Ventricular fibrillation in myopathic human hearts: mechanistic insights from in vivo global endocardial and epicardial mapping

Stéphane Massé, Eugene Downar, Vijay Chauhan, Elias Sevaptsidis, and Kumaraswamy Nanthakumar

Division of Cardiology, Department of Medicine, University of Toronto, Toronto, Canada

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METHODS

Protocol. This protocol was approved by the University Health Network Review Board and written informed consent was obtained from all patients before this study. The data used in this analysis were obtained from patients who were undergoing intraoperative ventricular tachycardia (VT) mapping during surgery and intraoperative VT mapping during Tetralogy of Fallot corrective surgery. After the heart had been placed on bypass, before instituting cold cardioplegia, we studied VF episodes that occurred during VT induction. The method used to induce was a rapid burst pacing as fast as 200 ms. The first few seconds of induced VF was usually polymorphic VT in appearance, which then degenerates to sustained, disorganized VF. The segments analysed were 1 s after the onset of VF.

IN PATIENTS WITH CARDIOMYOPATHY, ventricular fibrillation (VF) is an important etiology of sudden cardiac death (1, 11). Recent publications suggest significant spatiotemporal organization of VF in small (6, 13, 26) and large (9, 10, 37) animal hearts. Studies from small animal hearts posit that stable dominant rotors generating wavefronts, which conduct to other regions with intermittent conduction block, are responsible for the spatiotemporal organization (6, 26). However, in studies of large-animal in vivo hearts, using electrical mapping, evidence for sustained rotors on the epicardium has been lacking (17, 25).

One of the main analyses done by groups who have demonstrated rotors as the source of spatiotemporal organization of VF is the presentation of spatial activity in terms of the phase of oscillation (10) and the spatial distribution of dominant frequencies (DFs) throughout the preparation (6, 26). Their approach allows the core of a rotor to be identified as a phase singularity, around which a continuous progression of phase covering an entire cycle ($\pm 2\pi$) can be observed (10). A recent publication using the above phase singularity analysis on epicardial mapping data from patients with preserved ventricular function suggested that multiple mechanisms are responsible for the organization of electrical activity in VF (18). That study did not evaluate the endocardial surface or address the issue of the role of rotors in relation to multiple reentrant wavefronts (12). Most importantly, the mechanism of the organization of electrical activity in early VF is unknown in myopathic human hearts.

In myopathic human hearts, early VF wavefronts reveal significant organization and have been shown to repeatedly follow a few distinct pathways and traverse large areas on the endocardium (30) and epicardium (16). The source of this organization and its relationship to rotors in human VF are unknown. If the prediction that rotor activity is responsible for organization of electrical wavefronts in human VF, then, minimally, there have to be rotors that erupt on the epicardium or endocardium when the filament of the rotor attaches in these regions. There should be centrifugal activation from the core of the rotors to other regions of the myocardium. These rotors should colocalize to spatial domains in the human heart that activate faster than other slower domains and demonstrate intermittent block, resulting in fibrillatory conduction. Alternatively, if the rotors are transient and multiple or meandering rapidly between the epicardial, endocardial, and transmural regions, it would not be possible to demonstrate their relationship to spatiotemporal organization in human VF. We tested these predictions in the in vivo human myopathic heart during VF while mapping globally on the epicardium and endocardium during cardiopulmonary bypass.
Mapping tools. The electrode arrays construction and mapping system has been described previously (27). Figure 1A shows how the electrode arrays were deployed in the left and right ventricles. Each array is made of 112 bipolar electrodes (each represented here as a gray sphere) stitched on the exterior surface of an extensible balloon. The balloons are deflated during insertion and then gently inflated until the electrodes make contact. Each endocardial electrode consists of two silver beads (2 mm diameter) separated by 2.1 mm center to center. In Fig. 1B, the epicardial sock electrode array is also shown. Like the balloon electrode arrays, the sock is made of 112 bipolar electrodes organized in 14 rows of eight electrodes each, mounted on an extensible mesh. Simultaneous unipolar and bipolar electrograms were recorded from all electrodes. Unipolar signals were used for the frequency and phase singularity analysis, whereas bipolar signals were used to assess scar locations. Because these mapping arrays were clinical mapping tools, it was ensured that all 112 electrodes were functional with no broken electrodes.

To represent these electrode arrays in two dimensions, polar maps are used. Because they both exhibit axial symmetry, the sock and the left ventricular (LV) balloon are portrayed using a polar display, which shows the apex of the heart in the center and the base forming a circle at the edge of the display. Both maps are seen from an observer located at the apex of the heart looking up to the patient’s head. The electrode naming convention includes the row number and the position of each electrode within the row. Row numbers start from the left anterior descending artery (LAD) clockwise, while the electrode coordinate within the row starts from the base toward apex. The electrode naming convention includes the row number and the number of rotations completed by the rotors were computed from the phase maps. Cycle length was defined as the duration taken by the wavefront attached to the phase singularity to turn 360°.

DF mapping. Previous publications have described the use of DF mapping to assess domains on the epicardium (22). We use maximum DF as an estimate of VF cycle length. For the analysis, a two-dimensional power spectral density was estimated using the Welch averaged modified periodogram performed on the electrograms with a frequency resolution of 0.25 Hz. A DF corresponding to the highest peak in the power spectrum in the range of 3–9 Hz was determined for each signal.

Conduction block mapping. We also performed an analysis to evaluate the amount of block in the heart by looking at the double peaks of the fast Fourier transform as originally described by Evans et al. (8). This technique has been subsequently validated in multiple models for detection of conduction block in VF (19, 20). Briefly, the occurrence of double peaks, an estimate of conduction block, was identified at a time point if a secondary peak was present in the power spectrum that was within a maximum separation of 80% of the dominant (highest) peak frequency and that had an amplitude of at least 50% of the amplitude of the dominant peak.

Scar localization. Scar location was determined by assessing bipolar electrogram amplitude. Bipolar signals were recorded at 2-K samples/s with filter settings of 28–700 Hz. We mapped rotor locale in relation to regions with bipolar electrogram amplitude of <0.5mV.

Data acquisition and analysis. A recent publication described in detail the data processing in preparation for creating phase loops for the analysis described below (18). The filter settings for unipolar signals were set to 0.5–200 Hz, and the sampling rate was 1-K samples/s. After data acquisition, all electrograms were low-pass filtered at 60 Hz using a 112th-order FIR equiripple filter and then downsampled to 125 Hz. Each electrogram was then detrended using a technique described by Bray and Wikswo (5). A 120 × 120 grid of interpolated electrograms was constructed by using triangle-based cubic interpolation of the detrended electrograms. This technique ensured that the interpolated surface always passed through all data points with no discontinuities in the first and zero derivatives. The results of this processing gave a series of 120 × 120 pixel frames, each representing 8 ms of data.

Phase singularities and rotors. The technique of using contact electrode VF mapping data for creating phase loops and determining rotors is described in detail (18). We used this technique described in human VF signals obtained from contact extracellular mapping (18) on our signals obtained in a similar manner. Briefly, the unique time course of an excitable element in cardiac tissue can be represented as the phase of its trajectory in state space (10). Phase singularity was defined as a site with ambiguous phase while its neighboring pixels exhibited a continuous progression of phase from $-\pi$ to $+\pi$. The grid of virtual electrograms was processed using the Hilbert transform as described by Bray and Wikswo (5) to generate two sets of independent orthogonal signals. The original electrograms and corresponding phase-delayed signals were used to generate phase maps, also constructed in 120 × 120-point grids. These phase maps were then analyzed for locating phase singularity points. Rotors were defined as described by Kay et al. (14), waves that circulate around the region of a phase singularity and turn for more than 360° (14). The cycle length and the number of rotations completed by the rotors were computed from the phase maps. Cycle length was defined as the duration taken by the wavefront attached to the phase singularity to turn 360°.

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RESULTS

Patients. We studied 7 ± 4 s of early VF in vivo in myopathic patients simultaneously on the epicardium and endocardium in LV cardiomyopathy (n = 3) and the endocardium in right ventricular (RV) myopathy (n = 2). Patients 1 and 2 had RV myopathy secondary to Tetralogy of Fallot. They both had moderate to severe RV dysfunction. Patients 3, 4, and 5 all had ischemic cardiomyopathy with severe LV dysfunction due to previous anterior infarct. Patients 2 and 3 at the time of mapping were taking amiodarone. None of the other patients were taking antiarrhythmics.

Rotor organization. Using the technique of tracking singularity points, we identified rotors in all of the myopathic hearts studied during VF. The rotors cumulatively lasted a mean of 3.2 ± 2.0 s of the 7 ± 4 s of the VF segments analyzed. For each surface mapped, 3.6 ± 2.9 rotors were identified for the duration mapped. The average number of cycles completed by these rotors was 4.9 ± 4.9. The longest rotor lasted 10.2 ± 6.2 rotations and lasted 2.0 ± 1.2 s. When the rotors were present in pairs, they always rotated with opposite chirality. In the five hearts studied in endocardial episodes, rotors were present for 61 ± 25% of the time period compared with 27 ± 24% of the epicardial episodes (P = 0.10). The rotors on the endocardium had a cycle length of 192 ± 33 ms compared with the epicardium 220 ± 15 ms (P = 0.08). To evaluate the relationship between scarred myocardium and zones of anchoring of phase singularities, we analyzed myocardial locations with low-amplitude bipolar electrograms. Most of the regions...
mapped with infarction by the echocardiography and the electrocardiographic information had decreased bipolar voltage (0.5 mV) in amplitude. However, regions of low voltage were found in other regions using bipolar electrogram criteria. In four out of five patients, the sustained rotors colocalized to border zones adjacent to the areas of low-amplitude electrograms.

Rotor activity and resultant wavefronts. Figure 3A shows a series of snapshots of the rotors in VF that were found on the endocardium in the first patient with RV myopathy. Two rotors of opposite chirality were identified (supplementary video 1; please refer to the online version of this article for links to all the supplementary videos). A core of a rotor can also be identified by representing the phase of the oscillation in a time versus space plot (frame stack plot). Specific branches of relatively low amplitude that occur in the center of a time-space plot that occurs twice each cycle are the core of a rotor (22). Figure 3B illustrates one of the rotors as shown in a frame stack plot. This plot elegantly reveals six revolutions of the rotor, the cycle length of the rotor, and the slight meander of the rotor toward the point marked X1. Most importantly, Fig. 3B illustrates that the activation from the core spreads toward X1 and X2. This suggests that the myocardial segment X1 to X2 is under the direct influence of this rotor. The cycle length was 168 ms, and it lasted 2.6 s. The longest rotor in this patient lasted for 17 revolutions, and rotors cumulatively lasted 84% of the duration mapped.

Figure 4A (supplementary video 2) reveals snapshots of two rotors with opposite chirality that were visualized on the endocardium of the second patient with RV myopathy. These rotors had five rotations and had a cycle length of 144 ms. Figure 4B reveals a frame stack plot that illustrates the presence of the cores of the rotors. The figure shows that of the five activations, only three reached the myocardial point X2 and the presence of block in the activation band, illustrating intermittent block in conduction away from the rotor. Cumulatively, rotors were present in this patient for 44% of the duration mapped.

In patients with ischemic cardiomyopathy, the LV endocardium and all of the epicardium (RV and LV) were mapped simultaneously. A segment of VF from patient 3 is shown in Fig. 5. The segments were recorded simultaneously on a single spline over the LV free wall. The endocardial segments show organized wavefronts, whereas the simultaneous epicardial wavefronts show disorganization. Figure 6 shows a longer recording of this episode with corresponding phase maps. Initially, it shows the surface electrocardiogram, demonstrating slow VF (type 2) that transitions to fast VF (type 1) (35). A series of snapshots of the rotor on the epicardium reveals a stable rotor on the epicardium with a cycle length of
256 ms. Simultaneous mapping on the LV endocardium during the slow VF (type 2) shows one rotor with a faster rotational speed of only 200 ms (Fig. 6A and supplementary video 3). During the fast VF (type 1), there are no visible rotors evident on the epicardium. However, although the global epicardial mapping did not show any rotors and demonstrates multiple waves that are disorganized, there was a rotor on the endocardium with organized wavefronts with a rotational speed of 208 ms that lasted 416 ms (Fig. 6A and supplementary video 4). This explains the difference in organization seen between the epicardium and endocardium in this patient shown in Fig. 5.

In the fourth patient with ischemic cardiomyopathy, the endocardium revealed rotors that cumulatively lasted 36% of the duration mapped, whereas the epicardium revealed rotors that cumulatively lasted 32% of the duration mapped (9 s). In the fifth patient with ischemic cardiomyopathy, we could not identify any rotor on the epicardium, whereas the endocardium revealed rotors that cumulatively lasted 92% of the duration mapped (2.2 s).

Rotors, frequency domains, and conduction block. When rotors tend to cluster at a spatial domain and there is block to activation away from them, DF maps revealed domains of fast and slow activation. Figure 7A demonstrates an example of this from patient 2. The DF maps show domains with different activation rates. The faster region corresponds with the area of rotor shown in Fig. 4A, and the slower activating area corresponds to myocardial segment X2, as shown in Fig. 4B to where only three of the five activation bands propagated. This further illustrates the concept of centrifugal activation with intermittent block to neighboring myocardial segments. The double peaks in the power spectra shown in Fig. 6A illustrate that faster domains are separated from slower domains by zones of block.

An example from a patient with ischemic cardiomyopathy, as shown in Fig. 7B (patient 4), shows that the region of highest DF on the endocardium is centered in the region where the phase singularity anchored. The slower domain is separated by a zone of block in the corresponding power spectra. However, as seen in the rotor in Fig. 3, when there is no block to the activation band from the core of a rotor, DF analysis reveals power spectra with no double peaks and the absence of domains, as illustrated in Fig. 7C.

**DISCUSSION**

We have demonstrated for the first time that the organization of electrical activity on the endocardium and epicardium during early VF in myopathic human hearts is characterized by wavefronts emanating from a few rotors. There is centrifugal
activation of electrical activity from these rotors, and they give rise to domains that activate at faster rates with evidence of conduction block at the border with slower domains. When the rotors are not spatially clustered, their relationship to the organization in human VF cannot be established. The endocardial mapping in addition to the epicardial mapping allowed us to identify rotors that otherwise might have been missed by limited epicardial mapping.

Nanthakumar et al. (17) previously demonstrated that VF wavefronts are large on the epicardium and repeatedly follow only a few different pathways. Those findings were consistent with endocardial data of Walcott et al. (30), who reported VF

Fig. 5. Simultaneous local epicardial and endocardial electrograms during VF. A: a series of electrogram on the LV free wall epicardium with data presented as frame stack plots showing disorganization of electrical activity on the epicardium. B: a series of electrogram on the LV free wall endocardium with data presented as frame stack plots showing organization of electrical activity on the endocardium with repeating wavefronts.

Fig. 6. Simultaneous global epicardial and endocardial phase maps during VF. Surface ECG lead 1 reveals organized VF that disorganizes. A: a series of snapshots during the organized phase of the VF reveals 2 relatively stable counterrotating rotors anchored on the LV epicardium and 1 rotor on the endocardium rotating at higher speed than the epicardial rotor. B: simultaneous mapping of the LV endocardium and the epicardium of the same episode during the disorganized portion of the VF shows the continuing presence of the same endocardial rotor but absence of rotors on the epicardium.
wavefronts traveled, on average, 6 to 9 cm along a line of electrodes 4 mm apart on a catheter within the LV cavity. The source of these organized wavefronts that repeat themselves in similar pathways could not be explained by those studies, as both of those human studies only mapped a limited region (17, 30). It is, however, explained by the current study that globally mapped the endocardium and epicardium to reveal that rotor activity and repeated wavefronts emanate from it. Our study in humans is consistent with recent studies in animal models of heart failure that suggest that dominant sources that are endocardial or intramural are seen during VF in myopathic animal hearts (9, 29). In the hearts studied, there was a trend toward the presence of faster rotors and rotors that lasted longer on the endocardium compared with on the epicardium. We do not have adequate episodes to make definitive statements regarding these observations, since these findings did not reach statistical significance.

Witkowski et al. (32) studied normal explanted dog hearts and mapped 30% of the epicardium and came to the conclusion that rotors erupt transiently in early VF, and, as time progresses, rotor physiology is absent and is replaced by multiple reentrant waves. This leaves the possibility of rotor physiology in one region and fibrillatory conduction in another, which would appear as multiple reentrant waves. VF has also been classified as multiple reentrant-appearing VF and rotor-dominated VF (33). Figure 5 in our study suggests that these two mechanisms may coexist. Indeed, the endocardium reveals rotor-dominated VF, whereas the epicardium demonstrates multiple reentrant-like VF. In this study we do show that the waves are centrifugally activated from the phase singularity point or the anchoring point of the rotor. The fact that there are domains and evidence of block suggests that activation away results in fibrillatory conduction in other areas and is consistent with theoretical models and perfused heart models.

A recent study using similar global mapping technique only on the epicardium in patients with preserved ventricular function in the intraoperative setting found a low number of phase singularities (18). Our study in myopathic hearts including the

Fig. 7. Frequency domains during VF. A: the dominant frequency map corresponding to Fig. 1A with domains exhibiting different activation rates are shown, along with power spectrum of selected electrograms and the recorded unipolar electrograms showing areas of fast and slow activation (1 and 2) with border showing conduction block (3). B: an example from a patient with ischemic cardiomyopathy on the endocardium shows the region of maximum dominant frequency (DF max) is centred in the region where the phase singularity was anchored (1). The slower domain adjacent is shown (2) with the area in between showing conduction block (3). C: the dominant frequency map corresponding to Fig. 1B does not reveal significant domains that are fast and slow (1 and 2) when there is no conduction block present. FFT, fast Fourier transform.
endocardium found a few rotors during early VF consistent with their findings in normal hearts. The findings of our study are relevant to the clinical problem of sudden cardiac death, especially because they were made in hearts of cardiomyopathic patients where VF is a common cause of demise (1, 11). These mechanistic findings in humans in vivo are consistent with theoretical models that suggest the mechanistic notion that sources of rapid rotor activation exhibiting conduction block are responsible for the spatiotemporal organization in early VF in myopathic human hearts (7, 28). Most importantly, a demonstration of these rotors in human VF has therapeutic implications for targeted delivery of energy and application of low-energy electrical fields to modulate these rotors (3, 4) and thus VF.

Wu et al. (34) studied explanted hearts from transplant recipients and identified reentry for all episodes of VF. That study had the luxury of performing detailed pathological analysis since they were explanted hearts. In our case, since these patients were alive, we could not perform such analysis. However, using local bipolar electrogram criteria of scar localization, we found that the sustained rotors frequently localized to regions adjacent to the regions of low-bipolar electrogram amplitudes. However, the reverse was not true. All border regions were not the sites of rotor formation. The role of border zones has been investigated by others and has been found to play a significant role in wavebreak in VF (21, 36). Additionally, ablation of these border zones has been shown to have therapeutic implication in patients with ischemic cardiomyopathy and VF that are preceded by trigger beats (15).

Purkinje muscle junction is thought to play an important part in early VF and rotor formation (2). As time progresses in VF, it is thought that the Purkinje muscle junction is not vital for rotor stabilization. We were unable to record Purkinje potentials and thus investigate this possibility in early human VF. Although we related the vascular structures of LAD and posterior descending artery, to the mapping tool, we were unable to verify papillary muscle location on our mapping tools. It is difficult in the intraoperative setting where there is a risk of entrapping the mapping tool in the chordae to consistently localize intracavitary structures. Thus the possibility that the rotors anchored at the base of the papillary muscle was not excluded (35). Physiological reasons for rotor localization in these cardiomyopathy hearts need to be explored. It is quite plausible that differential downregulation of inward rectifier K⁺ current may provide a mechanistic reason for rotor formation (31).

Using plunge needle electrodes inserted within the myocardium during intraoperative setting, in severely myopathic human myocardium due to nonischemic-dilated cardiomyopathy, Pogwizd et al. (23) have demonstrated that focal mechanisms may also be responsible for spontaneous ventricular arrhythmias. In a feline ischemic, nonmyopathic model, Pogwizd and Corr (24) had demonstrated that VF may be mediated by mechanisms that could be reentrant or focal. Although our study deals with reentry as a mechanism of organization in early in vivo VF induced by burst pacing, whether it reflects mechanism of organization during VF induced by spontaneous rapid ectopic beats of myopathic patients is not resolved by this work.

In conclusion, the organization of electrical activity during early VF in myopathic human hearts is characterized by wavefronts emanating from a few rotors. These rotors frequently localized to border regions of myocardium with bipolar electrogram amplitude of <0.5 mV.

Limitations. The study consists of mapped intervals lasting 7 s each. Given this limitation, the role of rotors as a source of organization during prolonged periods of VF is unclear. Studying longer episodes of VF in humans in vivo is ethically problematic and probably best evaluated in a Langendorff model. It leaves the possibility that different mechanisms can be responsible during different phases of VF. However, the time frame analyzed is clinically relevant since it is the time frame in which interventions may prevent further progression. Since transmural diffusion is slower than diffusion along the epicardial and endocardial surfaces, the presence and behavior of phase singularities and rotors may be different in the transmural region compared with the epicardium or endocardium. However, it is also not practical or ethical to map the entire in vivo human heart, especially the intramural regions during VF. VF induced by burst pacing may not reflect clinically occurring VF and may be mechanistically different; however, mapping spontaneous VF is not possible. We were presented with the unique opportunity of comparing endo- and epicardial phase singularities recorded at the opposite surfaces. However, the placement of the mapping balloon through the mitral apparatus is risky, and we could not ensure alignment of endocardial electrodes to the epicardial electrodes. For this reason we do not feel confident in making observations on whether the rotors were related or independent.

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