Published in final edited form as:

Heart Rhythm. 2009 June ; 6(6): 784–792. doi:10.1016/j.hrthm.2009.02.017.

Mechanisms of Recurrent Ventricular Fibrillation in a Rabbit Model of Pacing-Induced Heart Failure

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Abstract

Objectives—To determine the mechanisms of spontaneous ventricular fibrillation (SVF) after initial successful defibrillation in a rabbit model of heart failure (HF).

Background—Successful defibrillation may be followed by recurrent SVF. The mechanisms of postshock SVF are unclear.

Methods—We performed simultaneous optical mapping of intracellular calcium (Ca_i) and membrane potential (V_m) in 12 rabbit hearts with chronic pacing-induced heart failure, in 4 sham operated hearts and in 5 normal hearts during fibrillation-defibrillation episodes.

Results—We recorded 28 SVF episodes after initial successful defibrillation in 4 failing hearts (SVF Group) but not in the remaining 8 failing hearts (no-SVF Group) or in the normal or sham operated hearts. The action potential duration (APD_{80}) before pacing-induced VF was 209 ± 9 ms (SVF-Group) and 212 ± 14 ms (no-SVF Group, $P=NS$). After successful defibrillation, the APD_{80} in SVF Group shortened to 147 ± 26 ms while in no-SVF Group shortened to 176 ± 14 ms ($P=0.04$). However, the duration of Ca_i after defibrillation was not different between these two groups (246 ± 21 ms vs. 241 ± 17 ms, $p=NS$), resulting in elevated Ca_i during late phase 3 or phase 4 of the action potential. Standard glass microelectrode recording in an additional 5 failing hearts confirmed postshock APD shortening and afterdepolarizations. The APD_{80} of normal and sham operated hearts was not shortened after defibrillation.

Conclusions—HF promotes acute shortening of the APD immediately after termination of VF in failing hearts. Persistent Ca_i elevation during the late phase 3 and phase 4 of the shortened action potential result in afterdepolarizations, triggered activity and SVF.

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Conflict of Interest: Medtronic Inc. donated the pacemakers used in the study.

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Keywords

heart failure; action potential duration; intracellular calcium; spontaneous ventricular fibrillation; electrophysiology; sudden cardiac death

Introduction

Late phase 3 early afterdepolarizations (EADs) and triggered activity are novel mechanisms for the immediate reinitiation of atrial fibrillation after initial successful defibrillation.¹ The same mechanism may be applicable to spontaneous atrial fibrillation that originates from the pulmonary veins.²⁻⁴ In atria, late phase 3 EADs have been proposed to occur when the intracellular calcium (Ca_i) transient outlasts the action potential duration (APD), resulting in excessive electrogenic I_{NCX} during repolarization. Whether or not persistent Ca_i elevation in late phase 3 or phase 4 of a shortened APD is important in ventricular arrhythmogenesis is unclear. Heart failure (HF) is associated with structural and electrophysiological remodeling, leading to tissue heterogeneity that enhances arrhythmogenesis and the propensity of sudden cardiac death.⁵⁻⁷ HF is also known to increase ventricular defibrillation threshold.⁸ In addition to difficulties in initial defibrillation, clustering of ventricular tachycardia (VT) and ventricular fibrillation (VF) occurs in approximately 10% of the patients with HF.⁹ The mechanisms of arrhythmogenesis in HF are usually attributed to abnormal intracellular calcium (Ca_i) handling and afterdepolarizations related to prolonged APD.⁵ To better understand Ca_i dynamics and the mechanisms of ventricular defibrillation in HF, we simultaneously mapped Ca_i and membrane potential (V_m) in a rabbit model of pacing-induced low output HF. Despite little expectation that APD shortening is also associated with arrhythmogenesis in HF, we unexpectedly documented the presence of dramatic transient APD shortening after fibrillation-defibrillation episodes. The shortened APD, together with persistent Ca_i elevation during phase 3 and phase 4 of the action potential, led to afterdepolarizations, triggered activity and spontaneous VF (SVF). These findings suggest that APD shortening coupled with persistently elevated Ca_i is a mechanism of recurrent SVF after initial successful defibrillation in HF.

Methods

The research protocol was approved by the Institutional Animal Care and Use Committees. New Zealand white rabbits (3.5 to 4.6 Kg) were used in the study (N=32). Among them, 27 received pacemaker implantation and 5 were used as normal control. Rapid pacing was performed in 23 of 27 rabbits to induce HF (experimental group). No pacing was performed in the remaining 4 rabbits (sham operated group). Among the 23 paced rabbits, 6 died suddenly within 4 weeks of commencement of pacing. The hearts from the remaining 17 rabbits were harvested for optical mapping studies (N=12) and for single cell transmembrane potential (TMP) recordings using standard glass microelectrodes (N=5) in intact hearts. Ventricular function was assessed by echocardiogram at baseline and after surgery in 4 sham operated rabbits and in 5 HF rabbits.

Surgery and Pacing-Induced Heart Failure

The surgery was performed with isoflurane general anesthesia. The chest was opened via a left lateral thoracotomy. An epicardial pacing lead was placed in the lateral wall of the left ventricle and connected to a modified Medtronic Kappa® pacemaker for tachycardia pacing. All hardware was implanted inside the thoracic cavity. After a week of convalescence, pacing was started and the rabbit ventricle was paced at 250 bpm for 3 days, 300 bpm for 3 days and 350 bpm for 3 weeks.

Optical mapping

The hearts were harvested 5 weeks after pacemaker implantation for optical mapping. The hearts were quickly removed and the ascending aorta was cannulated and retrogradely perfused with warm oxygenated Tyrode's solution equilibrated with 95 % O₂ and 5% CO₂ to maintain a pH of 7.40 ± 0.05 at a rate of 35-45 ml/min while the hearts were hanging in air. The composition of the Tyrode's solution (in mmol/L) is NaCl 125, KCl 4.5, NaHPO₄ 1.8, NaHCO₃ 24, CaCl₂ 1.8, MgCl₂ 0.5, and albumin 50 mg/L in deionized water. The coronary perfusion pressure was regulated and maintained at 70-80 cm H₂O. A Ca-sensitive dye (0.5 mg rhod-2 AM, Molecular Probes, $K_d = 0.57$) and a voltage-sensitive dye (RH 237, Molecular Probes) were given¹⁰ and the hearts were illuminated with a laser (Verdi, Coherent Inc.) at a wavelength of 532-nm. The emitted fluorescence was filtered and acquired simultaneously with two charge-coupled device (CCD) cameras (CA-D1-0128T, Dalsa Inc.) at 4 ms/frame. Previous studies showed no crosstalk between V_m and Ca_i with this method of dual mapping.^{10,11} The digital images (128×128 pixels) were gathered from the epicardium of the left ventricle (25×25 mm² area), resulting in a spatial resolution of 0.2×0.2 mm² per pixel. Four pins were inserted into the corners of the mapped surface for registration and the mapped fields of the CCD cameras were mathematically matched. Motion artifact was suppressed by 5 μM cytochalasin D.¹²

Experiment Protocol

Pseudo-ECGs were measured with widely spaced bipolar electrodes on right atrium and right ventricle (RV), and on RV and left ventricle (LV). A quadripolar catheter was inserted into the RV apex for pacing at 2X threshold and sensing. VF was induced by burst pacing. The hearts were defibrillated with a transvenous electrode in RV and a patch electrode on the posterior wall of LV. Three to 5 fibrillation-defibrillation episodes were mapped. At the end of the study, the hearts were harvested, formalin fixed, and sectioned for Masson's trichrome staining.

Construction and Interpretation of 2 Dimensional Maps

The average fluorescence level ($\bar{F}$) of an individual pixel was first calculated for the duration of recording. The ratio on each pixel is then calculated as $(F - \bar{F})/\bar{F}$. The image data were spatiotemporally filtered first with a 3×3×3 averaging. We assigned shades of red to represent above-average fluorescence (depolarization) and shades of blue to represent below-average fluorescence (repolarization) to generate the ratio maps.

Single Cell TMP Recordings

Single cell TMP recordings were done with standard glass microelectrodes filled with 3 M KCl in intact, Langendorff-perfused hearts. The signals were amplified by IE-251A Intracellular Electrometer (Warner Instruments, Hamden, CT) and sampled at 5K/s.

Data Analyses

The fibrotic tissues stain blue with Masson's trichrome. The percent of fibrosis (blue stained tissues) was determined in multiple slides per dog using computerized morphometry. The average was used as percent fibrosis. Continuous variables were expressed as the mean $\pm$ SD. Student's t tests were used to compare the mean between two groups. Analyses of variance (ANOVA) with Newman-Keuls tests were used to compare the means of multiple groups. A p value of ≤ 0.05 was considered statistically significant.

Results

Evidence of Heart Failure

All rabbits that survived rapid pacing protocol showed clinical signs of HF including appetite loss, tachypnea, lethargy, pleural effusion, ascites and the visible congestion of lung, liver and the gastrointestinal tract. Echocardiograms of sham operated rabbits (N=4) at baseline and at second surgery showed no changes of LV end diastolic dimension, end systolic dimension or fractional shortening. In contrast, there were significant increases in end diastolic dimension (14.5 ± 0.2 mm vs 19.9 ± 0.5 mm), end systolic dimension (8.4 ± 0.3 mm vs 17.9 ± 0.3 mm) and reduced fractional shortening (0.42 ± 0.01 vs 0.10 ± 0.01) ($P < 0.0001$ for all comparisons) in HF rabbits (N=5). The percent LV fibrosis was 4 ± 1 % for sham operated hearts and was 19 ± 6 % for failing hearts ($P = 0.0015$).

Spatial Gradient of APD and Ca_i Transient in Heart Failure

APD₅₀ and APD₈₀ were measured to 50% and 80% repolarization, respectively, and the same method was applied to measurements of Ca_i transient duration, $\text{Ca}_i\text{TD}_{50}$ and $\text{Ca}_i\text{TD}_{80}$. Three pixels each from the center of the base, the midportion and the apex of LV anterior wall were measured in 4 normal hearts and 11 failing hearts. (One normal and 1 failing heart were excluded for not having stable sinus rhythm on Langendorff perfusion). There were no significant differences in RR intervals during the sinus rhythm (578 ± 94 ms vs. 598 ± 104 ms, respectively) between normal and failing hearts. Figure 1 summarizes the APD and Ca_iTD changes in all hearts studied. There was increased APD and Ca_iTD gradient between base and apex. Typical examples of APD and Ca_i ratio maps are shown in Figure 2. The failing hearts had a longer APD (arrow) than the normal hearts, but the Ca_i transient duration was about the same.

Acute Electrical Remodeling of APD and Spontaneous VF

After fibrillation-defibrillation episodes in the failing hearts only, we observed acute transient APD shortening and recurrent episodes of SVF. Figure 3A shows a continuous pseudo-ECG recording in a failing heart. The initial sinus rhythm was interrupted by pacing-induced VF, which was terminated by defibrillation shocks (green arrows) and was followed by 7 SVF (SVF1 to SVF7) and 1 spontaneous ventricular tachycardia (“storms”). Figures 3B, 3C and 3D show V_m recording (white line) and the Ca_i (yellow line) optical signals obtained during baseline sinus rhythm, immediately after DC termination of pacing-induced VF and spontaneous conversion of sinus rhythm to SVF4, respectively. There was spontaneous Ca_i elevation in a second postshock beat in Figure 3C (arrow), but no VF was initiated. Figure 3D shows SVF4. The first beat of SVF occurred during late phase 3 of a short AP and when Ca_i was still elevated, consistent with late phase 3 EAD. Figure 3E shows single beats at four different time points during the experiment, including baseline (Ea), after fibrillation-defibrillation (Eb), immediately before SVF4 (Ec) and 15 min (Ed) after SVF7. Figure 3F shows time-dependent changes of APD and Ca_iTD after defibrillation, showing the transient nature of the APD shortening.

Among 12 failing hearts studied, 4 developed a total of 58 repeated episodes of SVF (SVF Group) and 8 did not (no-SVF group). Among the 58 episodes, 28 episodes of SVF (8, 12, 6 and 2 episodes per heart, respectively) were optically mapped. The shocks were given 259 ± 190 sec in 4 hearts with SVF and 216 ± 86 sec in 8 hearts without SVF ($P = \text{NS}$). The perfusion was maintained throughout the initial pacing-induced VF and postshock SVF. In 3 of the 4 SVF rabbits, multiple SVF episodes occurred in short intervals as shown in Figure 3A. The APD₈₀ immediately before first pacing-induced VF were 209 ± 9 ms (SVF-Group) and 212 ± 14 ms (no-SVF Group, $P = \text{NS}$). The APDs of the last 3 beats of VF averaged 57.1 ± 11.5 ms (SVF group), 63.4 ± 7.8 ms (no-SVF group) and 60.1 ± 10.7 ms (normal controls), respectively ($p = \text{NS}$).

After defibrillation, the APD_{80} of the immediate postshock beats was 147 ± 26 ms in SVF Group and 176 ± 14 ms in no-SVF Group ($P=0.04$). However, the Ca_iTD_{80} post-defibrillation were not different between the SVF and no-SVF groups (246 ± 21 ms vs. 241 ± 17 ms, $p=NS$). Because of the disproportionate shortening of APD relative to Ca_iTD in the SVF group, repolarization was almost complete when the Ca_i was still considerably elevated after an episode of defibrillation (Fig 3Eb). As a result, there was elevated Ca_i during the late phase 3 and phase 4 of the action potential.

No Electrical Remodeling in Normal or Sham Operated Rabbits

In normal hearts, Figure 4A shows after multiple pacing episodes (black arrows) which induced 6 episodes of VF. No SVF episodes occurred after repeated DC shocks (green arrows). Panels B and C show optical signals in sinus rhythm and after defibrillation. There was no acute shortening of APD immediately after a successful defibrillation shock. Panel D shows action potential and Ca_i at baseline (Da), immediately after shock termination of VF 6 (Db) and 11 min after the last rapid pacing attempt (Dc). There was no APD shortening after successful defibrillation. The APD_{80} of normal hearts were 183 ± 21 ms at baseline and were 184 ± 19 ms ($P=NS$) immediately after VF termination. In addition to these 4 normal rabbits, we also studied 4 sham operated rabbits. The APD_{80} at baseline were 183 ± 13 ms and were 188 ± 5 ms ($p=NS$) after episodes of VF lasting 142 ± 146 sec. Figure 5 shows representative V_m and Ca_i ratio maps of postshock sinus beats in normal and HF hearts, showing that repolarization occurred much earlier in failing hearts (arrow) than normal hearts.

Phase 3 and Phase 4 Ca_i Elevation and Repetitive Focal Discharges

Figure 6 shows more detailed analyses of SVF in the same failing heart shown in Figure 3. Figure 6A (same as Figure 3D) shows that the onset of SVF was associated with a very short APD coupled with an elevated phase 3 Ca_i amounting to greater than 50 % of the peak systolic Ca_i transient amplitude. The first beat of SVF began during late phase 3 of the preceding sinus beat. Isochronal maps show that the first 3 beats originated from slightly different sites on the basal portion of the LV anterior wall, each arose during persistently high Ca_i . The right two columns are ratio maps of V_m and Ca_i , respectively. At the onset of VF (1178 ms), the Ca_i remained elevated throughout the LV while the V_m has already repolarized, with the exception of the site of focal origin at the left upper quadrant which initiated the dominant wavefront. In the right lower quadrant of the mapped region, the Ca_i was also elevated. These elevated Ca_i induced depolarization (arrows in frames 1326 ms and 1330 ms), but these low amplitude depolarization did not propagate to the entire mapped region. Figure 6B shows another episode of SVF from the same heart. The SVF was just terminated by DC shock. After termination, VF occurred spontaneously from phase 4 of the action potential (asterisk and arrow), when V_m had repolarized to resting level while a large Ca_i persisted. The ratio maps (left two columns) show Ca_i elevation at the focal origin of repetitive epicardial activation. The isochronal map on the right is consistent with propagation from a focal site or with epicardial breakthrough. Figure 6C shows propagation of activation from the site of origin (asterisk) to the right lower portion of the mapped field in both episodes.

Single Cell TMP Recordings

Continuous and stable single cell TMP recording before and immediately after shock were successful in 4 of 5 failing hearts studied. Figure 7A shows an example. The recording within the yellow boxes marked B, C and D are shown in Figures 7B, 7C and 7D, respectively. Note that the APD_{80} was 221 ms before shock (B), and shortened to 118 ms and 101 ms (first and second beats, respectively,) after the shock (C). For a total of 10 episodes of fibrillation-defibrillation (2.5 ± 1 episode/heart), the APD_{50} shortened from 180 ± 9 ms to 139 ± 32 ms ($P=0.0059$), while the APD_{80} shortened from 210 ± 12 ms to 171 ± 20 ms ($P=0.001$) (baseline

vs. after the shock). Shock had no influence on the AP amplitude (104 ± 5 mV vs. 101 ± 9 mV, $P = \text{NS}$). The preceding RR intervals of these measurements were 560 ± 99 ms for baseline and 795 ± 329 ms for postshock measurements. In addition, there was evidence of delayed repolarization (blue arrows) and Vm oscillations that resemble delayed afterdepolarizations (DADs, red arrows) on these recordings. The Vm oscillations occurred either immediately postshock (Panel C) or after a blocked premature atrial contraction (PAC, Panel D). The TMP on the right of Panels C and D show overlapping tracings between beats b and c, and between beats d and e, respectively. These overlapping tracings show that the APD is longer in beat b than in beat c, and in beat e than in beat d.

Discussion

We documented acute transient APD shortening after fibrillation-defibrillation episodes in failing, but not normal or sham, rabbit hearts. APD shortening was associated with persistent Ca_i elevation during late phase 3 and/or phase 4 of the action potential and recurrent SVF. Single cell TMP recordings confirmed postshock APD shortening and afterdepolarizations in the failing hearts. These findings indicate that APD shortening and persistent postshock Ca_i elevation can be a mechanism of postshock SVF.

Shortening of APD and Recurrent SVF

Recurrent SVF after initial successful defibrillation is a well recognized phenomenon that may occur in both ischemic and non-ischemic heart diseases, and carries with it a poor prognosis.^{13,14} A major finding of this study is significant APD shortening after successful defibrillation in failing hearts, leading to SVF. The mechanism of acute APD shortening after fibrillation/defibrillation is unclear, but is probably multifactorial. Metabolism is abnormal in heart failure¹⁵ and a possible contributing factor is slower metabolic recovery after defibrillation, leading to activation of ATP-sensitive K current (I_{KAT})¹⁶ and transient shortening of APD. While it is possible that transient K_{ATP} activation played a role in the acute postshock APD shortening, persistent and irreversible ischemia or hypoxia after defibrillation in failing hearts, however, was unlikely to account for APD shortening. There was no change in AP amplitude during APD shortening and that there was gradual lengthening of APD during the sinus rhythm after termination of VF.

Mechanisms of Spontaneous Reinitiation of VF

The most likely mechanism for the first beat of SVF is late phase 3 EADs or DADs. Because Ca_iTD did not shorten proportionately to APD, persistently elevated Ca_i during phase 3 and phase 4 of the AP may promote afterdepolarizations via I_{NCX} (forward mode). The hearts with SVF had greater APD shortening than the ones without SVF. This finding further strengthens the conclusion that acute APD shortening and persistent Ca_i elevation may be causally related to the recurrences of SVF episodes. The involvement of afterdepolarization in the SVF is strengthened by the findings of TMP recordings, which confirmed postshock APD shortening and the emergence of afterdepolarizations in the postshock period in the failing hearts. As compared with known-mechanisms of triggered activity related to APD prolongation (EAD) and spontaneous SR Ca release (DAD),⁵ acute APD shortening and persistent Ca_i elevation may be a new mechanism of SVF initiation in the failing hearts.

Clinical Implications

The mechanisms of arrhythmogenesis in HF are usually attributable to APD prolongation, but it has recently been recognized that APD shortening can also promote arrhythmias in various “short QT” syndromes. We present evidence for the first time that acute transient APD shortening and persistent phase 3 or phase 4 Ca_i elevation is a mechanism for postshock SVF in HF. While these findings are most relevant to the clustering of tachyarrhythmia in patients

with HF, the same mechanisms might account for recurrent SVF in out-of-hospital cardiac arrest¹³ when APD is acutely shortened by myocardial ischemia.

Limitations

Since we were not able to predict the location of earliest activation in SVF, it was not possible to place a microelectrode at that site to record triggered activity. The absence of triggered activity by TMP recording is a limitation of the study. Yang et al¹⁷ previously reported that cytochalasin D lengthens APD in cells from hypertrophied rat ventricular cells by inhibition of I_{to} , which is a major repolarizing current for rat ventricular myocytes. It is possible that the use of cytochalasin D has affected the results of the study. However, a reduction of I_{to} cannot be used to explain APD shortening after shock. We do not think the use of cytochalasin D can explain the results of the present study.

Acknowledgements

This study was supported by the NIH Grants P01 HL78931, R01 HL78932, 58533, 71140, American Heart Association Grant-in-Aid, Western States Affiliate (0255937Y and 0555057Y), National Scientist Development Grant (0335308N), Established Investigator Award (#0540093N), Kawata, Laubisch, Price and Medtronic-Zipes Endowments, and a Chun Hwang Fellowship for Cardiac Arrhythmia Honoring Dr Asher Kimchi, Los Angeles, Calif. We thank Stephanie Plummer, Avile McCullen, Lei Lin and Elaine Lebowitz for their assistance, and Dr Xiaohong Zhou of Medtronic Inc. for providing the pacing system used in this study.

Abbreviations and Acronyms

APD, action potential duration
 Ca_i , intracellular calcium
 Ca_iTD , intracellular calcium transient duration
DAD, delayed afterdepolarization
EAD, early afterdepolarization
 $\bar{F}$, The average fluorescence level
HF, heart failure
SR, sarcoplasmic reticulum
SRm, sinus rhythm
SVF, spontaneous ventricular fibrillation
SVT, spontaneous ventricular tachycardia
TMP, single cell transmembrane potential
VF, ventricular fibrillation
 V_m , membrane potential

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Figure 1.

Action potential duration (APD) and Ca_i transient duration (Ca_iTD) in normal and failing hearts. The measurements were made during sinus rhythm in 4 normal and 11 failing hearts. Averages of the 3 APDs and Ca_iTDs were used as APD and Ca_iTDs for that site, respectively. The gradient is calculated by values maximal dispersion between LV base and apex.

Figure 2.

Ratio maps of APD and Ca_iTD in normal and failing hearts during sinus rhythm. The onset of action potential was used as time zero. The failing heart repolarized later than the normal hearts (red arrow).

Figure 3.

VF storm in a failing heart. There were a total of 7 episodes of SVF within 20 min after initial successful defibrillation. A shows continuous recording of pseudo-ECG. B shows baseline Vm (white line) and Ca_i (yellow line) recordings. C and D show Vm and Ca_i at termination and at the onset of SVF, respectively. Note the presence of short APD in the immediate postshock period (C) and that the first ectopic beat that initiated VF occurred from late phase 3 of the preceding action potential (D). The tracings in red boxes in panels B-D are also shown in Panel E, which highlights the Vm and Ca_i changes at different time points during the study. There was transient shortening of APD and to the lesser extent Ca_iTD after defibrillation. F shows the measurements of APD and Ca_iTD, showing the transient nature of these changes. The time points b and c are marked as Eb and Ec, respectively, in Panel A. The time points a and d are from baseline and 31 min after the last episode of SVF, respectively. The time point d is outside of the range and is not part of the figure.

Figure 4.

No acute APD shortening after successful defibrillation of 6 pacing-induced VF episodes in normal hearts. No SVF episodes occurred after defibrillation. A shows continuous recording of pseudo-ECG. B shows baseline V_m (white line) and Ca_i (yellow line) recordings. C shows the optical recordings after termination of pacing-induced VF. The tracings in red boxes in panels B-C are also shown in Panel D, which highlights the V_m and Ca_i changes at different time points during the study. There was no change of APD and Ca_iTD in spite of multiple attempts of rapid pacing to induce VF. E shows the measurements of APD and Ca_iTD , showing no changes of APD and Ca_iTD .

Figure 5.
The ratio map of the first postshock sinus beat. The HF hearts had a shorter APD and Ca_i transient duration than the normal hearts.

Figure 6.

Two episodes of spontaneous VF in a failing heart (same as that shown in Figure 3). A shows short APD and the first VF beat arising from late phase 3. Subsequent epicardial wavebreak lead to VF. B shows short APD, persistent Ca_i elevation and the first beat of VF arising from phase 4. The panel marked as “LV Anterior Base” shows the earliest sites of activation (asterisks) of beats 1, 2, and 3 in A and the first beat in B. The color panels correspond to the optical recordings shown in A and B directly above. C shows representative optical signals of V_m at the sites marked by dotted lines in the ratio maps above.

Figure 7. Delayed repolarization and Vm oscillation documented by single cell recordings using standard glass microelectrodes. A shows simultaneous continuous pseudo ECG (P-ECG) and TMP recordings. Pacing at 100 ms cycle length (CL) (black arrow) induced sustained VF, which was electrically converted to sinus rhythm 5 min later. B, C and D show the recordings immediately before VF induction, immediately after termination of VF and 1 min after successful defibrillation, respectively. Stable impalement was documented by the stable diastolic potential shown in Panel A.