≥ 148 ms	80	54	28	92
LAS ≥ 32.5 ms	100	72	45	100
RMS-40 < 23 μV	100	72	45	100
RD:LD ≥ 1.05	100	68	41	100

See table 1 for key to abbreviations.

Group A patients had longer standard as well as filtered QRS duration, longer low amplitude signal duration, lower RMS-40 voltage on the signal averaged ECG, a higher RD:LD ratio, higher right ventricular pressure, and a lower right ventricular ejection fraction than group B patients, but none of these differences was significant (table 1). The univariate logistic regression analysis showed that the only two variables associated with non-sustained ventricular tachycardia were fltQRS duration and RD:LD ratio (table 2). All patients had tricuspid and pulmonary regurgitation. Nine patients in group B had restrictive right ventricular physiology indicated by the presence of antegrade diastolic flow at the pulmonary valve. No patient in group A had restrictive right ventricular physiology. Using Fisher's exact test, this difference was not significant ($p = 0.302$).

STEPWISE MULTIPLE REGRESSION ANALYSIS

In model 1 of the multiple regression analysis (table 3) the contribution of low amplitude signal to the fltQRS changed their previous statistical significance, suggesting that fltQRS and low amplitude signal are confounding factors. In model 2, the contribution of fltQRS and RD:LD ratio changed their previous significance, suggesting again that fltQRS and RD:LD ratio are confounding factors. In model 3, the contribution of low amplitude signal and RD:LD ratio changed only the previous significance of the low amplitude signal, whereas the RD:LD ratio remained unchanged, suggesting that the RD:LD ratio affected low amplitude signal duration. Finally, in model 4, the contribution of fltQRS, low amplitude signal, and RD:LD ratio changed all the previously detected differences, suggesting that fltQRS duration, low amplitude signal duration, and RD:LD ratio are confounding factors.

CONTINGENCY TABLE ANALYSIS

ROC curves showed that fltQRS ≥ 148 ms, RMS-40 < 23 μV, low amplitude signal ≥ 32.5 ms, and RD:LD ≥ 1.05 were the cut off points for identifying patients with non-sustained ventricular tachycardia. The 2×2 contingency tables using the estimated cut off points from the ROC curves gave 100% sensitivity and negative predictive value for detecting patients with non-sustained ventricular tachycardia (table 4).

Discussion

In this study we showed that the presence of non-sustained ventricular tachycardia after repair of tetralogy of Fallot was significantly associated with a longer fltQRS duration on signal averaged ECG. This association was not found for the standard QRS duration, suggesting that at this early asymptomatic stage, signal averaged ECG findings are more sensitive predictors of ventricular arrhythmias. Age might have influenced fltQRS duration,[18] but in our study there was no difference in mean age between the two groups (table 1). We also showed that non-sustained ventricular tachycardia was significantly associated with a higher RD:LD ratio and possibly with low amplitude signal duration; however, additional analysis showed that fltQRS duration, RD:LD ratio, and low amplitude signal duration were confounding variables for the presence of non-sustained ventricular tachycardia.

Our data suggest a mechanoelectrical effect between right ventricular dilatation, expressed as the RD:LD ratio, and signal averaged ECG parameters. Gatzoulis and colleagues proved a similar interaction at a more advanced level of QRS prolongation.[6] They found that the risk for sustained ventricular arrhythmia was high when right ventricular enlargement and QRS prolongation developed, and that a standard QRS duration of ≥ 180 ms was the most sensitive predictor of life threatening arrhythmias.

Our patient population consisted of asymptomatic subjects without pronounced prolongation of the standard QRS on the 12 lead ECG. This mild degree of the unfiltered QRS prolongation could not identify patients with more complex ventricular arrhythmias such as non-sustained ventricular tachycardia. On the other hand, the presence of slow conduction areas most probably originating from an enlarged right ventricle—as shown by the results of signal averaged electrocardiography and echocardiography—was associated with the occurrence of non-sustained ventricular tachycardia on the 24 hour Holter recordings.

It could be argued that the signal averaged ECG might have been affected by the presence of right bundle branch block in our patients and thus be an inaccurate diagnostic tool.[19] However, other investigators have found that signal averaged ECG findings may be helpful in detecting high risk patients despite the presence of right bundle branch block.[12 13 20 21] Indeed, in our study we found a significant association between the filtered QRS duration on the signal averaged ECG and the presence of complex ventricular arrhythmias on the Holter recording. We also established a confounding effect between signal averaged ECG parameters and right ventricular enlargement for the development of complex ventricular arrhythmias. This mechanoelectrical effect might have been responsible for the early appearance of the critical conditions required to establish a right ventricular re-entry circuit. It may be that further slowing of the intraventricular conduction, as expressed by more advanced degrees of QRS prolongation, may lead to sustained ventricular tachyarrhythmias.

Because of Holter monitoring limitations such as arrhythmia variability,[22] we propose that patients with repaired tetralogy of Fallot should be periodically screened by signal averaged ECG and echocardiogram in order to detect those who should be followed more closely with repeat Holter assessments and possibly electrophysiological studies.

Harrison and colleagues found that most patients with sustained ventricular tachycardia have outflow tract aneurysms or pulmonary regurgitation, and believe that they should be approached by combined correction of the structural abnormalities and intraoperative electrophysiological guided ablation in order to facilitate arrhythmia management.[23] Saul and Alexander[24] believe that additional data are necessary to establish clear management guidelines in patients with congenital heart disease at risk of arrhythmic death.

LIMITATIONS

Our study is limited by the relatively small number of patients and the lack of clinical end points. A larger scale study with longer follow up is required to validate our observations.

CONCLUSIONS

Our study showed that fltQRS duration $\geqslant$ 148 ms, a low amplitude signal of $\geqslant$ 32.5 ms, an RMS-40 of $\leqslant$ 23 μV, or an RD:LD ratio of $\geqslant$ 1.05 are easily measured variables with an excellent sensitivity and negative predictive value for identifying patients with complex non-sustained ventricular arrhythmias after repair of tetralogy of Fallot. Closer follow up of these variables may facilitate early identification of patients with further haemodynamic deterioration who are at risk of sustained ventricular tachycardia.

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