Pathophysiological mechanisms of arrhythmogenic right ventricular disorders
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CHAPTER 2

Mechanism of right precordial ST-segment elevation in structural heart disease: excitation failure by current-to-load mismatch


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CHAPTER 2

Abstract

Background The Brugada sign has been associated with mutations in SCN5A and with right ventricular structural abnormalities. Their role in the Brugada sign and the associated ventricular arrhythmias is unknown.

Objective The purpose of this study was to delineate the role of structural abnormalities and sodium channel dysfunction in the Brugada sign.

Methods Activation and repolarization characteristics of the explanted heart of a patient with a loss-of-function mutation in SCN5A (G752R) and dilated cardiomyopathy were determined after induction of right-sided ST-segment elevation by ajmaline. In addition, right ventricular structural discontinuities and sodium channel dysfunction were simulated in a computer model encompassing the heart and thorax.

Results In the explanted heart, disappearance of local activation in unipolar electrograms at the basal right ventricular epicardium was followed by monophasic ST-segment elevation. The local origin of this phenomenon was confirmed by coaxial electrograms. Neither early repolarization nor late activation correlated with ST-segment elevation. At sites of local ST-segment elevation, the subepicardium was interspersed with adipose tissue and contained more fibrous tissue than either the left ventricle or control hearts. In computer simulations entailing right ventricular structural discontinuities, reduction of sodium channel conductance or size of the gaps between introduced barriers resulted in subepicardial excitation failure or delayed activation by current-to-load mismatch and in the Brugada sign on the ECG.

Conclusion Right ventricular excitation failure and activation delay by current-to-load mismatch in the subepicardium can cause the Brugada sign. Therefore, current-to-load mismatch may underlie the ventricular arrhythmias in patients with the Brugada sign.
Introduction

The Brugada sign of right precordial ST-segment elevation followed by a negative T-wave is associated with ventricular tachyarrhythmias and sudden cardiac death. In the Brugada syndrome, the sign occurs in the absence of gross structural abnormalities. However, the Brugada sign is not limited to structurally normal hearts. Right ventricular (RV) structural abnormalities have been demonstrated in a significant portion of patients with the Brugada sign. In addition, sodium channel blockers can provoke the Brugada sign in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and Chagas disease, conditions characterized by severe structural derangements. The role of structural derangements in the mechanism of the Brugada sign and the associated arrhythmias is unknown.

To date, two mechanisms of ST-segment elevation have been proposed for the Brugada sign: (1) early repolarization and (2) late activation in the RV wall. Sodium channel function is important in both mechanisms because sodium channel blockers can provoke the Brugada sign, and loss-of-function mutations in the gene encoding the cardiac sodium channel (SCN5A) can be identified in approximately 20% of patients with Brugada syndrome. Neither hypothesis has been confirmed in patients.

Structural abnormalities cause geometric variation in myocardial organization. Sites where structural abnormalities lead to sudden expansion of myocardium are susceptible to conduction block by current-to-load mismatch, especially when the available sodium current ($I_{Na}$) is reduced. If excitation fails at these sites, the potential gradient between the unexcited myocardium and the myocardium proximal to the site of conduction block will cause ST-segment elevation. Therefore, we hypothesized that RV excitation failure by current-to-load mismatch can cause the Brugada sign in patients with structural abnormalities, especially when $I_{Na}$ is reduced by loss-of-function mutations in SCN5A or sodium channel blockade. To test this hypothesis, we determined the activation and repolarization characteristics of the explanted heart of a patient with a loss-of-function mutation in SCN5A and structural discontinuities in the setting of dilated cardiomyopathy, before and after induction of ST-segment elevation by sodium channel blockade. Furthermore, we simulated the effect of $I_{Na}$ reduction and structural discontinuities on ECG in a computer model encompassing the heart and thorax.

Methods

The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient’s guardians. Cardiac transplantation was performed in May 2007 at the Erasmus Medical Center, Rotterdam, The Netherlands. The explanted heart was submerged in ice-cold modified Tyrode’s solution and transported (within 1 hour) to the Laboratory of Experimental Cardiology (Academic Medical Center, Amsterdam, The Netherlands).
Genetic study
Genomic DNA was extracted from lymphocytes using standard protocols. The entire coding regions of \textit{SCN5A} and \textit{LMNA} were screened for mutations by denaturing high-performance liquid chromatography followed by sequencing of amplicons displaying an aberrant elution profile. Screening of genes associated with ARVC (plakophilin-2 (\textit{PKP2}), junction-plakoglobin (\textit{JUP}), desmoglein-2 (\textit{DSG2}), desmocollin-2 (\textit{DSC2}), desmoplakin (\textit{DSP})) was performed by direct sequencing of the entire coding region.

Experimental setup
The right and left coronary arteries were cannulated, and the heart was connected to a perfusion setup. The heart was perfused with a mixture of washed erythrocytes (800 mL) and modified Tyrode’s solution. The potassium concentration was 4.0 mmol/L. Coronary flow was set to 300 mL/min. The heart was suspended in a cylindrical container (diameter 20 cm, height 14 cm) filled with perfusion fluid. Myocardial temperature was 37.0°–37.5°C throughout the experiment. The pH of the oxygenated perfusate was 7.34.

Electrophysiologic studies
Mapping experiment
Seven electrode strips (14 electrodes per strip in two rows, interelectrode distance 1.5 cm, distance between strips ≈2 cm) were equally distributed over and attached to the ventricular epicardium. An inflatable balloon (64 electrodes, interelectrode distance ≈1.5 cm) was inserted through the mitral orifice into the left ventricle (LV), and an inflatable balloon (32 electrodes, interelectrode distance ≈1.5 cm) was inserted through the tricuspid orifice into the RV. Three electrodes at the side of the container were used to record a pseudo-ECG. One electrode was positioned at the bottom below the apex of the heart, one faced the lateral LV, and one faced the lateral RV. A reference electrode was placed at the bottom of the container. Electrode positions were documented with digital photography.

The heart was stimulated from the basal RV septum at twice diastolic threshold (steady-state pacing at cycle length 2,000–1,500–1,000–800 ms). The stimulation protocol was repeated after addition of ajmaline 2.4 μmol/L (Solvay Pharmaceuticals GmbH, Hannover, Germany), a rate-dependent blocker of the cardiac sodium channel.

Data acquisition and analysis
Simultaneous recordings (sampling rate 2 kHz) were made from all electrodes during selected episodes. Signals were analyzed using a custom-made analysis program based on MATLAB R2006b (The MathWorks, Inc., Natick, MA, USA). The instant of maximal negative dV/dt in the QRS complex and the instant of maximal positive
dV/dt in the T wave of the unipolar electrogram were used as local activation and repolarization time, respectively. The local contribution to unipolar electrograms was determined by calculation of coaxial electrogram by subtracting the mean of values of neighboring electrodes from a central electrogram at each sample.

**Cellular electrophysiology**

After the mapping procedure, LV myocytes were isolated as previously described. $I_{Na}$ and action potentials were recorded using an Axopatch 200B amplifier (Molecular Devices Corp., Sunnyvale, CA, USA). Voltage control, data acquisition, and analysis were accomplished using custom software. Signals for $I_{Na}$ were low-pass filtered with a cutoff frequency of 5 kHz and digitized at 20 kHz. Action potentials were filtered and digitized at 10 and 40 kHz, respectively. Cell capacitance and series resistance were compensated for by at least 80%. Potentials were compensated for the calculated liquid junction potential.

$I_{Na}$ was recorded at room temperature (20°C) in the ruptured whole-cell configuration of the patch-clamp technique. The bath solution contained the following (in mmol/L): 7.0 NaCl, 133 CsCl, 1.8 CaCl$_2$, 1.2 MgCl$_2$, 11.0 glucose, 5.0 HEPES, and 0.005 nifedipine; pH 7.4 (CsOH). Patch pipettes (1.5–2.0 MΩ) were filled with the following (in mmol/L): 3.0 NaCl, 133 CsCl, 2.0 MgCl$_2$, 2.0 Na$_2$ATP, 2.0 TEACl, 10 EGTA, and 5.0 HEPES; pH 7.3 (CsOH). $I_{Na}$ amplitude and (in)activation properties were measured using a double-pulse protocol (see Figure 2A). Voltage dependence of (in)activation was determined by fitting a Boltzmann function to the individual curves. Current density was calculated by dividing whole-cell current amplitude by the cell capacitance.

Action potentials were recorded at 36°C ± 0.2°C with the amphotericin B perforated patch-clamp technique. Action potentials were elicited at 1 Hz by 3-ms, 1.5× threshold current pulses through the patch pipette. The bath solution contained the following (in mmol/L): 140 NaCl, 5.4 KCl, 1.8 CaCl$_2$, 1 MgCl$_2$, 5.5 glucose, and 5 HEPES; pH 7.4 (NaOH). The pipette solution contained the following (in mmol/L): 125 K-gluc, 20 KCl, 5 NaCl, 0.22 amphotericin-B, and 10 HEPES; pH 7.2 (KOH). We analyzed resting membrane potential, action potential duration at 90% repolarization (APD$_{90}$), and maximal action potential upstroke velocity (dV/dt$_{max}$), a measure of $I_{Na}$ availability. Values from 10 consecutive action potentials were averaged.

**Histology**

After the electrophysiologic studies, the remainder of the heart was fixed in 4% buffered formalin. Transmural tissue samples from the RV outflow tract, basal RV free wall, and basal LV free wall were routinely processed and embedded in paraffin. Sections 7-μm thick were stained with picrosirius red F3A for visualization of collagens in fibrous tissue. The content of adipose and fibrous tissue in the subepicardial rim of myocardium (outer 1 mm) was quantified by computerized morphometry on
10× objective fields of each section (mean 11.4 fields per section). Red (fibrous tissue) and white (adipose tissue) areas were expressed as a percentage of the total area using Image-Pro 6.2 (Media Cybernetics, Inc., Bethesda, MD, USA). The epicardial fat and large areas of perivascular adipose tissue were excluded from measurements. Transmural sections of six structurally normal hearts sampled from the same sites and obtained at autopsy from patients without a history of cardiac disease served as control samples.

**Computer simulations**
Propagating action potentials were simulated with a whole-heart reaction-diffusion model containing 90 million nodes, each represented by a membrane model of the human ventricular myocyte. Transmural fiber rotation was represented in the model. Membrane ionic currents were computed with a human membrane model that included the differential characteristics of subendocardial, midmyocardial, and subepicardial myocytes. The ECG was computed using a bidomain model of the human heart and torso, including lungs and intracavitary blood volumes. Structural discontinuities were simulated by the introduction of barriers (thickness 0.4 mm) in the outer 50% of the RV wall. In these barriers, no intercellular coupling was present, but the interstitium was unaffected. The barriers contained gaps of 0.2 mm width in which intercellular coupling was present. Intercellular coupling in the gaps was reduced in steps from 100% to 8% of normal to simulate smaller gaps. Sodium channel conductivity \( G_{Na} \) was reduced in steps from 100% to 20% of normal in the entire heart. Single cardiac cycles were simulated in 12 hours on 128 processors of an SGI Altix 4700 supercomputer.

**Statistical analysis**
Values are given as mean ± SD unless specified otherwise. Unpaired, two-tailed, Student’s t-tests were used for statistical comparison of normally distributed data. \( P < 0.05 \) was considered significant.

**Results**

**Patient data**
The female patient (age 13 years) presented for medical attention after experiencing syncope during exercise in 2004. She had a low exercise tolerance and reported two episodes of syncope over the last year, one of which occurred at rest. Her ECG showed atrial flutter with a flutter rate of 258/min and ventricular rate of 43/min, left axis with QRS duration of 150 ms, poor R-wave progression in the precordial leads, and negative T waves in leads I, aVL and \( V_2-V_6 \) (Figure 1). Echocardiography revealed LV fractional shortening was reduced (21%) and LV end-diastolic diameter was increased (53 mm, >95th percentile). No RV abnormalities
were reported. A dual-chamber pacemaker was implanted. Two weeks after discharge, the patient was readmitted due to fatigue, loss of ventricular capture of the pacemaker, and pericardial effusion. Pericardiocentesis was performed, and the ventricular lead was repositioned. Over the next year, the patient developed episodes of exercise intolerance during paroxysms of atrial flutter. A trial radiofrequency ablation to terminate the atrial flutter was performed. However, the symptoms progressed, and cardiac transplantation was conducted 2.5 years after initial presentation for end-stage heart failure in dilated cardiomyopathy. No sodium channel provocation test was performed, no spontaneous Brugada sign was observed, and the patient was not diagnosed with the Brugada syndrome. The patient did not receive antiarrhythmic drugs prior to transplantation.

**Family history and genetic data**

The patient had a heterozygous mutation in SCN5A (c.2254G>A; numbering according to NM_198056.2) with substitution of glycine by arginine at position 752 (p.Gly752Arg) located in the second transmembrane segment of channel domain II. This mutation previously has been shown to reduce cardiac sodium channel function and was associated with the Brugada syndrome in a French family. No mutation was found in LMNA or in the ARVC–associated genes PKP2, JUP, DSG2, DSC2, and DSP. The patient’s mother and grandmother also carried the G752R mutation in SCN5A. The family history revealed that a great-uncle and a great-aunt (brother and sister of the grandfather on the mother’s side of the family) had died suddenly at the age of 35 years and ~45 years, respectively. The mother’s ECG did not show any abnormalities, but the Brugada sign was induced by flecainide.

**Cellular electrophysiologic studies**

Figure 2A shows typical examples of $I_{Na}$ in an isolated ventricular myocyte. $V_{1/2}$ of activation and inactivation was $-40.0 \pm 4.4$ mV and $-85.2 \pm 8.3$ mV, respectively.
(n = 6, Figure 2B). Figure 2C shows representative action potential upstrokes. The dV/dt\textsubscript{max} is compared to that of single LV myocytes from a patient with a heterozygous mutation (G1935S) in SCN5A with unaltered sodium channel characteristics except for enhanced slow inactivation as previously reported.\textsuperscript{2} The average dV/dt\textsubscript{max} in G752R ventricular myocytes was 165 ± 101 V/s versus 337 ± 74 V/s of those in G1935S ventricular myocytes (n = 3 and n = 7, respectively, \(P < .05\)). Resting membrane potential was −79.0 ± 6.3 mV, and APD\textsubscript{90} was 502 ± 124 ms.

\[\text{Figure 2.} \quad \text{Sodium channel characteristics and action potential upstrokes of isolated left ventricular myocytes. Typical whole cell-current recordings (A) and corresponding current–voltage relations (mean ± SEM) (B) show a normal voltage dependency of the sodium current. C: Typical action potential upstrokes and dV/dt show significantly reduced upstroke velocities compared to myocytes of a previously reported control patient. Insets illustrate the voltage and stimulus protocols.}\]

\textit{Isolated heart}

At baseline, ST segments of the pseudo-ECG were isoelectric during stimulation at any cycle length. At a cycle length of 800 ms, QRS and QT duration were 150 and 710 ms, respectively. After ajmaline, the ST segment in pseudo-aVR was elevated by 0.3 mV at a cycle length of 800 ms, whereas QRS and QT duration increased to 180 and 750 ms, respectively (Figure 3).
Activation and repolarization mapping
Figure 4 shows the activation (panel A) and repolarization (panel B) times projected on pseudo-aVR and a three-dimensional reconstruction of the activation and repolarization pattern after ajmaline. Reference times were earliest activation or repolarization, respectively. ST-segment elevation was present after the moment of latest activation and before the moment of earliest repolarization. Latest recorded activation coincided with the J point, and earliest repolarization occurred at the start of the T wave, 250 ms after the J point. A three-dimensional reconstruction shows the spread of activation from the RV septum over both ventricles. Latest activation was recorded at the RV free wall and LV free wall, and crowding of isochrones was most pronounced at the endocardium of the RV. Earliest repolarization occurred at the basal endocardium of the RV and LV. Of note, epicardial repolarization was later than endocardial repolarization at the RV (mean 128 ms and 84 ms, respectively).
ST-segment elevation in unipolar electrograms

ST-segment elevation after ajmaline in pseudo-aVR coincided with ST-segment elevation in unipolar electrograms (Figure 5A, site indicated by asterisk in Figure 5B). A voltage map of epicardial unipolar electrograms 100 ms after the J point in pseudo-aVR illustrates that ST-segment elevation in unipolar electrograms was limited to the basal epicardial RV (Figure 5B, time indicated by arrow in Figure 5A). Calculated coaxial electrograms confirmed that the local ST-segment elevation was not the result of far-field effects, contrary to the initial deflection in the unipolar electrogram. ST-segment elevation increased with stimulation frequency. Note that the local activation signal in the unipolar and coaxial electrogram virtually disappeared when ST-segment elevation was observed (Figure 5A).

Figure 4. Activation and repolarization after sodium channel blockade (right ventricular septal stimulation at cycle length of 800 ms). Activation (A) and repolarization (B) times are depicted on the corresponding complex in pseudo-aVR and on a three-dimensional reconstruction of the heart. Anterior view of the heart is depicted on the left; posterior view is depicted on the right. The epicardium is viewed as transparent. No sign of activation or repolarization was found throughout the ST segment. Lines are 20-ms isochrones.
Figure 5. Regional ST-segment elevation in unipolar electrograms after sodium channel blockade. A: Pseudo-aVR (top row), unipolar electrogram (middle row), and calculated coaxial electrogram (bottom row) from the epicardial basal right ventricle (site indicated by asterisk in panel B) during stimulation from the right ventricular septum at increasing frequencies (cycle length indicated at top). ST-segment elevation in pseudo-aVR increased with higher stimulation frequencies and coincided with disappearance of the main activation signal followed by monophasic ST-segment elevation in the unipolar electrogram. The local origin of ST-segment elevation was confirmed using coaxial electrograms. B: Three-dimensional reconstruction of ST-segment amplitude on unipolar epicardial electrograms 100 ms after the J point in pseudo-aVR (moment indicated by arrows in panel A) at cycle length of 800 ms. ST-segment elevation was limited to the basal epicardial right ventricle. Right ventricular view is shown on the left; left ventricular view is shown on the right. Color scale is given in millivolts. LV = left ventricle; RV = right ventricle.
CHAPTER 2

Pathology of the heart

Macroscopically, the heart showed hypertrophy and dilation of both ventricles. Pronounced endocardial fibroelastosis was seen, particularly in the LV. A thick layer of epicardial fat covered the RV. The coronary arteries, including coronary ostia, and all heart valves were normal. Microscopically, the myocardium showed cytonuclear features of hypertrophy and multizonal distinct cytoplasmatic vacuolization of myocytes.

The subepicardial myocardium of the RV outflow tract and basal RV free wall, but not of the basal LV free wall, was locally interspersed with adipose tissue. The fatty

Figure 6. Subepicardial histologic sections and quantification of subepicardial fibrous and adipose tissue. A–C: Subepicardial sections from the right ventricular outflow tract (RVOT; A), basal right ventricular free wall (RVFW; B), and basal left ventricular free wall (LVFW, C). Low-magnification images show fatty infiltration (white) in the subepicardial myocardium of the RVOT and RVFW and interstitial-type fibrosis (red) at all locations. Picrosirius red staining; bar = 500 μm. Note that the epicardial rim of collagen seen in panel C was excluded from measurements. D, E: Morphometric analysis of fibrous (D) and adipose (E) tissue content as percent of total measured myocardial area in the heart of the patient (red dots) and in the hearts of controls (black dots). Analysis reveals that the heart of the patient contained more fibrous tissue at any location than did any of the control hearts, and that the adipose tissue content of the RVOT and RVFW was greater than in the LVFW. However, no difference in adipose tissue content was found between the patient and the control hearts. Bars in panel D indicate mean ± SD of controls.
infiltration focally reached the subendocardium but was not transmural at any site (Figures 6A, 6B, and 6C).
Both ventricles showed focal increase of lymphocytes, including sparse clusters, indicating borderline myocarditis. Morphometric analysis showed that the subepicardium of the RV outflow tract, RV free wall, and LV free wall of the patient (red) contained more fibrous tissue than did any of the controls. The adipose tissue content of the RV outflow tract and RV free wall was greater than of the LV free wall in both the patient and the controls (Figures 6D and 6E).

**Computer simulations**
The ECG derived from the simulated heart without structural abnormalities had QRS duration of 80 ms and isoelectric ST segments (Figure 7A, black ECG). Reduction of $G_{Na}$ in the normal heart to 30% of normal caused global activation delay, and QRS duration increased to 130 ms but did not lead to ST-segment elevation (Figure 7A, red ECG).
The introduction of structural discontinuities with 30% of normal coupling in the gaps at normal $G_{Na}$ resulted in QRS prolongation to 100 ms and negative T waves in the right precordial leads but not in ST-segment elevation (Figure 7B, black ECG). The negative T wave was caused by activation delay of the RV subepicardium (Figure 7C). Reduction of $G_{Na}$ after introduction of these structural discontinuities caused excitation failure at the anterior RV subepicardium (Figure 7D, black sites). The current received from and given to surrounding elements and corresponding action potentials at five neighboring sites in and immediately distal to the gaps are shown in the left and right graph, respectively. Subepicardial excitation failure occurred when insufficient depolarizing current was received distal of the introduced structural discontinuities to reach threshold potential. The potential gradient between the excited and unexcited myocardium caused ST-segment elevation in the right precordial leads. Activation at other RV subepicardial sites was delayed, leading to a negative T wave in the right precordial leads (Figure 7B, red ECG).
In the presence of structural discontinuities with 30% of normal coupling in the gaps, the percentage of elements that were not excited throughout the cardiac cycle depended on $G_{Na}$ and correlated well with cumulative ST-segment elevation in leads $V_1$ and $V_2$ of the third and fourth intercostal spaces. Both increased markedly when $G_{Na}$ was reduced below 50% of normal (Figure 8A). Likewise, a decrease of the size of the gaps in the barriers at normal sodium conductance resulted in a reduction in excited elements. The amplitude of ST-segment elevation by excitation failure after reduction of the size of the gaps was limited by the increased resistance between the excited and unexcited myocardium (Figure 8B).
Figure 7. Simulated subepicardial discontinuities and sodium channel dysfunction. A, B: ECGs of the heart without (A) and with structural discontinuities in the right ventricular subepicardium (B) at baseline (black) and after (red) reduction of sodium channel conductivity \( (G_{Na}) \) to 30% of normal. Bars = 200 ms, 1 mV. C, D: Basal short-axis view of the heart with structural discontinuities at the right ventricular subepicardium before (C) and after (D) reduction of \( G_{Na} \) to 30% of normal. Colors indicate activation time; sites that failed to excite throughout the cardiac cycle are depicted in black. The current received from and given to surrounding elements and the corresponding action potentials at five neighboring sites are depicted in the left and right graphs, respectively. The locations of these elements were 0.2 mm (black) and 0.4 mm in (brown) and 0.2 mm (red), 0.4 mm (orange), and 1.0 mm (yellow) behind the gaps in the barriers. After reduction of \( G_{Na} \), insufficient current was received by many elements behind the introduced structural discontinuities to reach threshold potential. This resulted in excitation failure and activation delay of the right ventricular subepicardium and in ST-segment elevation followed by a negative T wave in the right precordial leads. LV = left ventricle; RV = right ventricle.
Discussion

This study shows for the first time the activation and repolarization characteristics of the complete heart of a carrier of a loss-of-function mutation in \textit{SCN5A} after provocation of right-sided ST-segment elevation by sodium channel blockade. ST-segment elevation coincided with the local disappearance of the initial activation and the appearance of monophasic ST-segment elevation in unipolar electrograms at the basal epicardial RV. At these sites, fibrosis and fatty infiltration caused discontinuities in the subepicardium. In a computer model encompassing the heart and thorax, structural discontinuities were simulated by the introduction of nonconducting barriers containing gaps in the RV subepicardium. Successful conduction through these gaps depended on their simulated size and was modulated by the available cardiac sodium current. Excitation failure and activation delay of the RV subepicardium resulted in
ST-segment elevation and a negative T wave in the right precordial leads of the ECG, respectively. Therefore, current-to-load mismatch may underlie the Brugada sign in patients with RV structural discontinuities.

In the isolated heart, we found no support for either of the preexisting hypotheses of ST-segment elevation in the Brugada sign. Latest activation coincided with the end of the QRS complex and earliest repolarization with the start of the T wave on pseudo-ECG, leaving 250 ms of ST-segment elevation that could not be explained by either late activation or early repolarization. Other causes of ST-segment elevation that were not assessed directly in this heart are regional differences in resting membrane potential or in plateau potential amplitude. A regional difference in resting membrane potential generates TQ-segment depression that cannot be distinguished from true ST-segment elevation by AC electrograms. However, the resting membrane potentials in isolated myocytes were similar to those previously found in dilated and ischemic cardiomyopathy, and \( I_{Na} \) reduction has no direct effect on the resting membrane potential. Likewise, regional differences in plateau potential amplitude likely did not play a role as local ST-segment elevation was accompanied by the virtual disappearance of the QRS complex in unipolar electrograms.

The computer model is based on a membrane model of human ventricular myocytes that incorporates transmural differences in the density of the transient outward current. Reduction of \( I_{Na} \) alone did not cause either early repolarization or a reduced plateau potential amplitude at the RV subepicardium and did not result in ST-segment elevation. However, reduction of \( I_{Na} \) did result in the Brugada sign after the introduction of discontinuous barriers in the RV subepicardium. The cause was the combination of excitation failure (ST-segment elevation) and activation delay (negative T-wave) of the subepicardium by current-to-load mismatch. The plateau potential amplitude was reduced proximal to the site of excitation failure. However, this was caused by electrotonic interaction with the unexcited myocardium.

Whether current-to-load mismatch can also cause the Brugada sign in patients with the Brugada syndrome is unclear because its diagnosis requires exclusion of structural heart disease. Several histologic and imaging studies recently demonstrated that a variety of myocardial changes, not recognized during standard clinical investigation, are present in many patients with Brugada syndrome. In addition, late potentials on signal-averaged ECGs, usually associated with structural heart disease, are a common finding in the Brugada syndrome. Therefore, lack of sensitivity of standard imaging modalities may render structural abnormalities at the RV subepicardium undetected. Thus, excitation failure in discontinuous myocardium can be the mechanism of the Brugada sign in the Brugada syndrome as well.

The heart of our patient showed the gross pathology of an end-stage dilated cardiomyopathy. Histologically, we found structural abnormalities that have been described as occurring in biopsy samples from patients with Brugada syndrome and proven \( SCN5A \) mutations (fibrosis, cardiomyopathic cellular changes); however,
these pathologic changes also have been reported in patients with Brugada syndrome but no such a mutation, particularly lymphocytic myocarditis. Therefore, whether the current-to-load mismatch in the RV subepicardium relates to structural pathology resulting from the SCN5A mutation, other coincidental inflammatory pathology, or both remains unsettled.

An argument against the involvement of excitation failure by current-to-load mismatch in the Brugada syndrome is the observation that ST-segment amplitude and risk of ventricular arrhythmias appear largest during slow heart rhythms (at night or at rest). In our study, ST-segment elevation increased with stimulation frequency. This can be explained in part by the use of ajmaline, which has a rate-dependent capacity to block sodium channels. Another explanation is the absence of autonomic innervation in the isolated heart. When the safety factor for conduction is reduced, the depolarizing current of the L-type calcium channel can be crucial for conduction success. The L-type calcium current decreases during increased vagal and decreased sympathetic activity. Therefore, the autonomic nervous system may modulate the success of conduction in current-to-load mismatch and ST-segment elevation by excitation failure. In addition, the decrease of ST-segment elevation in the Brugada syndrome by beta-adrenergic stimulation and the increase by acetylcholine can be explained by the effect of the L-type calcium current on conduction.

The rapid variability of the Brugada sign over time likely is not related to structural changes. Besides modulation by pharmacologic agents and the autonomic nervous system, other factors may influence the Brugada sign by excitation failure. Fish oil reduces the cardiac sodium current after acute administration and reduces the L-type calcium current both after acute administration and in feeding experiments. Therefore, intake of fish oil may reduce the success of conduction in current-to-load mismatch and may augment the Brugada sign by this mechanism. Furthermore, the load at sites of sudden myocardial expansion depends on the intercellular resistance with the surrounding myocardium and is modulated by electrical coupling via connexin43. The half-life of connexin43 is short (~1.3 hours). Changes in the turnover of connexin43 can have a rapid effect on excitation failure by current-to-load mismatch and on the Brugada sign by this mechanism.

Excitation failure by current-to-load mismatch provides a unifying hypothesis for the ST-segment elevation and predisposition to ventricular arrhythmias seen in patients with the Brugada sign. Previous studies have demonstrated that unexcited tissue shortens the action potential duration and effective refractory period of myocardium proximal to the site of block by electrotonic interaction. This combination of unidirectional block and a local decrease in refractoriness can initiate reentry even without the need for a premature beat. It also explains why the duration of ST-segment elevation in unipolar electrograms observed in this study was shorter than the activation-recovery interval, which is a measure of action potential duration, before sodium channel blockade.
CHAPTER 2

Study limitations
No sodium channel provocation protocol was performed prior to cardiac explantation, which hinders extrapolation of the pseudo-ECG to the patient’s ECG. However, the concentration of ajmaline used in our study was similar to those used clinically to provoke the Brugada sign, and our simulations confirm that subepicardial excitation failure and activation delay at the RV shows as the Brugada sign in the right precordial leads. Therefore, the mechanisms described in our study likely would have occurred in the patient as well.

Conclusion
Structural discontinuities at the RV subepicardium can cause excitation failure and activation delay by current-to-load mismatch, especially when the available cardiac sodium current is reduced. Excitation failure and activation delay at the RV subepicardium show as the Brugada sign on ECG. Therefore, current-to-load mismatch may underlie ventricular arrhythmias in patients with the Brugada sign and RV structural discontinuities.

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ST-segment elevation after $I_{Na}$ reduction

References


