Signal-Averaged Electrocardiogram in Ebstein's Anomaly

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We sought to establish pathogenetic links between electrophysiology, histopathology, and ventricular tachyarrhythmias in patients with Ebstein's anomaly. The atrialized right ventricle (ARV) is the site of mechanically inducible ventricular tachyarrhythmias, but relations between the arrhythmogenic substrate, the type of tachyarrhythmias, and the trigger(s) have not been established. This study comprised 23 patients (10 men and 13 women; aged 18 to 58 years; mean 32 ± 3) who did not undergo surgery and 6 pre- and postoperative patients with Ebstein's anomaly, diagnosed by transthoracic and transesophageal echocardiography. Twenty-one patients had classic Ebstein's anomaly and 2 had mild forms. Signal-averaged electrocardiograms (SAECGs) identified slow conduction by using 3 time-domain variables calculated by an automated algorithm and inspected visually. Two variables were required to establish the presence of late potentials. SAECGs were repeated in 6 patients after surgical exclusion of the ARV. Five surgical specimens of the ARV and the true right atrium were examined histologically. Mathematic simulations were used to illustrate anchored and unanchored spiral/scroll waves. SAECGs were positive in 21 patients with classic Ebstein's anomaly and were negative postoperatively in the 6 so studied. The ARV was characterized histologically by clusters of cardiomyocytes isolated within a fibrous matrix. We hypothesize that SAECGs identify slow conduction residing in the ARV, and that excitation of this arrhythmogenic substrate provokes spiral/scroll waves that cannot anchor because clusters of cardiomyocytes are isolated within a fibrous matrix. The waves meander erratically as polymorphic ventricular tachycardia or break up into ventricular fibrillation. **(Am J Cardiol 2004;93:432–436)**

In 1956, Paul Wood wrote, "Ebstein's disease is dangerous. Out of 6 I have personally catheterized, 1 died immediately of ventricular fibrillation and 1 developed paroxysmal tachycardia that could have been ventricular."[1] In 1974, Hamish Watson reemphasized the risk of tachyarrhythmic death during cardiac catheterization in Ebstein's anomaly.[2] These observations suggest a vulnerable arrhythmogenic substrate mechanically triggered by a catheter. The segment of the right ventricle between the tricuspid annulus and distally displaced tricuspid leaflets is functionally integrated into the right atrium, but electrically integrated into the right ventricle.[3] Unique electromechanical properties of this atrialized right ventricle (ARV) establish the diagnosis of Ebstein's anomaly based on an intracavitary right ventricular electrogram that coincides with a right atrial pressure pulse.[4,5] Links between the arrhythmogenic ARV,[3,5,6] ventricular tachycardia/fibrillation, and the trigger(s) have not been established. We sought to establish such a link by examining the electrophysiologic implications and histopathology of the ARV.

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METHODS

Patients: Six of 23 patients with Ebstein's anomaly underwent exclusion of the ARV by plication during surgical reconstruction of the malformed tricuspid valve. Preoperative studies were repeated within 1 and 4 months after operation. Twenty-one patients had classic Ebstein's anomaly with typical apical displacement of the septal tricuspid leaflet, large segments of ARV, and severe tricuspid regurgitation.[3,7,8] Two had mild anomalies with small ARVs and mild tricuspid regurgitation.

Signal-averaged electrocardiogram (SAECG): SAECGs detected late potentials generated by slow conduction[8–11] (Figure 1), and were interpreted by the same experienced electrophysiologist (HRM). With use of the Marquette module data box with its electrocardiographic cart (Milwaukee, Wisconsin), bipolar X, Y, and Z leads of the Frank electrocardiogram were recorded until a noise level of $<0.3\ \mu V$ was achieved. Each beat was digitized with a sampling frequency of 2,000 Hz and was bidirectionally filtered at 40 Hz. Noisy or ectopic beats were automatically rejected. Filtered leads were combined into a vector magnitude ($X2+Y2+Z2$).[9] The 3 time-domain variables that were calculated by an automated algorithm and visually inspected included: (1) filtered QRS duration (in milliseconds), (2) root-mean-square voltage (in microvolts) of the terminal 40 ms of the filtered QRS, and (3) duration (in milliseconds) of low-amplitude signals ($<40\ \mu V$) of the terminal filtered QRS. All patients except the 2 with mild anomalies had QRS durations of >100 ms. Late po-

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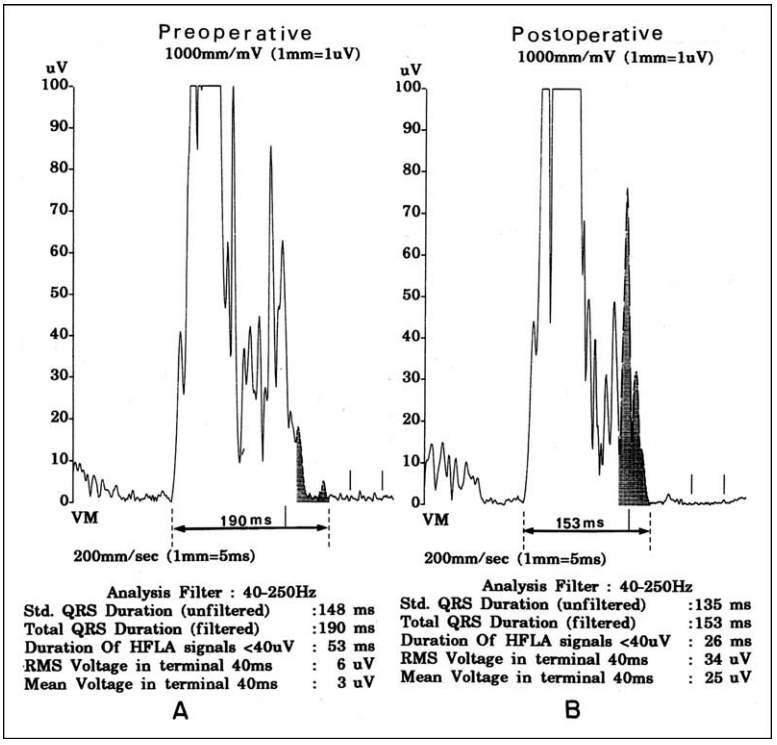

FIGURE 1. SAECGs before and after surgical exclusion of the ARV. *(A)* **Late potentials were recorded before surgery (positive (SAECG).** *(B)* **Late potentials were absent after surgery (negative SAECG). RMS = root-mean-square.**

tentials in the presence of QRS prolongation[10,11] were identified by (1) filtered QRS >145 ms, (2) root-mean-square of the terminal 40-ms voltage of the filtered QRS <17.5 μV, and (3) duration of >50 ms of low-amplitude signals of the terminal filtered QRS (Figure 1). Two of these 3 criteria were required to identify late potentials in the presence of QSR prolongation[10,11] (Figure 1). SAECGs were repeated in 6 patients whose ARVs were excluded by surgical plication (Figure 1).

Preoperative scalar electrocardiograms: Preoperative scalar electrocardiograms were analyzed for P-wave amplitude and duration, QRS duration, right precordial lead Q waves, and delta waves of accessory conduction.[12]

Transthoracic echocardiograms with color flow imaging and Doppler interrogation were recorded in 23 patients.[7,12] Transesophageal echocardiograms were recorded in 10 patients, including the 6 surgical patients and the 2 with mild anomalies. Septal tricuspid leaflet displacement was measured in systole from the anatomic tricuspid annulus to the septal leaflet attachment, measured as milliliters per square meter of body surface.[7,8,12] ARV was defined as the maximum systolic distance from the anatomic tricuspid annulus to the functional tricuspid annulus at the leading edge of the displaced leaflets.[3]

Histopathology: Five surgical specimens of ARV and true right atrium were examined histologically.[3] Trichrome stains of the ARV identified cardiomyocytes and collagen (Figure 2). Hematoxylin/eosin stains of the true right atrium identified cardiomyocytes and their nuclei (Figure 2).

Computer-generated mathematic simulations were designed to illustrate anchored and unanchored spiral/scroll waves[13,14] (Figure 3).

The Office for Protection of Research Subjects approved the study.

RESULTS

SAECGs were positive for late potentials in all 21 patients who did not undergo surgery with classic Ebstein's anomaly (Figure 1), and were negative in the 6 patients who underwent surgical plication exclusion of the ARV and in the 2 patients with mild anomalies (Figure 1).

Scalar electrocardiograms: In 21 patients with classic Ebstein's anomaly, P waves were increased in amplitude and duration, and PR intervals were 210 to 240 ms (mean 219 $\pm$ 4). Increased durations of P waves and PR intervals reflected prolonged conduction in the enlarged right atrium.[15] Delta waves (accessory conduction) were absent. QRS durations of 120 to 190 ms (mean 140 $\pm$ 3) were attributed to prolonged depolarization of the ARV.[5,12] In 3 patients, a distinctive bizarre "second" QRS originating in the ARV was attached to the preceding "normal" QRS.[5,12] Q waves in lead V_1 in 11 patients extended to lead V_3 in 3 patients, reflecting precordial electrode placements that were topographically over the enlarged right atrium, thus recording intracavitary right atrial potentials.[5,12] The 2 patients with mild anomalies had normal QRS complexes and normal P waves. In 1 patient, the PR interval was 120 ms, and the frontal plane QRS axis was left superior but without a delta wave.

Echocardiograms: Transthoracic echocardiograms established the diagnoses in the 21 patients with classic Ebstein's anomaly.[7,12] In the 2 patients with mild malformations, diagnoses were confirmed by transesophageal echocardiograms that disclosed a small ARV and mild tricuspid regurgitation, but septal tricuspid leaflet displacement was >8 mm/m^2.[8,12]

Histopathology: Cardiomyocyte clusters in the ARV were isolated by networks of fibrosis, and the endocardium was thickened and fibrotic[3] (Figure 2). In contrast, cardiomyocytes in the true right atrium were not isolated, fibrosis was scarce to absent, and enlarged hyperchromatic nuclei reflected myocyte hypertrophy (Figure 2).

DISCUSSION

Essential to our electrophysiologic hypotheses is the validity of SAECGs in identifying slow conduction in the presence of QRS prolongation,[10,11,16] and validity of the assumption that slow conduction iden-

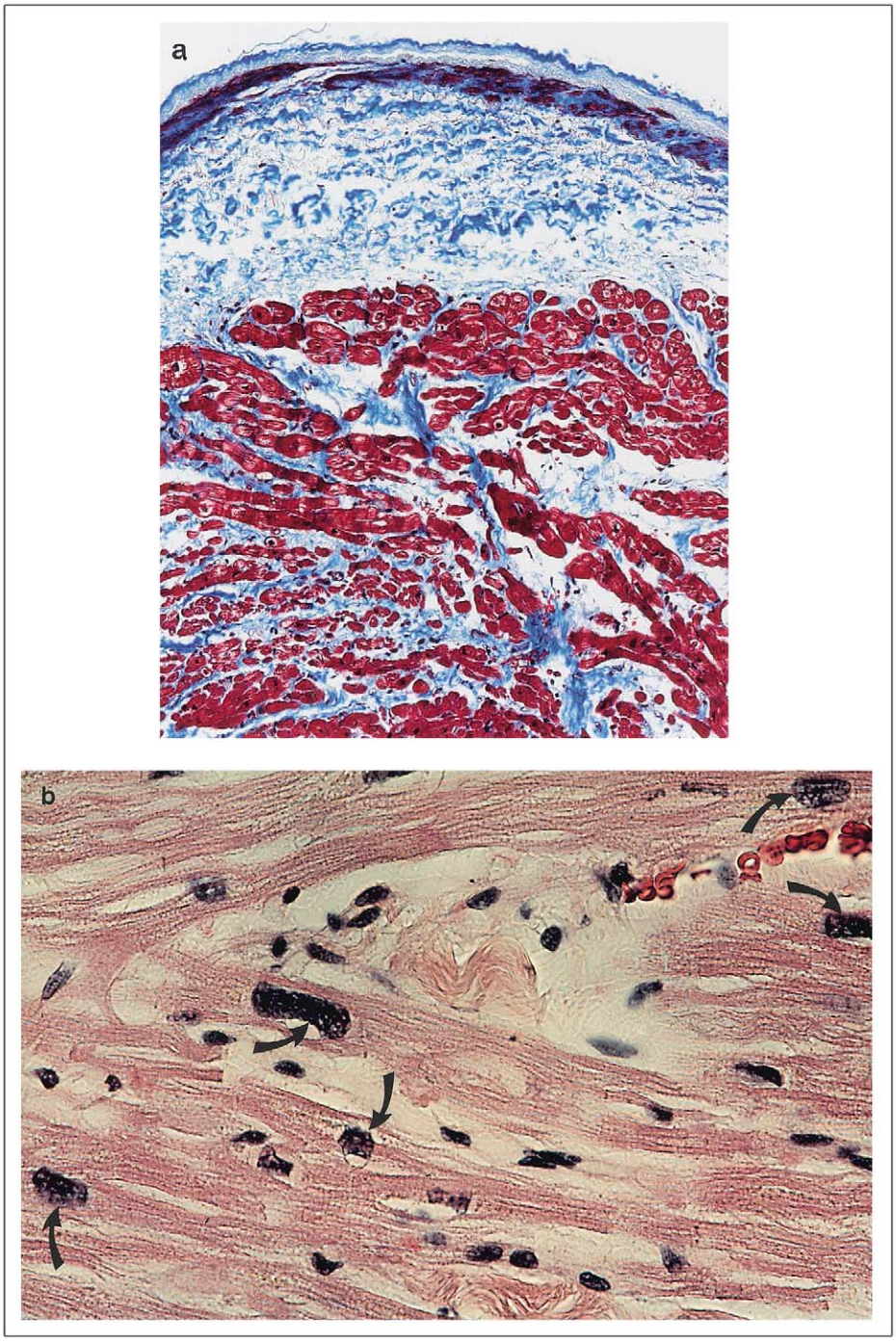

FIGURE 2. *(A)* In the ARV, fibrous tissue *(blue area)* separates and isolates bundles of cardiomyocytes *(red area)* (trichrome stain × 33, reduced 28%). The endocardium *(top)* is thickened and fibrotic. *(B)* In contrast, in the true right atrium, fibrosis is scant, and there is a normal array of cardiomyocytes with enlarged hyperchromatic nuclei *(arrows)* indicating hypertrophy (hematoxylin eosin × 132, reduced 40%).

tified this way originates in the ARV.[4,6,8,17,18] Positive preoperative SAECGs in all 21 patients with classic Ebstein's anomaly (Figure 1) and negative SAECGs after intraoperative exclusion of the ARV serve to validate our criteria for interpretating the SAECG in the presence of a QRS prolongation, and support our belief that slow conduction originates in the ARV (Figure 1). Scrutiny of postoperative SAECGs indicated that slow conduction was occasionally not entirely eliminated. Intraoperative cryoablation after placation of the ARV promises to eliminate potentially arrhythmogenic residua.

Activation mapping during cardiac surgery was not done because of constraints imposed by the institutional review board, but evidence that slow conduction (positive SAECG) originates in the ARV is persuasive[4,10,17,19] because of (1) the disappearance of slow conduction (negative SAECG) after surgical exclusion of the ARV (Figure 1), (2) mechanically inducible ventricular tachycardia/fibrillation in the ARV,[1,2,12,19] (3) 3-dimensional mapping and electrographic localization of the origin of ventricular tachyarrhythmias in the ARV just distal to the His bundle recording,[20] and (4) inexcitability of the parchment

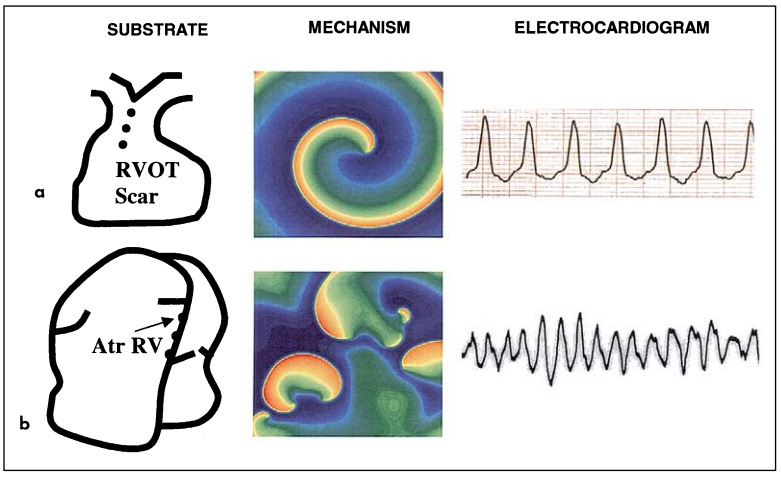

FIGURE 3. *(A)* **Substrate: post-ventriculotomy scar in the right ventricular outflow tract (RVOT). Mechanism: computer-generated mathematic simulation of orderly anchored spiral/scroll reentrant waves. Electrocardiogram: monomorphic ventricular tachycardia.** *(B)* **Substrate: Ebstein atrialized right ventricle (Atr RV) with displaced tricuspid leaflets** *(arrow)*. **Mechanism: computer-generated mathematic simulation of disorderly unanchored spiral/scroll waves that have broken up. Electrocardiogram: polymorphic ventricular tachycardia/fibrillation.**

right ventricle of Uhl's anomaly, which is devoid of an ARV.[12,21]

It is unclear just how large an ARV is required to provide a substrate for slow conduction, but the answer is suggested by the 2 patients with mild anomalies and negative SAECGs. Transesophageal echocardiograms identified small ARVs while confirming distal septal tricuspid leaflet displacement of 8 mm/m^2.[8]

Ventricular tachyarrhythmias did not occur in our patients with classic Ebstein's anomaly, but 21 patients was a small sample in light of the low incidence of ventricular tachyarrhythmias.[6,12,17,19] The ARV permits unique access to right ventricular myocardium without traversing the right atrioventricular valve, and mechanical stimulation of the atrialized right ventricular myocardium triggers polymorphic ventricular tachycardia/fibrillation.[1,2,6,12,19] In addition, other triggers may be operative, including catecholaminergic polymorphic ventricular tachycardia,[22] neurohumoral activation in adults with congenital heart disease,[23] in patients who are excessively emotional,[24] and in patients with ventricular premature beats originating in the arrhythmogenic ARV that are analogous to premature ventricular beats originating in the Purkinje system that trigger ventricular tachycardia/fibrillation.[20] Although the thin-walled ARV expands aneurysmally during right ventricular systole, stretch, per se, does not appear to serve as an arrhythmogenic trigger.[25]

Reentry is related to spiral (in 2-dimensional) and scroll (in 3-dimensional) waves of excitation.[13,14] Monomorphic ventricular tachycardia is a reentrant tachyarrhythmia that depends on a combination of slow conduction, unidirectional block, and a substrate that permits anchoring of spiral/scroll waves[14] (Figure 3). When spiral/scroll waves are not anchored, they meander erratically as polymorphic ventricular tachycardia or break up into ventricular fibrillation[14] (Figure 3). The ARV in Ebstein's anomaly consists of clusters of right ventricular cardiomyocytes that are isolated within a fibrous matrix,[3] thus preventing spiral/scroll reentrant waves from anchoring[14] (Figure 2). Accordingly, excitation of the arrhythmogenic ARV does not result in reentrant monomorphic ventricular tachycardia, but instead in polymorphic ventricular tachycardia/fibrillation (Figure 3, as originally proposed by Wood[1] and Watson.[2] Because the ARV is arrhythmogenic and does not contribute to right ventricular systolic function, tricuspid repair should include exclusion by plication or excision, accompanied by cryoablation to eliminate potentially arrhythmogenic residual tissue.

Study limitations: The Office for Protection of Research Subjects imposed constraints on intraoperative activation mapping of the ARV. Our patients with classic Ebstein's anomaly did not experience ventricular tachyarrhythmias before or after operation, but the sample size was small. Two possible but unlikely sources of late potentials were not examined, namely: (1) a left ventricular source[18,26,27] that might have been obscured by prolonged right ventricular activation, and (2) the large anterior tricuspid leaflets that contain muscular strands.[3]

Conclusion: Links were established between the electrophysiology and histopathology of the ARV, ventricular tachyarrhythmias, and exciting triggers in Ebstein's anomaly. The arrhythmogenic ARV is believed to be the site of slow conduction identified by positive SAECGs that normalized after surgical exclusion of the arrhythmogenic substrate. Cardiomyocytes in the ARV are isolated within fibrous networks that prevent anchoring of reentrant spiral/scroll waves, which break up into polymorphic ventricular tachycardia that promptly degenerates into ventricular fibrillation. Our proposal that spiral/scroll waves in the ARV cannot be anchored is an hypothesis that is supported by sound electrophysiologic and histopathologic observations.

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