

Usefulness of Post-Ventriculotomy Signal Averaged Electrocardiograms in Congenital Heart Disease

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Signal-averaged electrocardiography is a sensitive and specific technique for detecting the slow conduction electrophysiologic substrates of reentrant monomorphic ventricular tachycardia. Although well established, the method has not been used for electrophysiologic assessment after right ventriculotomy for the intracardiac repair of congenital heart disease. This 8-year prospective study provided this assessment. Recordings were obtained from 242 post-ventriculotomy patients with congenital heart disease aged 16 to 72 years (139 males, 103 females). Because ventricular volume or pressure overload can prolong the QRS duration, 40 unoperated patients with hemodynamic overload served as controls. Orthogonal X, Y, and Z body surface electrodes were used to detect ventricular late potentials by permitting the examination of portions of the electrocardiogram otherwise obscured by noise and artifacts. Positive signal-averaged electrocardiographic (SAECG) results were based on established criteria derived from 3 time-domain variables calculated by an automated algorithm. Late potentials were detected in 151 of 242 patients (62%) and were significantly higher than controls ($p = 0.0001$). Radiofrequency ablation of an inducible slow conduction substrate rendered 20 of 23 positive post-ventriculotomy SAECG results negative, and surgical revision of the ventriculotomy scar rendered 19 of 19 positive SAECG results negative. In conclusion, negative SAECG results connote the absence of a reentrant substrate, and therefore, the absence of risk for reentrant monomorphic ventricular tachycardia, whereas positive SAECG results connote the presence of a slow conduction substrate and the potential risk for monomorphic ventricular tachycardia. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:1646–1651)

Although signal-averaged electrocardiography is a sensitive and specific means for detecting the slow conduction substrate of monomorphic ventricular tachycardia (MVT),^{1–3} the technique has heretofore not been used in electrophysiologic assessment after right ventriculotomy for the intracardiac repair of congenital heart disease. Our 8-year prospective study provided this assessment.

Methods

The University of California, Los Angeles, Institutional Review Board approved this study. Informed consent was signed before signal-averaged electrocardiographic (SAECG) recordings were made.

Patient population: This study was prospective, extending from July 1997 to July 2005, and included 242 consecutive patients in whom signal-averaged electrocardiograms were recorded after right ventriculotomy for the intracardiac repair of congenital heart disease. All patients were in sinus

rhythm. None had pacemakers or clinical evidence of ischemic heart disease. There were 139 male and 103 female patients aged 16 to 72 years (mean 38 ± 6). Signal-averaged electrocardiograms were recorded before and after ventriculotomy in 20 patients, 19 with tetralogy of Fallot and 1 with double-outlet right ventricle and pulmonary stenosis. Follow-up periods ranged from 3 to 12 months after the initial outpatient data collection.

Positive SAECG results connote the presence of a slow conduction substrate and the potential for reentrant MVT.^{1,3,4} Negative SAECG results connote the absence of a reentrant substrate. Patients with systemic-to-pulmonary arterial shunts were excluded because left ventricular volume overload can result in slow conduction, and patients with right ventricular-to-pulmonary arterial conduits were excluded because slow conduction substrates were likely to be complex.

Transthoracic echocardiograms with color flow imaging and Doppler interrogation established the diagnosis of tetralogy of Fallot in 141 patients, ventricular septal defects in 97 patients, double-outlet right ventricles in 26 patients, and double-outlet left ventricles in 2 patients.

Three subgroups were analyzed: 32 patients in whom signal-averaged electrocardiograms were recorded before and after ventriculotomy, 23 with recordings before and after the radiofrequency ablation of an inducible substrate, and 19 with recordings before and after the surgical revision of the ventriculotomy scar.

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Because right ventricular pressure or volume overload increases ventricular mass and can prolong the QRS duration,⁵ 33 unoperated patients with ventricular overload served as controls. Right ventricular pressure overload was represented by tetralogy of Fallot in 8 patients, primary pulmonary hypertension in 3 patients, Eisenmenger's syndrome with ventricular septal defects in 10 patients and with atrial septal defects in 5 patients, truncus arteriosus in 5 patients, and patent ductus arteriosus in 2 patients. Right ventricular volume overload was represented by ostium secundum atrial septal defect in 7 patients.

The signal-averaged electrocardiograms were all obtained by the same experienced technologist (GDG). Orthogonal X, Y, and Z leads were recorded until a noise level $<0.3 \mu\text{V}$ was achieved (Corazonix, Oklahoma City, Oklahoma). Beats were digitized with a sampling frequency of 2,000 Hz and bi-directionally high-pass filtered at 25 Hz. Noisy or ectopic beats were automatically rejected. Filtered leads were combined into a vector magnitude ($X2 + Y2 + Z2$).

Three time-domain variables were calculated by an automated algorithm and visually inspected: (1) filtered QRS duration in milliseconds, which indicates the degree to which the QRS was prolonged by late potentials; (2) root-mean-square (RMS) voltage in microvolts of the terminal 40 ms of the filtered QRS, which represents the amount of late potential energy; and (3) the duration in milliseconds of low-amplitude signals (LAS) $<40 \mu\text{V}$ in the terminal filtered QRS. Positive SAECG results were defined as a filtered QRS duration >145 ms plus RMS duration of the terminal 40 ms of the filtered QRS $<17.5 \mu\text{V}$ and/or LAS of the terminal filtered QRS >50 ms. These definitions represent the recommendations of the American Heart Association, the American College of Cardiology, the European Society of Cardiology, and independently published sources.^{3,6-8}

Criteria for identifying late potentials in the presence of QRS prolongation have included a RMS range from <14 to $100 \mu\text{V}$. This broad range was established because of concern that QRS prolongation might obscure late potentials and was justified by adjustments of SAECG parameters for age and body surface area in children, a concern not relevant to our study, which was confined to adults.

Scalar electrocardiography: The incidence of QRS durations ≥ 180 ms and the incidence of an increase in QRS duration ≥ 30 ms over 4 to 6 months were also determined.^{9,10}

Ambulatory electrocardiography: Ambulatory electrocardiograms were recorded in 102 patients <3 months after the signal-averaged electrocardiography using a Del Mar Avionics system DMS Scientific model 419 (Del Mar Avionics, Irvine, California). Two-channel 24-hour records were analyzed on a semi-automated scanner (Zymed Quick-page model 1210, Eindhoven, The Netherlands) and reviewed by 1 investigator (HRM) for premature ventricular depolarizations or monomorphic ventricular couplets with an incidence of $\geq 5/\text{min}$ and the incidence of ≥ 3 consecutive monomorphic complexes (nonsustained MVT).

Exercise stress tests: Treadmill stress tests using a symptom-limited protocol were conducted in 86 patients <3 months after signal-averaged electrocardiography. Premature ventricular complexes and monomorphic couplets were reported as absent during control and exercise periods, present during control but decreasing during exercise, and induced or increased by exercise. Special attention was focused on ≥ 3 consecutive exercise-induced monomorphic ventricular complexes.

Echocardiography: Two-dimensional echocardiograms with Doppler interrogation and color flow imaging were recorded <2 months after initial signal-averaged electrocardiography and were interpreted by the same echocardiographer (JSC). Congenital cardiac diagnoses, right ventricular size, the ejection fraction, systolic function, right ventricular incisional aneurysms, and degrees of pulmonary and/or tricuspid regurgitation were based on published norms.

Risk factors for MVT: Established MVT risk factors include scalar QRS durations ≥ 180 ms, an increase in QRS duration ≥ 30 ms over ≤ 6 months,^{9,10} severe pulmonary regurgitation,⁹ depressed right ventricular systolic function, ventricular ectopic beats induced or increased by exercise, ≥ 3 consecutive monomorphic ventricular complexes, age at ventriculotomy, and ≥ 10 years of time elapsed after ventriculotomy.¹¹ Right ventricular fibrosis detected by magnetic resonance imaging might prove to be an additional risk factor.¹²

Intracardiac electrophysiology: Programmed electrical stimulation^{11,13,14} was performed in 16 of 151 post-ventriculotomy patients. The rationale for selection was based on positive SAECG results plus ≥ 1 established MVT risk factor.^{2,9,10,14}

Statistical analyses: Summary statistics are reported as mean \pm SD. Statistical significance was defined a p value <0.05 . Subject grouping was based on negative or positive SAECG results or on QRS durations ≥ 180 versus <180 ms and were evaluated using the chi-square test for homogeneity. A QRS duration <180 ms was the standard. Calculations of sensitivity, specificity, and odds ratios were also performed. Confidence intervals using a 95% level were calculated using the exact method of Clopper and Pearson.¹⁵

Statistical evaluations of QRS, RMS, and LAS were based on comparison with negative and positive SAECG groups and relied on the Mann-Whitney U-statistic test, which was also used to compare these 2 groups on the basis of QRS dichotomy according to age. An analysis-of-covariance model was used to determine whether age was a mitigating factor in the SAECG group comparison. A multiple regression model evaluated the 3 independent variables (SAECG group, QRS duration group, and age) with respect to the 3 quantitative outcomes.

Results

Follow-up ranged from 1 to 8 years (mean 4.2 ± 4). There were no occurrences of sustained MVT, perhaps because the time elapse was short and because patients with positive SAECG results and established MVT risk

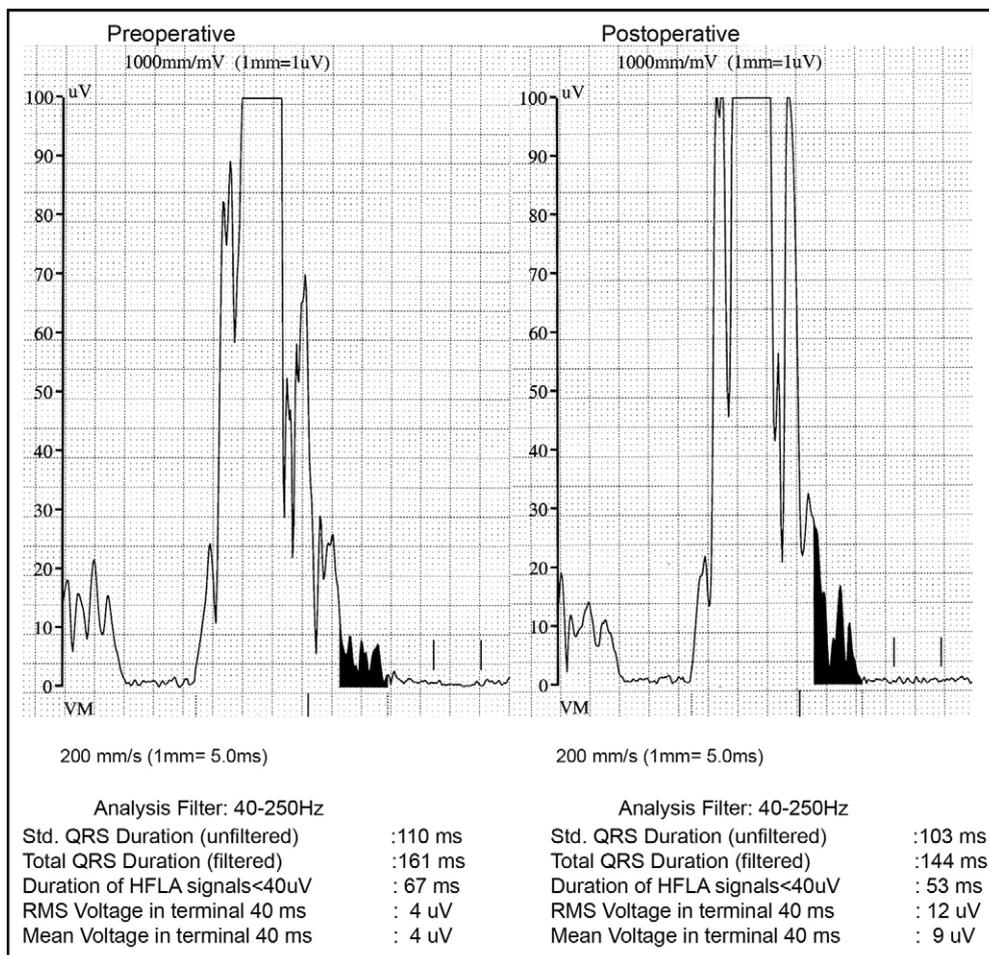


Figure 1. Positive preoperative SAECG results: before ventriculotomy scar revision, total filtered QRS duration was 161 ms, and RMS voltage in the terminal 40 ms was 4 μ V. Negative postoperative SAECG results: after ventriculotomy scar revision, total filtered QRS duration decreased to 144 ms, and RMS voltage increased to 12 μ V.

factors were selected out for radiofrequency substrate ablation or ventriculotomy scar revision.

Scalar electrocardiography: QRS duration was ≥ 180 ms in 78 post-ventriculotomy patients and increased ≥ 30 ms in ≤ 6 months in 23 patients. QRS duration remained unchanged in the pressure or volume overload controls (115 to 140 ms).

Signal-averaged electrocardiograms and statistical analyses: Figure 1 is an example of positive and negative SAECG results. Late potentials (positive SAECG results) were detected in 151 of 242 post-ventriculotomy patients (62%). Mean filtered QRS duration and LAS were significantly longer, and RMS voltage was significantly less in post-ventriculotomy patients compared with controls (46% vs 9%, $p = 0.0001$).

There was a large difference in the proportion of abnormal SAECG results in patients with QRS durations of >180 ms compared with <180 ms ($p < 0.0001$). Of patients with positive SAECG results, 59% had scalar QRS durations ≥ 180 ms, whereas 15% of patients with negative SAECG results had QRS durations ≥ 180 ms. Put differently, there was an 8 times greater odds of a prolonged scalar QRS

Table 1

Comparison of findings from QRS dichotomy and signal-averaged electrocardiographic results

SAECG Results	Scalar, QRS ≥ 180 ms	Scalar, QRS <180 ms
Normal	14	77
Abnormal	89	62

duration if SAECG results were positive rather than negative (95% confidence interval 2.7 to 13.1). Using scalar electrocardiography as a standard, the sensitivity of signal-averaged electrocardiography for predicting QRS prolongation was 86% (95% confidence interval 78% to 92%), and the specificity was 55% (95% confidence interval 47% to 64%). It is important to note that QRS durations ≥ 180 ms did not reliably predict positive SAECG results, and therefore, are not acceptable substitutes.

Patients with positive SAECG results were significantly older (mean age 40 ± 14 years), whereas the corresponding age for the group with negative results was 36 ± 17 years ($p = 0.01$ by the Mann-Whitney U-statistic test). When QRS, RMS, and LAS findings were reanalyzed using the

Table 2
Risk factors for monomorphic ventricular tachycardia

QRS Duration \geq 180 ms	Age at Ventriculotomy	Ambulatory ECG: PVCs/ Monomorphic Couplets	Exercise: PVCs/Monomorphic Couplets	Echocardiography
78/242 Increase over \leq 6 months: 23/242	25 \pm 17 yrs	12–20/hr: 72/242 \geq 350/hr: 4/242 \geq 3 consecutive/hr: 26/242	Exercise-induced: 39/242 Decreased with exercise: 13/242 Increased with exercise: 16/242	Decreased RV ejection fraction: 96/242 RV enlargement: 76/242 Incisional aneurysm: 14/242 Severe PR: 16/242

ECG = electrocardiography; PR = pulmonary regurgitation; PVC = premature ventricular complex; RV = right ventricular.

covariance model with age as the covariate, the *p* values for the comparison of positive and negative SAECG groups were unchanged. Nor was a difference found when age distribution for longer and shorter QRS duration dichotomy was considered; the mean age for the former was 30 \pm 13 years and for the latter was 38 \pm 17 years (*p* = 0.30 by the Mann-Whitney test).

In evaluating the simultaneous effects of positive and negative SAECG groupings, QRS dichotomy, and age on the 3 quantitative outcomes (QRS, RMS, LAS), a multiple regression model identified significant predictive value for the 2 SAECG groupings (*p* < 0.000001). Age was a predictive variable for QRS duration (*p* = 0.009) but not for RMS (*p* = 0.53) or LAS (*p* = 0.19). Comparison of the findings from the QRS dichotomy and the SAECG results yielded the 2 \times 2 Table 1.

The relation between MVT risk factors and late potentials is listed in Table 2. Patients with positive post-ventriculotomy SAECG results were significantly older at operation than those with negative SAECG results (25 \pm 17 vs 11 \pm 9 years, *p* < 0.05) and were likely to have scalar QRS durations \geq 180 ms. The prevalence of other MVT risk factors did not differ significantly in patients with negative versus positive SAECG results. Except for a scalar QRS duration \geq 180 ms, no correlation existed between positive SAECG results and MVT risk factors. Of 23 positive post-ventriculotomy SAECG results, 20 became negative after radiofrequency ablation.¹³ Although 17 of 20 negative pre-ventriculotomy SAECG results were positive after operation, 11 of 19 positive SAECG results became negative after surgical revision of the ventriculotomy scar (Figure 1).

Ambulatory electrocardiography: The average number of premature ventricular beats and/or monomorphic couplets was 12 to 20 per hour in 72 patients and \geq 5 per hour in 4 patients. Three or more consecutive monomorphic complexes per hour were recorded in 26 patients.

Exercise stress tests: Ventricular premature complexes and/or monomorphic ventricular couplets were either increased or induced by exercise in 34 patients.

Echocardiography: Right ventricular wall motion and ejection fractions were moderately to markedly reduced in 96 post-ventriculotomy patients, 14 with moderate to marked incisional aneurysms. The right ventricle was moderately to markedly enlarged in 76 patients, 16 with severe pulmonary regurgitation and 14 with severe tricuspid regurgitation. Left ventricular enlargement was moderate in 8 patients with aortic regurgitation.

Intracardiac electrophysiology: Sustained MVT was inducible in 14 of 16 patients with positive SAECG results and mapped to the ventriculotomy scar in each. All inducible patients underwent radiofrequency ablation with reversal of SAECG results to negative.

Discussion

Electrophysiologic mechanisms of ventricular tachyarrhythmias include reentry, automaticity, and triggered activity.⁹ Inducible sustained ventricular tachycardia is usually monomorphic (30%), with inducible sustained polymorphic ventricular tachycardia much less common (4%).^{9,11} Our study focused on MVT that requires a slow conduction substrate capable of sustained reentry. However, a slow conduction substrate remains dormant unless activated. Accordingly, a susceptible substrate and an effective trigger are necessary for the overt expression of reentrant MVT.^{14,16,17} The combination of substrate and trigger underscore why sustained MVT is difficult to induce in normal hearts that do not harbor slowed conduction substrates,¹⁸ why MVT occurs in <30% of patients after myocardial infarctions despite the presence of inducible substrates,¹⁹ and why MVT is rare in Ebstein's anomaly despite the almost universal presence of slow conduction in the atrialized right ventricle.²⁰

Tetralogy of Fallot was our largest category, because the malformation was the most common post-ventriculotomy disorder in the Adult Congenital Heart Disease Registry. That category included a slow conduction substrate and a trigger in the form of severe pulmonary regurgitation.^{9,11}

SAECG results were positive after right ventriculotomy in 62% of patients, in contrast to 9% of controls. Post-ventriculotomy QRS durations of 140 to 180 ms were the rule but were virtually absent in controls (QRS durations 115 to 140 ms). Positive SAECG results occurred in patients who were significantly older at the time of ventriculotomy, and older age has been implicated as a post-ventriculotomy MVT risk factor because of age-related increases in scarring at incisional sites. Ventricular tachyarrhythmias are rare when intracardiac repair is performed before the age of 5 years.²¹

A single precisely timed ventricular ectopic beat in the presence of positive SAECG results can trigger MVT.¹³ The coupling interval is established by moving the depolarization stimulus incrementally through the cardiac cycle (programmed electrical stimulation).¹³ It is important to note that slow conduction substrates are not necessarily capable of sustaining reentry.¹³

Triggers can also take the form of impaired autonomic nervous system regulation after the intracardiac repair of tetralogy of Fallot^{9,22,23} or increased adrenergic discharge.^{24,25} Fright can provoke a catecholaminergic surge that triggers a susceptible substrate—literally “scared to death.”²⁶

Pulmonary regurgitation but not tricuspid regurgitation is regarded as an independent trigger of MVT after repair of tetralogy of Fallot.^{9,27} Pulmonary regurgitation does not reduce right ventricular wall stress, because ejection is into the pulmonary trunk, in contrast to tricuspid regurgitation, in which wall stress is reduced because ejection unloads the right ventricle into the low-pressure right atrium.

The most common site of a slow conduction substrate is along the ventriculotomy scar.²⁸ However, the substrates are sometimes adjacent to the ventricular septal defect patch, or elsewhere in the right ventricle, especially in a dilated chamber with depressed systolic function or in a volume-overloaded left ventricle (aortic regurgitation or aortopulmonary shunt)²⁹ or, rarely, in the pulmonary trunk.³⁰ Substrates can be localized by mapping and eliminated by radiofrequency ablation.^{13,28} Ventriculotomy scar revision during operation for pulmonary valve replacement can normalize SAECG results, thus eliminating substrate and trigger.

Three consecutive monomorphic ventricular ectopic beats recorded by any means prefigure reentry and are therefore potential harbingers of MVT.⁴ When an ambulatory electrocardiogram records few or no ventricular ectopic beats or monomorphic couplets, the risk for MVT should be low, because the fewer the number, the less likely one will coincide with the crucial coupling interval. Ventricular ectopic beats can be excessive without occurring at the crucial coupling interval. If single or coupled monomorphic ventricular depolarizations are absent or rare and remain so during exercise, or if ventricular ectopic beats decrease or disappear during exercise, then isotonic exercise per se should be an unlikely trigger. Conversely, if ectopic ventricular beats or monomorphic couplets are provoked or significantly increased by exercise, then isotonic stress should be considered a potential risk.

Sudden cardiac death (SCD), defined as unexpected demise without premonitory symptoms or immediately after the onset of symptoms, was known to Hippocrates 2,400 years ago.³¹ Many studies have sought to establish risk factors for post-ventriculotomy SCD, but with limited success.^{9,10} The most common tachyarrhythmic cause of this relatively rare but dreaded sequel of right ventriculotomy is reentrant MVT,^{11,20} which was a central focus of our study. Although our study did not address SCD as an end point, a potential link between positive SAECG results, a slowed conduction substrate, MVT, and SCD is difficult to ignore. We showed that signal-averaged electrocardiography identifies slow conduction substrates for reentrant MVT, and we also showed that radiofrequency ablation or the revision of a ventriculotomy scar can render a positive SAECG result negative, thus eliminating the reentrant substrate. However, statistical validation of signal-averaged electrocardiography in stratifying post-ventriculotomy risk for SCD cannot currently be achieved, even by a large multicenter study, for the following reasons. The estimated overall incidence of post-

ventriculotomy SCD is 1.7% to 1.8%, and after repair of tetralogy of Fallot, the incidence is estimated at 1.5 per 1,000 patient-years.^{21,31} A study capable of detecting a risk reduction from 1.5 to 0.75 per 1,000 patient-years (50%) would require 31,359 patient-years of observation in the positive and negative SAECG risk categories to achieve 80% power for detecting this difference with a 2-sided 5% significance level. If the lower risk group alone were compared with an assumed rate of 1.5 per 1,000 patient-years, a risk reduction to 0.3 per 1,000 patient-years (80%) would require 4,814 patient-years with 80% power and 5% 2-tailed significance.

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