Published in final edited form as:

Heart Rhythm. 2008 June ; 5(6): S53–S58. doi:10.1016/j.hrthm.2008.03.028.

Mechanistic insights into ventricular arrhythmias From mapping studies in humans

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Keywords

cardiac mapping; ventricular tachycardia; ventricular fibrillation; nonreentrant mechanism

Sudden cardiac death in patients with organic heart disease is usually due to ventricular tachycardia (VT) degenerating to ventricular fibrillation (VF).¹ In many cases, implantable cardiac defibrillators (ICDs) have been successful in treating these lethal arrhythmias. However, for the large number of at-risk patients who either do not receive ICDs or who fail to meet criteria for ICD implantation, additional treatment approaches are required. Development of novel antiarrhythmic approaches will require an understanding of the electrophysiologic (and ultimately, cellular) mechanisms that underlie VT and VF in the human heart.

Progress in the understanding of VT and VF mechanisms has been made possible by recent technological innovations in cardiac mapping and advances in studying of cellular and molecular aspects of heart disease. Studies in diseased human hearts using three-dimensional electrical mapping (as well as recent optical mapping approaches) have demonstrated the complexity of mechanisms that initiate, maintain and terminate VT, as well as initiate and maintain VF in the heterogeneous myocardial architecture of the diseased human heart. Here we will focus on mechanistic insights into ventricular arrhythmias that have been obtained from such high resolution cardiac mapping studies in patients with ischemic and nonischemic heart disease.

Mechanisms of VT in chronic ischemic heart disease

The relationship of anatomical structure with the electrophysiological characteristics of the heart has been the focus of studies as early as 1909 when Sir Thomas Lewis showed that VT could be induced by coronary ligation in dogs. Intense investigations in studying monomorphic VT in human and animal models started in 1970s and 1980s,^{2, 3} with the development of approaches to simultaneously record from multiple sites throughout the heart (i.e. cardiac mapping).

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Endocardial mapping in the infarcted human heart

Harris et al⁴ recorded simultaneously from 110 endocardial sites and 110 epicardial sites during a total of 45 VT episodes in 20 patients with ischemic heart disease undergoing cardiac surgery. Continuous activation throughout the VT cycle, a prerequisite for reentry, was infrequently observed. In more than 90% of the VT episodes, endocardial activation preceded epicardial activation. For this reason, Downer et al⁵ recorded with both unipolar electrodes and bipolar electrodes at high gain from the left ventricular endocardium in patients undergoing surgery for VT. From the high gain bipolar electrode recordings, they obtained indirect evidence of an intramural sheet of surviving myocardium that was an integral part of the majority of reentrant circuits during VT. This result indicated the need for intramural recordings to fully elucidate activation pathways during VT.

deBakker et al⁶ performed mapping from 62 left ventricular (LV) endocardial sites, to characterize the activation pattern of VTs in 72 patients with chronic ischemic heart disease and drug refractory VT. They found that the majority of VTs exhibited focal initiation, with centrifugal spread of endocardial activity from a small zone referred to as “site of origin.” Endocardial mapping demonstrated macroreentry in only 3 of 108 VTs. In some cases, they found low-amplitude ($< 500 \mu\text{V}$) late presystolic activity (suggesting the possibility of reentry involving deeper subendocardial regions) as well as conduction block that interfered with the centrifugal activation pattern. Recordings from resected endocardial tissue showed normal action potentials, but fragmented extracellular electrograms, and histological examination at VT initiation sites revealed complex anatomical heterogeneities such as fibrous tissue and necrotic tissue in the infarcted myocardium surrounded by surviving myocytes. Overall, deBakker et al postulated that nonuniform tissue anisotropy (normal longitudinal conduction and slow transverse conduction) could underlie slow conduction and reentry, but higher resolution mapping, especially of intramural regions, was necessary to further characterize arrhythmia mechanisms in the human heart.

Intraoperative 3-dimensional mapping in the human heart

Three dimensional mapping studies of the sustained (SuVT) and non sustained VT (NSVT) in patients with ischemic heart disease have provided important insights into arrhythmia mechanisms.⁷⁻⁹ In these studies, transmural ventricular mapping from up to 160 transmural sites was performed using plunge-needle electrodes (each containing four bipolar electrode pairs separated by 4 mms) inserted throughout the left (LV) and right ventricle (RV) and the interventricular septum. Pogwizd et al⁷ performed intra-operative 3-dimensional cardiac mapping of SuVT induced by programmed stimulation. Electrode localization offline was performed by means of a video camera mounted above operating table. Mapping revealed that in 50% of cases, SuVT was due to intramural reentry that involved delayed conduction in the midmyocardium or subendocardium that was accompanied by fixed anatomical or functional conduction block. Intramural reentry was observed in the LV and RV as well as in the interventricular septum. Fig. 1A shows 3-D activation maps of sinus rhythm (left) and two consecutive beats of SuVT. Activation during SuVT beat X_N initiates in the basal lateral LV (level II, *), propagates in a clockwise direction, then apically to level III. Late counterclockwise activation in level III proceeds intramurally (from epicardium to midmyocardium around an endocardial region of conduction block (shown in black). Late endocardial activation (220 ms isochrone) leads to activation of an adjacent site in level II (beat X_{N+1} , *) to initiate the next VT beat by intramural reentry. A close-up of the map and the intramural electrograms (Fig. 2) further shows that the reentrant pathway would not be evident from endocardial mapping alone, and helps to explain the low incidence of VT detected in the endocardial mapping study of de Bakker et al.⁶ While one would anticipate reentrant circuits to be entrainable, it is possible that an enclosed intramural reentrant circuit such as this one

might be difficult to entrain. Moreover, these data also suggest that successful ablation of VTs due to intramural reentry might need to include sites immediately adjacent to the breakthrough site and possibly deeper intramural regions.

Intramural reentry was found in the septum as well as the LV free wall, and in some cases, late midmyocardial activation led to intramural reentry arising in the epicardium.⁷ Moreover, at times, a beat of SuVT could initiate by more than one intramural reentrant circuit, resulting in nearly simultaneous initiation from two widely separated sites. Histological examination showed an infarct core and surviving myocardium with interstitial fibrosis, but viable myocardium along the zone of late intramural activation. Regions of fixed and functional conduction block corresponded to infarct and fibrotic peri-infarct muscle. Moreover, the zones of slow conduction were primarily located transverse to fiber orientation.⁷

However, in the other 50% of cases, sustained monomorphic VT in the infarcted human heart initiated by a focal mechanism.⁷ Focal activation was identified by the lack of electrical activity between the termination of one beat and the initiation of the next beat when multiple intervening electrode recording sites were present. Fig. 3 shows 3-D activation maps for 2 consecutive beats of SuVT that initiated by a focal mechanism. Beat X_N initiates in the apical lateral wall (*) in level III and activation spreads radially in both a clockwise and counterclockwise direction. Latest activation in the basal RV (+, level I) is followed 156 msec later by initiation of beat X_{N+1} at the same apical lateral site (*, level III) by a focal mechanism. Focal activation primarily arose in the subendocardium, but at times could arise in the midmyocardium or epicardium. The coupling interval (CI) of VT beats with a focal mechanism was longer than those of VT beats initiated by intramural reentry. Moreover, some patients exhibited SuVT of one morphology that initiated by intramural reentry and SuVT of another morphology that initiated by a focal mechanism.⁷

Nonsustained vs sustained VT in the infarcted heart

Later 3-D mapping studies focused on the initiation, maintenance, and termination of nonsustained VT (NSVT) in the same patients with prior infarct in which sustained VT (SuVT) had been mapped.^{8,9} The direct comparison of NSVT vs SuVT in the same individuals allowed a novel opportunity to assess how these VTs are initiated and maintained, and what allows VT to terminate in some cases (NSVT) but not others (SuVT).

The comparison of SuVT and NSVT characteristics⁶ revealed that NSVTs had less conduction delay during the preceding extrastimuli, and the sites at which NSVT was initiated and maintained were frequently different from those initiating and maintaining SuVT. NSVT beats could be initiated by either a reentrant or a focal mechanism. For example, the first few beats of NSVT could initiate by a focal mechanism, but with development of marked conduction delay, subsequent NSVT beats could initiate by intramural reentry (and vice versa). As in SuVT, intramural reentry in NSVT developed because of intramural conduction delay, and focal activation arose primarily in the subendocardium and was associated with less conduction delay of the preceding beat (vs. reentrant beats).

The characteristics of NSVT termination were also investigated⁷ and three characteristics were found:

- a. Group 1 (45%) – VT termination was associated with the last several VT beats arising from multiple (different) subendocardial or subepicardial initiations sites that were different from those responsible for SuVT.
- b. Group 2 (24%) – VT termination was associated with repetitive firing from sites different from those responsible for SuVT. However, VT termination was usually preceded by sudden variations in CI (with or without variations in total activation

time (TA) for individual VT beats) or a sudden change in initiation site. Variations in CI that might be related to dispersion of refractoriness occurred with 93 beats from 44 NSVTs. In 53 cases (57%), CI variations preceding VT termination were associated with a change in VT initiation sites, while in 40 cases (43%), CI variation occurred despite firing from the same site. The basis for this is unknown, but 33 of 40 cases of CI variation occurred for up to the first 3 beats after a shift in initiation sites. Only 4 VTs terminated with no variation of CI or TA, often due to changes in initiations sites.

- c. Group III (31%) – VT termination despite repetitive firing from sites that were concordant with those underlying SuVT. In some cases, NSVT beats demonstrated initiation at a concordant initiation site, but then failed to “switch” to a second concordant SuVT maintenance site (and thus the VT terminated). In other cases, there was initiation and maintenance at concordant sites, but sudden termination (for unexplained reasons).

The terminal beats of NSVTs more frequently initiated by a focal mechanism than by intramural reentry. These focal activations had less conduction delay of the preceding beat than terminating reentrant beats, and their termination was not associated with significant variations in CI or TA. In some cases, the reentry mechanism was replaced with focal activation prior to termination when the TA of the reentrant beats was inadequate to maintain the reentry circuit. Other important factors for VT termination were both anatomic and functional conduction blocks in the midmyocardial regions, the critical site of conduction block, and change in the activation sequence along the reentrant circuit.^{8, 9} Conduction delay was a necessary but not sufficient condition for developing reentry. For example, an NSVT beat with marked conduction delay could fail to initiate a subsequent beat by reentry (and thereby terminate the VT) if the conduction delay was distant from the reentrant VT circuit found in SuVT.

Mechanisms of Ventricular Tachycardia in Dilated Cardiomyopathy

There are limited data about the VT mechanism in patients with nonischemic dilated cardiomyopathy.¹⁰ Anderson et al¹¹ performed epicardial grid mapping and demonstrated slow conduction in failing human myocardium, but no evidence of reentry.

Pogwizd et al¹² studied the mechanism underlying spontaneous VT or VT induced by programmed stimulation in patients with idiopathic dilated cardiomyopathy. This study used three-dimensional cardiac mapping from up to 160 intramural sites that was performed for up to 10–15 minutes at the time of cardiac transplantation. Excision of the heart with plunge electrodes in place allowed precise electrode localization for construction of 3-D activation maps.

While premature extrastimuli exhibited progressive conduction delay and some degree of intramural conduction block, all beats of VT induced by programmed stimulation initiated by a focal mechanism arising primarily from the subendocardium.¹² The identification of focal activation was the same as described previously, with latest activation from the preceding beat occurring distant from the site of VT initiation (despite multiple intervening plunge electrodes), and demonstrated centrifugal spread of activation that was rapid with no evidence of slow conduction, fractionation or conduction block. Focal activation could arise at a number of different sites (i.e., endocardial, midmyocardial, and epicardial), although the terminal beats of VT arose from the subendocardium. Histological changes at the sites of focal initiation were variable, with some sites demonstrating no (or minimal) interstitial fibrosis, while others exhibited a considerable degree of fibrosis.

Additionally, mapping of spontaneous rhythm revealed that a focal mechanism was responsible for initiation and maintenance of all beats of spontaneous NSVT, couplets and PVCs (which demonstrated QRS morphologies similar to those recorded on Holter monitoring pre-operatively).¹²

In all of these 3-D mapping studies in the human heart, the resolution of intramural mapping was inadequate to rule out microentry. However, 3D mapping in an arrhythmogenic rabbit model of heart failure at a much higher resolution (240 sites in a failing rabbit heart, equivalent to mapping from over 1,300 sites in a canine or human heart) revealed similar focal activation with no evidence of slow conduction even within mms of the initiation sites, suggesting that the arrhythmia mechanism was nonreentrant.¹³

Cellular mechanisms

The nature of this focal nonreentrant mechanism remains unknown, but it could involve triggered activity arising from delayed afterdepolarizations (DADs, depolarizations arising from the resting potential after the preceding action potential is fully repolarized) and/or early afterdepolarizations (EADs, depolarizations arising from the end of the normal action potential plateau).¹⁴ DADs occur in the setting of intracellular calcium overload and are due to spontaneous release of calcium from the sarcoplasmic reticulum (SR), with activation of a transient inward current (I_{ti}) mediated by the Na/Ca exchange (NCX).^{14, 15} EADs involve reactivation of the L-type calcium current during a prolonged plateau phase of the action potential. Norepinephrine induced both DADs and EADs in ventricular myocytes from failing human hearts,^{16, 17} further supporting triggered activity as the nonreentrant mechanism. In addition, studies in the arrhythmogenic rabbit HF model that exhibits initiation of spontaneously occurring VT by a nonreentrant mechanism¹³ have revealed that DADs can be induced by β -adrenergic stimulation that are mediated by an I_{ti} that is due to upregulated NCX, and that can be enhanced by decreased activity of inward rectifying I_{K1} (which results in destabilizing of resting membrane potential).¹³ Elevated catecholamines, as well as rapid pacing, are likely to produce a rise in SR calcium levels that would contribute to DADs.¹³ Action potential prolongation in HF may also predispose to development of EADs,¹⁸ as well as to the potential for spontaneous SR calcium release from SR Ca overload.

While slowing of conduction in infarct zones arise from interstitial and replacement fibrosis, altered conduction in nonischemic HF may involve the downregulation and dephosphorylation of gap junctional proteins such as connexin 43.^{19, 20}

Mechanism of Ventricular Fibrillation in Cardiomyopathy

VF is known to be one of the most common causes of sudden death for more than a century and yet understanding of VF mechanisms in the human heart has remained elusive. Experimental studies in animal models have proposed two theories for VF mechanism. The “multiple wavelet VF” theory involves the breakup of a single or double rotor into multi wavelets that initiate and maintain VF.²¹ The other theory suggests that VF is the result of a high frequency rotor which is stabilized in a small area of myocardium, and that the complex pattern of VF activation is the result of such a single drifting rotor.²²

Limited studies of diseased human hearts have shown that both mechanisms may exist simultaneously depending on the location of mapping and the resolution of the mapping system. For example, the effect of fibrosis on the activation patterns of VF in patients with dilated cardiomyopathy was investigated in Langendorff-perfused transplant recipient hearts.²³ Epicardial mapping was recorded by plaque electrode array with 477 bipolar electrodes (1.6 mm resolution) for five hearts including one in which transmural recordings were performed. VF was mapped either in the right ventricle or left ventricle for each heart. The majority of

wavefronts in the epicardium during VF were not reentrant, initiating incomplete rotating circuits that could rotate around a line of conduction block parallel to the epicardial fiber orientation. Other observed activation patterns included transmural scroll waves (rotor) in the right ventricle, wave fronts that were initiated by epicardial breakthrough with a line of conduction block parallel to the epicardial fiber orientation, and wave fronts crossing roughly perpendicular to the tail of another wave front to create a wave break. These wavefronts were terminated either by interference with other wave fronts or terminated spontaneously. Histological examination revealed significant fibrosis in each heart between muscle fibers and bundles, corresponding to areas of conduction block that created the arrhythmogenic substrate for generation of new wave fronts during VF.²³ *In vivo* recording of epicardial wavefronts during human VF²⁴ also showed that reentry was infrequent and that VF exhibited a significant degree of organization. However, recordings were only made from <16 cm² of the epicardium, so that some reentrant circuits were probably missed.

When the entire epicardium and endocardium were mapped by Masse et al²⁵, rotors were found to be present in myopathic hearts of patients during the initial phases of induced VF. These investigators used an intracavitary balloon electrode for endocardial mapping and an epicardial sock electrode array for epicardial mapping of right and left ventricles. Counter-rotating rotors (with and without the presence of conduction block) were present in all of the hearts studied, on the endocardium as well as on the epicardium of the myopathic hearts.

In another study in which only an epicardial sock array was used with patients undergoing cardiac surgery, Nash et al²⁶ found that epicardial reentry was present during VF in all patients. In some cases, multiple complex waves were present, while in other cases, VF was driven at times by a single reentrant wave that swept over the entire epicardium for several cycles. Thus, these results suggest that both theories for the maintenance of VF are correct.

A recent study²⁷ used optical mapping approaches (voltage-sensitive dye di-4-ANEPPS) in Langendorff-perfused human cardiomyopathic hearts (all with ejection fraction <20%). Optical imaging provided some advantages over extracellular electrode mapping in the determination of local activations, and demonstrated reentrant, colliding and fractionating wave fronts during VF. In addition, in some experiments, sustained high-frequency rotors were shown to be maintaining overall fibrillatory activity in the heart. While more studies are needed to explore the dynamic activations in the normal and diseased human hearts, the application of optimal imaging approaches provides new opportunities for further delineating arrhythmia mechanisms of VF (and VT) in the intact human heart.

Conclusion

Mapping studies of VT and VF in the human heart have provided important mechanistic insights that have been complemented by cellular studies from failing human hearts as well as from animal models of HF. In the setting of ischemic cardiomyopathy, reentrant excitation can underlie development of VT. However, reentry occurs intramurally, thereby accounting for the difficulty with finding complete reentrant circuits when mapping is limited to the endocardial or epicardial surface. Slow conduction is related to altered histological characteristics of the infarct, along with cellular changes such as Cx43 downregulation and dephosphorylation. However, in 50% of cases, sustained monomorphic VT was due to a focal, and what we believe to be nonreentrant, mechanism, that could be due to triggered activity from DADs (involving changes in intracellular calcium handling) and/or EADs (from prolongation of repolarization). 3-D mapping in the human heart has shown the complexity of the arrhythmogenic substrate with some VT initiating by reentry and others by a focal mechanism, some beats of VT initiating by multiple reentrant circuits. Moreover, runs of VT can have some VT beats initiating by reentry while others initiate by a focal mechanism. In nonischemic HF, focal mechanisms

appear to play an important role in the initiation and maintenance of VT, but the role of intramural during SuVT in this setting remains to be determined. While VT can initiate by either a reentrant or a focal mechanism, VF in the human heart typically involves reentrant excitation. Here again, intramural activation is important and 3D mapping of VF is necessary to visualize transmural scroll waves and counter-rotating rotors. Refinement of 3D mapping techniques, development of optical imaging approaches, and continued focused cellular studies in human myocytes (based on work in animal models of HF) will all provide additional mechanistic insights into VT and VF. This will lead to the development of novel therapeutic approaches including ablative approaches^{28, 29} to target both reentrant and focal mechanisms, and to improve on the benefit that has been achieved with the use of implantable defibrillators.

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Fig. 1.

Intramural reentry during sustained monomorphic VT: Electrocardiogram (top) and three-dimensional activation maps (bottom) of a sinus beat (A) and 2 beats of sustained VT (X_N , X_{N+1}) in a patient with a prior myocardial infarction. Heart cross sections (I–IV) are oriented with the base at top and the apex on the bottom. LV and RV are labeled at upper left. Sites of earliest activation are denoted by the *. Conduction block is denoted by the thickened lines and black areas. The arrows show the spread of activation during intramural reentry. Reproduced with permission from reference 7.

Fig. 2.

At left is a schematic of levels II and III from beat X_N of Fig. 1 with A–F denoting intramural recording sites along the reentrant pathway. Arrows show the spread of activation during intramural reentry. At right are bipolar electrograms for sites A–F (with A shown again). After initiation of beat X_N in level II at site A, activation proceeds clockwise (A→B→C), then apically (C→D) to level III. Counter-clockwise epicardial to endocardial activation (D→E→F) leads to very late activation (220 ms isochrone at site F) which then proceeds basally (F→A) to complete the intramural reentrant circuit. Reproduced with permission from reference ⁷.

Fig. 3. Focal mechanism during sustained VT: Electrocardiogram (top) and 3-D isochronal activation map (bottom) of 2 beats of sustained monomorphic VT (X_N , X_{N+1}) in a patient with prior infarct that initiated by a focal mechanism. Reproduced with permission from reference ⁷.