Wave similarity of human ventricular fibrillation from bipolar electrograms

Stephane Masse, Eugene Downar, Vijay Chauhan, Elias Sevaptidis, and Kumaraswamy Nanthakumar

University of Toronto, Toronto, Canada

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Aims: The aim of this report was to review existing techniques for assessment of directionality in fibrillation and to describe the concept of wave similarity analysis in human VF.

Methods: We applied a technique called wave similarity analysis to bipolar electrograms to study directionality during various rhythms (sinus rhythm, ventricular tachycardia and ventricular fibrillation) in humans. This technique uses the barycentre to determine the activation time and a similarity index is calculated using a technique described previously for AF studies.

Results: We show here that using the wave similarity concept it is possible to recognize myocardial regions that are activated from multiple directions and differentiate those areas from regions that are activated by wave fronts in similar direction or at the exact mirror angle in ventricular fibrillation.

Conclusions: Wave similarity analysis provides a tool for assessing directional organization in human VF. This analysis of directional organization may have implications for the study of mechanisms of VF in the clinical arena.

KEYWORDS
Ventricular fibrillation; Bipolar electrograms; Directionality

Introduction

The dominant source hypothesis suggests that a dominant rotor present in one region in the ventricle is responsible for the maintenance of ventricular fibrillation (VF) in other parts of the ventricle. It follows that the wavefronts that emanate from that dominant source are responsible for activation away from the dominant source, with fibrillatory conduction at a distance from the dominant source. Adjacent to the dominant source, the directionality of the wavefronts would be stable and constant, compared with away from the source where fibrillatory conduction is occurring. Thus the directional assessment takes on a practical significance as it would be a valuable tool to study mechanisms of VF in the clinical arena. As directional assessment in fibrillation is a complex topic, by way of introduction, we review in detail techniques used by various investigators, which are indirect and direct assessments of directionality in VF, and introduce a concept to assess temporal evolution of directional organization at a bipolar electrode site during VF.

Previous methods

Dominant frequency gradient mapping

In the landmark papers that developed the idea of dominant source in recent times, Jalife and coworkers have used activation rate mapping to show that the dominant rotor co-localized with the areas of highest activation rate. The anterior LV, where the stable mother rotor was identified in the guinea pig, demonstrated the highest activation rate, as shown by its dominant frequency (DF) using fast Fourier transform (FFT) analysis. Away from the dominant source, the activation rate was decreased, demonstrating a gradient in activation rates, which suggested that the activation spread from the dominant source with conduction block and slower activation away from the dominant source.

Jalife and coworkers demonstrated with simultaneous endocardial and epicardial optical mapping in sheep atrium that pacing at increasingly higher frequencies (2.0–6.0 Hz) led to increasing delays in activation distal to major branching sites of the crista terminalis and pectinate bundles, culminating in spatially distributed intermittent blockade at or above ~6.5 Hz. At this 'breakdown frequency,' the direction of right atrium (RA) propagation became completely variable from beat to beat and thus was transformed into fibrillatory conduction. In addition, this group demonstrated that directionality in fibrillation has practical implication by showing that ablating the Bachman’s bundle resulted in...
decrease in activation rate in the RA, whereas the activation rate in the left atrium (LA) did not change.\(^4\)

Chen and coworkers\(^5,6\) have shown from DF mapping in rabbits that the mother rotor anchors to the base of the papillary muscle with conduction away from it. DF mapping using FFT in models where there is a stable dominant source may provide assessment of directionality. This evidence is indirect in nature and is ascertained from gradients in the DF.

**Wavefront centroid tracking**

Rogers et al.\(^7,8\) developed a computerized technique for analysing and quantifying VF activation patterns. By grouping together active samples (electrodes with \(\Delta V/\Delta t > -0.5\) V/s) that were adjacent in space and time, individual wavefronts can be isolated. Nanthakumar et al.\(^9\) using this technique calculated the directionality of VF from the propagation velocity of each wavefront on the porcine left ventricle (LV) epicardium. The wavefront velocity was estimated by computing the location of the centroid of the wavefront at each time point. The ratios for the basal edge adjacent to the AV groove and the apical edge adjacent to the LV apex were not statistically different from 1.\(^9\) These observations are consistent with the directionality of the velocity vector calculated by centroid tracking of the wavefront, pointing from the posterior to the anterior LV and both findings indicate a significant trend for VF wavefronts to enter the mapped region from the posterior border of the mapped region and to propagate towards the anterior border.

**Unipolar vector method**

Ideker and coworkers\(^11\) introduced an automated method to estimate vector fields of propagation velocity from observed epicardial extracellular potentials. Using data from a 528 unipolar electrode array sutured to the right ventricular epicardium during sinus rhythm and pacing, the technique was validated and then applied to VF in pigs. This method relies on fitting polynomial surfaces \(T(x, y)\) to the space–time \((x, y, t)\) coordinates of activity. This technique allows calculation of speed and direction of propagation from the gradient of the local polynomial surface. Using this technique, Bayly et al.\(^12\) estimated the conduction velocity at multiple epicardial locations during VF and displayed it as vector fields.

**Derived bipolar vector method**

Kadish and coworkers\(^13–19\) extensively investigated directional assessment in activation using vector loops. They employed a technique using vector loop, which is created by summing two orthogonal bipolar electrograms (representing the x and y axes). The direction of the maximum vector of a given vector loop in that technique represented the direction of local activation in cardiac tissue.\(^13–15\) Orthogonal bipolar electrograms were derived by summing orthogonal unipolar electrodes in groups of four.\(^13\) In this technique, the specific inter-electrode distance and cathodal and anodal orientations of the grid of mapping electrodes have to be known. Kadish and coworkers\(^16–18\) showed that this concept can be used in VF and applied it to characterize VF patterns in various situations. However, in cases where there are complex local activation patterns, a common situation in fibrillation, this technique may not adequately represent the complexity in directionality.\(^16\)

Kadish et al.\(^19\) furthered this technique such that it requires recording from only four simultaneously unipolar electrodes in the ensemble vector index (EVI) method. In general, the advantage of this technique relates to the fact that it does not require assignment of activation times. In the EVI technique, although multiple sites can be analysed, only four unipolar recordings are required to construct the EVI.

**Wave similarity assessment on bipolar VF electrograms**

Electrical mapping of VF has mostly been performed with unipolar electrodes. This is mainly due to the presumed random nature of activation and the complexity of local
bipolar electrograms in VF. A rapid technique that would allow for directional assessment from a set of dipoles that are not part of a rigid mapping grid could be of clinical use.

The proof of concept of the technique detailed below is adapted from a technique described by Faes et al.\textsuperscript{20} The basic tenet behind this technique is that if a dipole were to record a wavefront that activated in the same direction, the bipolar electrogram inscribed by it would be morphologically similar in nature. Thus, at the heart of this technique is a template-matching system that matches the template of the bipolar electrogram with the electrograms activating the same dipole over time. This provides a temporal evolution of directionality. Ravelli \textit{et al.}\textsuperscript{21} used this technique in atrial fibrillation data acquired from a basket catheter recently, and concluded that quantification of spatiotemporal distribution is feasible in atrial fibrillation.

The data used in our proof concept exercise were obtained from 112 bipolar electrograms from an LV endocardial balloon used in patients who were undergoing intraoperative VT mapping during aneurysctomy surgery. In these patients, we tested the wave similarity assessment for sinus rhythm and VT with known directional activation and applied it to VF.

**Proof of concept of wave similarity assessment**

**Method**

Electrograms were recorded with a mapping system described previously at a sampling rate of 2 kHz\textsuperscript{22} and a band-pass filter of 28–400 Hz, in order to eliminate baseline shifts and high-frequency noise. Each bipolar electrode was made with two 2 mm diameter silver beads with a centre-to-centre distance of 2 mm. The ventricular waveforms were then detected by threshold crossing of the first negative derivative of the electrograms. To avoid multiple detection on a single waveform, a blanking period of 80 ms was used. After automated detection was performed, the waveforms were manually confirmed. Once these ventricular complexes were identified, their activation times were estimated by calculating the barycentre of the waveform, as described by Faes \textit{et al.}\textsuperscript{20} using slightly longer window length (100 ms instead of 90 ms). The barycentre is defined as the time that divides in two equal parts the length (100 ms instead of 90 ms). The barycentre is found on the positive zero crossing of the waveform. It is acceptable to assume in normal sinus rhythm that a dipole formed by the electrodes or electrode contact variation. After normalization, each LAW was used to define the activation time for that waveform. LAWs were then normalized to take into account waveform orientation respective to the the bipolar electrograms recorded from two different locations on the LV endocardium in normal sinus rhythm. The corresponding isolated activation waves are superimposed and their respective regularity indexes tend to 0. Recordings used for this study were selected from data obtained during intraoperative mapping. The recordings chosen for the similarity analysis had an average duration of 5 ± 1 s. The number of waveforms used to calculate the similarity index varied between 6 and 30 per electrogram, depending on the heart rate.

**Sinus rhythm**

It is acceptable to assume in normal sinus rhythm that a location within the LV would be activated repeatedly in a similar direction. Thus the regularity index at this location would be high and would be close to 1. Figure 1B shows the the bipolar electrograms recorded from two different locations on the LV endocardium in normal sinus rhythm. The corresponding isolated activation waves are superimposed and their respective regularity indexes are shown in Figure 1C. Both bipolar electrode signals show regular and repetitive waveforms and the activation waves are well superimposed indicating maximal similarity ($S = 1$). As the signal complexity increases, the similarity between waveforms as well as the index decreases. Fully disorganized signals will show minimal similarity and the corresponding indexes tend to 0. Recordings for this study were selected from data obtained during intraoperative mapping. The recordings chosen for the similarity analysis had an average duration of 5 ± 1 s. The number of waveforms used to calculate the similarity index varied between 6 and 30 per electrogram, depending on the heart rate.

Figure 1A shows a simplified diagram in three-dimensions that illustrates this concept.

We quantified for each of the 112 bipolar electrograms, the degree of similarity of its waveforms during sinus rhythm, VT, and VF. The rationale for this exercise being that waveforms that activated a dipole from a similar directional activation produce repetitive and similar waveform morphology. The morphological similarity between two LAWs was evaluated by computing their distance, expressed as the angle formed by the two vectors on the unitary sphere.\textsuperscript{20}

$$d(s_i, s_j) = \arccos(s_i, s_j)$$ \hspace{1cm} (2)

Two LAWs were considered to be similar when their distance or angle on the sphere was lower than a predefined threshold parameter $\epsilon$. Here, a distance of 0 indicates two identical LAWs; a value of $\pi$ means two similar LAWs but running opposite in phase, and a value of $\pi/2$ is seen when two LAWs are completely dissimilar. To quantify similarity among all waveform parts of an electrogram, a similarity index, $S$, was defined as the relative number of similar pairs of waveforms in the analysed recording as:

$$S(\epsilon) = \frac{2}{N(N - 1)} \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \Theta(\epsilon - d(s_i, s_j))$$ \hspace{1cm} (3)

where $N$ is the number of activation waveforms for a given electrogram, $\Theta$ is the Heaviside function ($\Theta(x) = 0$ for $x \leq 0$ and $\Theta(x) = 1$ for $x > 0$), and $\epsilon$ is a threshold. The similarity index calculation used here is from published work from Faes \textit{et al.}\textsuperscript{20} and Ravelli \textit{et al.}\textsuperscript{21} in atrial fibrillation and we used the threshold they found optimal for discriminating among various degree of organization in atrial fibrillation ($\pi/3$). For signals with regular and repetitive waveforms, the waves will superimpose indicating maximal similarity ($S = 1$). As the signal complexity increases, the similarity between waveforms as well as the index decreases. Fully disorganized signals will show minimal similarity and the corresponding indexes tend to 0. Recordings used for this study were selected from data obtained during intraoperative mapping. The recordings chosen for the similarity analysis had an average duration of 5 ± 1 s. The number of waveforms used to calculate the similarity index varied between 6 and 30 per electrogram, depending on the heart rate.

Figure 2A shows bipolar recordings from the LV endocardium at an electrode that shows subtle differences in bipolar signal...
morphology during an atrial bigeminal rhythm in another patient. This difference is easily exposed by this technique. The corresponding isolated activation waves are superimposed and their respective regularity indexes are shown in Figure 2B. The signals show two different populations of morphology and a regularity index of $s = 0.52$. When the populations are separated, their respective regularity indexes reveal high similarity as demonstrated in the right panel of Figure 2B.

The entire LV endocardium was studied and a similarity map was constructed for the 112 LV endocardial electrodes for this bigeminal atrial rhythm, by repeating the analysis at these different sites. Values of the similarity index were colour-coded for a scale from 0 to 1. Results are displayed on a polar colour-coded map by interpolating the indexes obtained at the recording locations in Figure 3. As expected, most of the LV endocardium was activated in a similar direction, except for electrodes that showed subtle variations in bipolar morphology as illustrated in Figure 3A. The differences during the bigeminal atrial rhythm could have resulted in a low regularity index for two reasons. One is local activation delay, the other being change in direction of activation wavefront. To study this, we created the isochrones (Figure 3B) and a vector map (Figure 3C) using gradient function of the two beats, that is, the normal and premature beat with slight aberrancy. These maps illustrate that in fact the difference in directionality is not due to local delay but rather due to a change in directionality in

Figure 1  (A) Simple diagram illustrating how LAWs are compared. Each LAW can be represented as a single point on a p-dimensional sphere, where $p$ is the number of samples comprising the LAW. In this fictitious example, two LAWs each made of three samples are compared on a 3D sphere. Morphological similarity is defined by measuring the angle formed by the two vectors created when connecting each LAW to the centre of the sphere. (B) Two rhythm strips are shown. 4.8 is located on spline 4, channel 8 and 7.5 refers to spline 7, channel 5 from an endocardial balloon deployed in the left ventricle during sinus rhythm. As evident, the waveform morphology of both bipolar electrograms is constant beat to beat. (C) The waveform morphology analysis shows that when these waveforms are aligned on their barycentre and superimposed one on top of another, they exhibit almost identical morphological characteristics, giving a similarity index of one for both channels 4.8 and 7.5.
the neighbourhood region, in this case the right upper corner. Thus, in this case, the change detected by the method was a change in directionality.

Ventricular tachycardia

During VT, depending on the location of the re-entrant circuit and activation away from it, most of the LV would be activated repeatedly in a similar direction. Thus the regularity index at most locations would be high and close to 1. Figure 4A, from another patient with ischaemic VT, shows bipolar electrograms recorded from two different locations on the LV endocardium. The corresponding isolated activation waveforms are superimposed and their respective regularity indexes are shown in Figure 4B. While one bipolar electrode signal shows relatively regular and repetitive waveforms, resulting in wave similarity analysis producing well-superimposed electrograms indicating high similarity, the other electrode reveals a dual population of electrogram. The activation map in Figure 4D shows that this is the result of re-entrant activity seen in diastole in the sub-endocardial region with directionality of the wave propagation that is exactly opposite to each other. The LV endocardial similarity map was constructed for the 112 LV endocardial electrodes during VT in this patient. Results displayed as a polar colour-coded map by interpolating the indexes obtained at the recording locations is shown in Figure 4C. As expected, most of the LV endocardium was activated in a similar direction. It is remarkable that the critical area of re-entry, where there is reversal in direction seen by activation mapping, is easily identified by the wave similarity technique.

Ventricular fibrillation

It is generally believed that VF in humans is the result of chaotic small wavefronts that change paths cycle to cycle, thus it is expected that electrodes in general will be activated from multiple directions. Hence in human VF, the regularity index would be expected to be low and close to 0. Figure 5A shows the bipolar electrograms recorded from two different locations on the LV endocardium in VF. The corresponding isolated activation waveforms are superimposed and their respective regularity indexes are shown in Figure 5B. Both bipolar electrode signals show irregular waveforms and the activation waves are not superimposed indicating poor similarity index ($S = 0.08, 0.09$).

We found that directional disorganization is not always the case for all of the LV endocardium in VF. Bipolar recordings from the LV endocardium show wavefronts that are relatively identical to each other in VF (Figure 6A). The corresponding isolated activation waves are superimposed and their respective regularity indexes are shown in Figure 6B. The LV endocardium was studied and a similarity map was constructed for all of the 112 LV endocardial electrodes, for a VF episode lasting 4 s in Figure 6C. As expected, most of the LV endocardium was not activated in a similar direction. However, there were regions that demonstrated directional organization that can be identified by their higher wave similarity index.

These two regions, interestingly, showing directional organization have very different cycle lengths. We can only speculate that the region with higher activation rate might be located close to the rotor(s), although it is clear that at the closest recording point to the rotor the frequency should be even higher. This could not be seen...
Temporal evolution of wave similarity is not captured in this analysis, where a whole segment of VF is analysed. However, it is quite clear from small and large animal VF studies that there is significant temporal evolution of VF. In an attempt to quantify this, we applied the wave similarity technique using a sliding window. We computed the similarity index [using formula (3)] for a 1 s long electrogram, positioned over every sample of data and plotted the index values over time, along with the actual bipolar electrogram. We found that 1 s was a reasonable compromise between similarity index accuracy and time resolution. The results for this VF are shown in Figure 7. We see in Figure 7A that regions that exhibit poor directional analysis over a significant period of time may show transient directional organization. Conversely, regions that show significant directional organization may contain transient directional disorganization as illustrated in Figure 7B. At the same time, most regions remain disorganized during the whole segment as shown in Figure 7C.
Figure 4  (A) A rhythm strip of ventricular tachycardia is shown from two different dipoles. Channel 0.8 is away from the critical portion of the VT circuit with passive activation in one direction. Channel 6.4 is located in the region where the re-entrant isthmus lies and it reveals two populations of wavefronts including a diastolic potential. These differ from each other in that the first has a qS complex, whereas the second one is an rS complex. (B) The wave similarity analysis of this rhythm as shown reveals a similarity index of 0.52. When these beats are split into two populations, the one in systole vs. the one in diastole, they each reveal a similarity index of 1 and appear literally superimposed. This figure illustrates that in ventricular tachycardia, the wave similarity index can assess directional changes in wavefronts. (C) This is a polar representation of the similarity indexes obtained from the LV endocardial balloon during VT. As shown, the map reveals a very high similarity index except for the same region, where the re-entrant isthmus is present as illustrated by the isochrones in (D). (D) An isochronal map of VT demonstrates the activation sequence with the presence of systolic activation and the diastolic activation in subendocardial fibres at the same location.

Figure 5  (A) In this rhythm strip of a patient with ischaemic cardiomyopathy, VF electrograms from two different channels are shown. They differ in polarity and morphology from each other and are irregular. (B) The wave similarity analysis of this rhythm is shown and it reveals that the electrograms are not superimposable and have a poor similarity index of 0.08 and 0.07.
Discussion

In this concept paper, we demonstrated that directional assessment of VF is possible from bipolar electrograms. Using the wave similarity concept, it is possible to recognize myocardial regions that are activated from multiple directions and differentiate those areas from regions that are activated in similar direction or activated at the exact mirror angle in VF. This technique does not require multiple electrodes at fixed inter-electrode spacing. It provides temporal evolution of directionality at a single bipolar electrode site. One key advantage of this technique is that the orientation of the bipolar electrode does not need to be known; the only requirement is that such orientation should not change over time. Bipolar electrograms present key advantages over their unipolar counterparts: They depict local electrical activity, while suppressing far-field effects. Bipolar recordings are sensitive to electrode orientation and this technique allows the comparison of wavefronts by normalizing their amplitude. However, since only wavefront morphologies are compared, other information (such as cycle length) is lost, which means that the wave similarity technique should preferably be used along with other analysis methods, such as DF analysis. This is particularly important when studying entrance block and fibrillatory conduction.

Owing to the inherent limitation of bipolar recording, this technique would not differentiate between areas that are activated by successive, repetitive wavefronts arriving at the exact mirror angle respective to the bipolar electrode axis. The technique will differentiate areas that are activated from multiple directions as in multiple re-entry VF wavefronts. The inability to differentiate exact mirror angle wavefronts may not have significant clinical implications, as the chance of repetitive wavefronts arriving at the exact mirror angle at the same electrode is highly unlikely in VF.

Catheter techniques for the ablation of AF based on electrograms is already underway. Directional evolution is a...
method that may be useful in identifying regions necessary to modulate VF by catheter-based techniques in addition to identifying the fastest activating region. It is obviously premature to comment on the possible benefits of catheter-based modulation of areas in the ventricle based on electrogram morphology; however, the concept of identifying such areas would be the first step in testing that hypothesis.

In small animal models, rotors tend to be stable. In such situations, including DF analysis is helpful, as the directionality adjacent to the rotor would be constant, and indeed away from the rotor, where fibrillatory conduction is present, directionality is not constant. In large animal models and presumably in humans, rotors are rarely anchored continuously to a certain portion of the heart and they are meandering or multiple in nature. Since the rotors could meander from area to area and the DF analysis is usually performed in a 2 s window, we found DF does not provide correlation with the directionality analysis, as the movement of high-frequency source is blurred. Indeed the temporal evolution of directionality demonstrated in Figure 7 suggests that directional organization lasts only for a brief period consistent with the notion that the rotors do not last in one location for prolonged periods.

Directional regularity in some regions may be due to anatomic constraints rather than areas adjacent to a dominant source. For instance, in the publication by Mansour et al., the directional organization in Bachman’s bundle, the connection between the chamber (left atrium) in which the dominant source was present to passive conduction and the chamber in which fibrillatory conduction was present (RA), is due to the anatomical constraints rather than the proximity to a rotor. In our data, in the example shown in Figure 6, the areas that demonstrate directional organization have very different cycle lengths. We can only postulate that the region with a higher activation rate might be located close to a rotor(s), and the regions with slower activation and directional organization are due to anatomical constraints or conduction block. However, if the specific direction could be ascertained, then that may help direct the search for the source of the wavefront.

Refractoriness and its change due to the restitution and memory effects may also have a part to play in directional organization, as partial or complete block in a myocardial region may be responsible for directional irregularity.

In epicardial mapping studies in humans, repeated breakthrough sites (electrical activity originating from the middle of mapping plaque without extraneous waves invading from the borders of the plaque) have been seen. Bipolar electrodes adjacent to these areas may demonstrate directional organization. Thus, identifying regions of directional organization has implications for identifying epicardial or endocardial regions in proximity to rotor activity.

Ciaccio used a piecemeal linear adaptive template matching technique to quantify phase shifts in electrograms. This technique was exclusively applied to far-field deflections in monomorphic VT by recording in the unipolar configuration. In that technique, a 40-ms sliding window was used to match short segments of two successive

![Figure 7](https://example.com/figure7.png)

(A) This figure illustrates the bipolar VF electrogram from an endocardial balloon electrode (shown in black) and temporal evolution of the wave similarity index (shown in red). The similarity index for the entire segment of VF is poor, but the temporal evolution shows a period during which the similarity index is high (1.0). (B) This figure illustrates a bipolar VF electrogram from an endocardial balloon electrode (shown in black) and temporal evolution of wave similarity index (shown in red). The similarity index for the entire segment of VF is high, suggesting general directional organization, but the temporal evolution shows a period during which the similarity index is poor (0.38). (C) This figure shows a bipolar electrogram taken from another electrode during the same VF as in the other panels, which shows a relatively constant disorganization over the entire segment of VF. This behaviour was seen in the majority of the recording sites during this VF.
electrograms. Parameters of two-dimensional scale (amplitude and time base or duration) and shift (phase lag and average baseline) were also used in that technique of template matching. The technique, however, has not been used for VF or with bipolar electrode configurations to determine local electrical activity. The wave similarity index introduced in this paper has the advantage of ascertaining directional activation at the sampling site, allowing for the possibility of intervention at that site.

Limitations
Since the orientation of the bipolar electrodes was not known, with the non-rigid mapping tool, an understanding of global propagation mapping could not be achieved. In addition, due to inherent limitations of bipolar recording, the technique will not differentiate waves arriving at the exact mirror image within a programmable threshold. This could, however, be alleviated if sets of orthogonal bipolar electrograms were used instead. Anatomical correlates with the areas that showed directional organization were not evaluated in this study. Histopathological correlation with the area mapped is, indeed, an interesting question especially in relation to the Purkinje system.

Conclusion
Wave similarity analysis can identify myocardial regions that are activated from multiple directions and differentiate those areas from regions that are activated by wavefronts in a similar direction or at the exact mirror angle in VF. This analysis of directional organization may have implications for the study of mechanisms of VF in the clinical arena.

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