33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Relating Spatial Heterogeneities to Rotor Formation in Studying Human Ventricular Fibrillation

J. Jeyaratnam[1], K. Umapathy[1], S. Masse[2], K. Nair[2], T. Farid[2], S. Krishnan[1], and K. Nanthakumar[2], Ryerson University[1], and Toronto General Hospital[2], Toronto, Canada

Abstract— **Ventricular fibrillation (VF) occurs due to disorganized electrical activity in the ventricles. This leads to rapid uncoordinated contractions of the ventricles and sudden cardiac death if not treated within minutes of its occurrence. The mechanism of VF initiation and maintenance is still elusive, however the mother rotor and multiple wavelet theories attempt to explain the mechanism behind this lethal arrhythmia. In mother rotor theory, VF is believed to be maintained by high frequency periodic sources called rotors that could be tracked using the phase progression along and through the myocardium using spatio-temporal electrical mapping of the heart. There are exiting works including our previous works that have related the formation of these rotors to anatomical and physiological heterogeneities observed in the myocardium. In this study we performed an correlation exercise of the locations of rotors with scar boundary maps and dominant frequency maps and elucidated this relation using human VF data acquired from isolated human hearts. The results suggest that in 14 rotors over 6 human hearts that we studied, all rotors co-localized to boundary zones of scar and low-high dominant frequency locations. The mean variance of the dominant frequency over the spatial location of the rotor was found to be 0.55 with average minimum of 4.15 Hz to a maximum of 5.71 Hz. This results in human VF data strongly suggest that boundary zones of healthy-non-healthy tissues and low-high frequency boundaries form a favorite substrate for rotor formation.**

Index Terms— **Rotors, Ventricular Fibrillation, Dominant Frequency, Scar Maps, Phase Maps.**

I. Introduction

Ventricular fibrillation is the leading cause of cardiac arrest, or sudden cardiac deaths. In VF, the heart muscle twitches randomly instead of contracting in a coherent manner, thus preventing cardiac output and causing oxygen deprivation to the organs which can escalate to lethality within a matter of minutes. The two existing theories that attempt to explain the mechanism of rotors is the mother rotor theory and the multiple wavelets theory. The mother rotor theory proposes that a high-frequency periodic excitation source is responsible for generating multiple irregular activation patterns [1]. On the other hand, the Multiple Wavelet Theory proposes that VF is maintained by multiple wavelets that break away from the cardiac signal propagation and self-regenerate themselves on reentry [2]. There are also studies that have shown that both mechanisms co-exist during VF [3]. Recent studies conducted in both small and large animals have shown that there is a significant spatio-temporal organization of cardiac activation patterns during VF induction [4]. Our previous works also have reported organization of electrical activity in the form of rotors and that these rotors have a greater affinity to occur around scar border zones [5]. If rotors are believed to be the source of VF, then it is important to relate it to anatomical and physiological markers that could eventually lead a clinician to track the rotor and ablate it to terminate VF.

In this proposed study, we approached the task of correlating the localization of the rotors and the spatial heterogeneities in a systematic way to validate or evaluate if there exist a consistent relation between scar boundaries (healthy-non-healthy tissue boundaries) and dominant frequency boundaries over the surface of the myocardium. More importantly the exercise was carried out on human VF data acquired from sick isolated human hearts (IHHs) received from transplant patients with informed consent. The paper is organized as follows: Section II covers the methodology including details on the data, acquisition protocol, electrical mapping system, construction of phase, frequency, and scar maps. Section III covers the results and discussions and conclusions are provided in Section IV.

II. Methods

A. Database and Data Acquisition

Six IHHs were utilized to acquire VF data for this study (45-62yrs, 3 males and 3 females, 3 dilated

Thanks to [NSERC, Ryerson University](K. Umapathy) and [CIHR, HSFC-CPR federation fund grant](K. Nanthakumar) for funding this project.

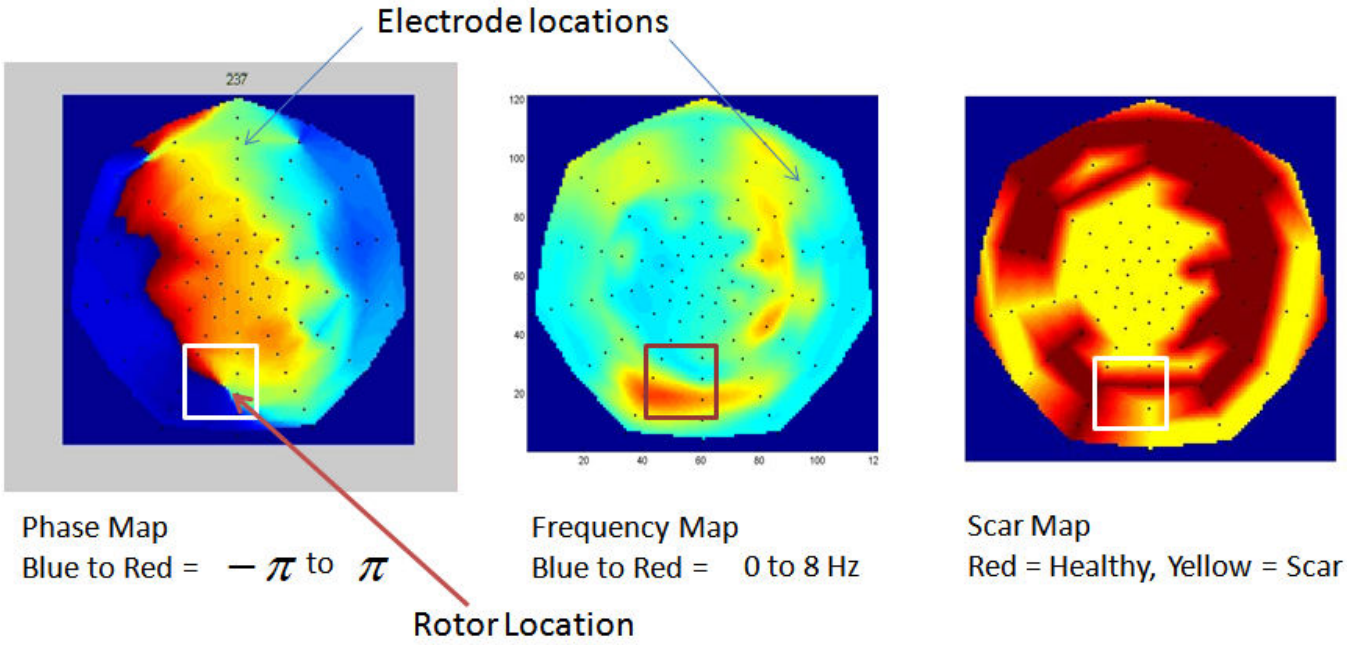

Fig. 1. Phase Map, Frequency Map, and Scar Map

cardiomyopathy and 3 ischemic cardiomyopathy) ; the experimental protocol is outlined in the following. Soon after the heart was explanted from the recipient, it was placed in cold Tyrode's solution (95% O2 + 5% CO2) and transported to a location that was less than 5 minutes away and subsequently flushed in order to remove blood particles. The hearts were selectively cannulated in the left and right coronary arteries and then fitted into a Langendorff setup. Following this, they were perfused with Tyrode's solution with a flow rate and pressure of 0.9-1.1 ml/min and 60-70 mmHg, respectively, and maintained at a temperature of approximately 37C and a temperature difference between the epi- and endocardium of no more than 0.25C [5]. A 620 channel electrical mapping system was used to acquire electrograms from the epicardium of the left (LV) and right ventricles (RV) and consists of an array of 112 unipolar and 112 bipolar electrode locations. Each electrode location consists of two silver beads (2mm in diameter) separated by 2.1 mm center-to-center facilitating the possibility of acquiring unipolar and bipolar electrograms simultaneously. For the purpose of this paper, only the data from the unipolar electrogram was utilized. These electrodes were organized into eight arms and were arranged radially as shown by black dots in Fig. 1. The heart was paced at a cycle length of 600 ms, and VF was induced by briefly bringing a 9-V battery into contact with it. VF was allowed to last 30s before defibrillation. Recordings were made 5s after the induction of a stable VF. From this, twenty seconds of data was extracted, and 7 minutes were allowed between subsequent VF inductions. More details on the acquisition and Langendorff setup is available in [5]. Each 20s episode was analyzed in 4s epochs. Using this method, a total of 12 VF episodes were extracted from 6 different hearts, and this was utilized in our analysis.

B. Phase Maps

As the goal of this work is to correlate location of rotors with spatial heterogeneities, we first construct phase maps using the multi-channel electrical recordings from the epicardium of the hearts [6]. Rotors can be tracked using phase maps over time. Phase maps (i.e., spatial changes of phase of the multi-channel electrograms over time during VF) were constructed for each instant of time and when played as a movie, the phase progression over space and time can be visualized. Instantaneous phase can be computed by the Hilbert Transform method as follows [6]. Let $x(t)$ be the signal under study, then the analytical version of it is

$$z(t) = x(t) + jH[x(t)] \tag{1}$$

Where $H[x(t)]$ is the Hilbert transform of $x(t)$ given by

$$H[x(t)] = \frac{1}{\pi}\int_{-\infty}^{\infty}\frac{x(\tau)}{(t-\tau)}d\tau \quad (2)$$

Then the complex signal $z(t)$ can be written as $z(t) = A(t)e^{\phi(t)}$, where $A(t)$ is the instantaneous amplitude and $\phi(t)$ is the instantaneous phase.

Since we cover the whole heart with evenly spaced 112 electrodes, data interpolation is carried out to pseudo increase the spatial resolution of the mapping area. The core of the rotors appear as a phase singularity points around which the phase of the surrounding tissue progresses cyclically. Phase maps were constructed as explained in [6]. A sample phase snapshot at a particular time instance is shown in Fig. 1 left most column. The figure shows the 2D mapping of the electrode array over the 3D epicardial surface. The color map varies from (blue=-π) to (red=π). The location of one of the phase singularity (PS) point (in this case core of a rotor) is shown using a rectangle. All PS points do not constitute a rotor, only those points where the phase progresses cyclically around it at least for 2 rotations qualify as rotor. The 2 rotations is not rigid, but in general it is accepted as a criteria for the presence or absence of a rotor. Once we locate the rotor and it is migratory path, we need to correlate this location with scar and frequency maps.

C. Dominant Frequency Maps

In order to analyze the spatial frequency distribution of the epicardium we need to construct dominant frequency (DF) map [5]. DF maps have been widely used in the literature for studying cardiac fibrillation, although lacks time localization within the analysis segment, it is computationally less expensive and provides a spatial map of frequency distribution over the epicardium. For each of the 112 electrodes, power spectral density (PSD) was estimated using the Welch averaged modified periodogram [5]. Each PSD was then scanned between 1.5 and 12 Hz and the frequency associated with the highest energy component was extracted as the DF; the aforementioned frequencies for scanning was appropriately chosen in order to avoid high-frequency artifacts as well as to simulate the range of frequencies exhibited in human VF. Interpolated maps, representing the epicardial electrode arrays in 2-D were generated to analyze the spatial distribution of DFs. In Fig. 1 the middle column shown a sample DF map constructed using 4s of data. The color map varies from (blue = 0Hz) to (red = 8Hz). The location matching to the rotor on the phase map (the left most 2D plot) is shown using a rectangle and it could be observed in the location of the frequency map equivalent to the location of the rotor there is a high-low frequency variation forming a boundary. Six electrodes around the location of the rotor were selected in the frequency map and the variance of dominant frequency was computed as a quantifier to measure frequency variation around the rotor.

D. Scar Maps

Scar maps are used as a surrogate measure to evaluate the healthiness of a underlying tissue. Scar maps were constructed by utilizing peak-to-peak voltage of the bipolar electrocardiograms on the (epicardial in this study) surface of the heart [7]. In this established method, during a pacing protocol, the electrode locations that had a peak-to-peak amplitude value of less than 0.5 mV was identified as scar areas and the locations with more than 0.5 mV is classified as healthy area. The bipolar electrodes, as aforementioned, were utilized to measure the peak-to-peak amplitude of the electrograms over the entire epicardium of the heart, from which we could identify locations of scar areas (i.e., $<$ 0.5 mV response). As mentioned earlier, data interpolation was performed to increase the spatial resolution. These scar maps provide a coarse anatomical substrate mapping. A sample scar map is shown in the right most column of Fig. 1, the red color areas are healthy areas and the yellow color are scar. Since the isolated hearts used in this study were received from patients undergoing heart transplant, we did observe considerable amount of scar. A rectangle is drawn around the equivalent area of the rotor location in the left most 2D plot. We could observe the location is in the vicinity of the border between healthy and scar tissue. once we generated phase, frequency, and scar maps, rotors were identified in the phase maps and their locations were correlated with scar and frequency maps.

III. Results and Discussions

We analyzed 14 rotors in 6 IHHS. The results of the correlation are summarized in Table 1 and 2. Table 1 shows the number of rotors detected in each of the IHHs and if the rotor locations occur in the boundary regions of scar and low-high frequency boundaries. There is a 100% correlation suggesting that all the rotors that we have detected in the IHHs do have a strong afffinitly to occur at the boundary regions of scar and frequency variation. In correlating data with scar

IHH	No. of Rotors	Co-localization with Scar Boundary	Co-localization with DF Boundary
1	4	Yes	Yes
2	2	Yes	Yes
3	1	Yes	Yes
4	1	Yes	Yes
5	3	Yes	Yes
6	3	Yes	Yes

TABLE I

CO-LOCALIZATION OF ROTOR LOCATIONS WITH SCAR AND DF BOUNDARIES

IHH	DF max (Hz)	DF min (Hz)	Variance
1	5.74	3.70	0.84
2	5.82	4.94	0.15
3	4.67	4.38	0.01
4	6.45	5.25	0.22
5	4.91	3.62	0.35
6	6.49	4.30	0.93

TABLE II

AVERAGE DF MAX, DF MIN, AND VARIANCE OF DF AMONG 6 ELECTRODES AROUND THE ROTOR FOR EACH OF THE IHHS

maps, although many PS points were seen throughout the VF episode, the ones that stabilized into a rotor were always seen at the boundary zone between the scar and healthy tissue. Although the rotors co-localized in the boundary zones between scar and healthy tissue, they did not co-localize in or near the same boundary zone area during subsequent VF inductions. However, in many VF episodes, within the episode, multiple short-lived rotors can be seen localizing to the same scar boundary area.

In Table 2 we have provided the DF variability of 6 electrode locations around the rotor location. The range of frequencies in the area around rotor and the variability of these frequencies among the locations around the rotor does not follow any pattern or at least it is not evident for the given data. This eliminates the possibility of a certain gradient requirement of either dominant frequency variations or scar-healthy tissue variations to favor rotor formation. Although the database is too small to arrive at any conclusions, it seems a gradient of scar-healthy and frequency is observed in the area around rotor but it is not a requirement for the formation of the rotor.

IV. CONCLUSIONS

We studied the relation between the rotor locations and the spatial heterogeneities measured in the form of scar-healthy underlying tissue and spatial variation of the frequency distribution. The results strongly suggest that the rotor locations co-localize to the scar-healthy and low-high frequency boundary regions. This validation of the affinity of rotors to border zones using human VF data might have implications in the mechanistic rationale on the role of the rotors in initiation and maintaining VF. The degree of variability of DF and their impact on rotor formation is inconclusive but needs to be verified with a larger database.

REFERENCES

[1] J. Chen, R. Mandapati, O. Berenfeld, A. Skanes, and J. Jalife, "High-frequency periodic sources underlie ventricular fibrillation in the isolated rabbit heart," *Circulation research*, vol. 86, no. 1, p. 86, 2000.

[2] G. Moe, W. Rheinboldt, and J. Abildskov, "A computer model of atrial fibrillation* 1," *American Heart Journal*, vol. 67, no. 2, pp. 200–220, 1964.

[3] M. Nash, A. Mourad, R. Clayton, P. Sutton, C. Bradley, M. Hayward, D. Paterson, and P. Taggart, "Evidence for multiple mechanisms in human ventricular fibrillation," *Circulation*, vol. 114, no. 6, p. 536, 2006.

[4] T. Everett IV, E. Wilson, S. Foreman, and J. Olgin, "Mechanisms of ventricular fibrillation in canine models of congestive heart failure and ischemia assessed by in vivo noncontact mapping," *Circulation*, vol. 112, no. 11, p. 1532, 2005.

[5] S. Masse, E. Downar, V. Chauhan, E. Sevaptsidis, and K. Nanthakumar, "Ventricular fibrillation in myopathic human hearts: mechanistic insights from in vivo global endocardial and epicardial mapping," *American Journal of Physiology- Heart and Circulatory Physiology*, vol. 292, no. 6, p. H2589, 2007.

[6] K. Umapathy, K. Nair, S. Masse, S. Krishnan, J. Rogers, M. Nash, and K. Nanthakumar, "Phase Mapping of Cardiac Fibrillation," *Circulation: Arrhythmia and Electrophysiology*, vol. 3, no. 1, p. 105, 2010.

[7] K. Soejima, W. Stevenson, W. Maisel, J. Sapp, and L. Epstein, "Electrically unexcitable scar mapping based on pacing threshold for identification of the reentry circuit isthmus: feasibility for guiding ventricular tachycardia ablation," *Circulation*, vol. 106, no. 13, p. 1678, 2002.