Induction and Termination of Ventricular Tachycardia by Programmed Electrical Stimulation in a 7-day-old Canine Myocardial Infarction

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SEVERAL investigators have indicated that reentry is a likely mechanism for ventricular tachycardia induced by programmed electrical stimulation in a canine myocardial infarction model¹⁻⁴. The demonstration of continuous diastolic electrical activity with a technique of composite electrode recording has been thought to constitute the necessary "missing link" long sought to document reentry^{1,2}. Recent advances in epicardial mapping have allowed more precise analysis of the sequence of activation within the area of myocardial infarction⁵⁻⁹. Although epicardial mapping reveals some of the limitations of composite electrode recordings, it provides direct proof of circus movement within the surviving epicardial layer overlying the infarct.

In this study, we used a similar mapping system to analyse epicardial activation sequences during programmed electrical stimulation and induced ventricular tachycardia.

METHODS

Mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated with a Harvard pump. An angiographic catheter was inserted through the right carotid artery into the left coronary ostium under fluoroscopy. The position of the catheter was confirmed by

injection of contrast medium. Then, a 2-French Fogarty balloon-tipped catheter was passed through the catheter so that a balloon was positioned in the proximal left anterior descending artery (LAD), 1 to 3 cm from the tip of the angiographic catheter. The balloon was inflated with 0.03–0.04 ml of diluted Urografin 75 to produce complete coronary occlusion. This procedure was associated with characteristic ST segment elevation in Lead I. Inflation was maintained with a stopcock and terminated after a period of 3 to 6 hours.

On the 7th day after initial operation, the 36 surviving dogs were used for electrophysiological study.

Electrophysiological study: The dogs were again anesthetized with pentobarbital and ventilated mechanically. The heart was exposed through left thoracotomy. After pericardectomy, bipolar plunge wire electrodes were positioned in the free wall of the right ventricle for stimulation. The stimuli were rectangular pulses with a duration of 2 msec at twice the diastolic threshold. Programmed single (S_2) and double (S_2 , S_3) premature ventricular stimuli were delivered during fixed-rate ventricular pacing (S_1), at a cycle length of 260 to 360 msec using a programmable electronic stimulator (Fukuda-Densi Inc).

Epicardial mapping: A 4 × 5 cm patch electrode containing 48 (6 × 8) close bipolar (0.5 mm) electrodes with an interelectrode distance of 6 mm was used to map the epicardial activation sequence during programmed stimulation and induced ventricular tachycardia. The

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Fig.1. Inducibility of ventricular tachycardia and size of infarction.

Abbreviations: LV = left ventricle; PVC = premature ventricular contractions; VT = ventricular tachycardia; PES = programmed electrical stimulation

mapping system (Fukuda-Densi, HPM-6500) consisted of high input impedance (50 Megaohm) differential amplifiers with a filter setting of 5–860 Hz. The bipolar signals were amplified, multiplexed, sampled at 1–2 msec and converted to a 12-bit digital format. Local excitation time was identified as the point of most rapid change in potential of each bipolar electrogram. Computer-generated isochronal maps of 10 or 20 msec intervals were constructed for selected paced beats (S_1 , S_2 or S_3) beginning with the time of stimulation and for induced beats beginning with the last stimulus spike. On interpretation of the epicardial activation sequence, a conduction block was arbitrarily thought to be present when calculated conduction velocity between two adjacent electrodes was less than 10 cm/sec. This value was selected on the basis of reported conduction velocities in infarcted

regions (12 ± 7 cm/sec, $M \pm SE^{10}$). Functional conduction block was defined as a block not identified during sinus rhythm or basic ventricular stimulation.

Postmortem studies: After electrophysiological study, the heart was excised and cut transversely into 5–10 mm thick slices. The anatomy of infarction was determined by triphenyl-tetrazolium-chloride (TTC) staining.¹¹ The positions of map electrodes were identified with reference to infarcted myocardium. Each slice was weighed and photographed. The areas of infarcted myocardium were planimetered on each slice and expressed as a percent fraction of the total left ventricular weight.

RESULTS

1. Inducibility of ventricular tachycardia and size of myocardial infarction

Out of 36 dogs, sustained and non-sustained ventricular tachycardias were reproducibly induced in 11 and 6 dogs, respectively. Mean infarct size was significantly more extensive in the groups with sustained and non-sustained ventricular tachycardia ($26.1 \pm 7.4\%$, $25.5 \pm 8.3\%$) than in dogs without inducible tachycardia ($8.1 \pm 7.5\%$) ($p < 0.001$) (Fig. 1). All dogs with inducible tachycardia had transmural infarction, that is, infarction involving at least two-thirds of the transmural thickness, although 6 of 19 dogs without tachycardia also had transmural extension.

2. Patterns of epicardial activation and inducibility of ventricular tachycardia

Epicardial activation sequence was classified into 3 types (Fig. 2). In type I (11 dogs), isochrones were equally separated and no conduction delay or block was observed during basic and premature ventricular stimulation. This pattern of activation was associated with non-transmural infarction or transmural infarction with most of the epicardial muscle layer surviving. In type II (8 dogs), functional block developed during premature stimulation. In two type III dogs, nonexcitable areas where no discernible electrogram was recorded were identified during basic stimulation, and functional block developed in the surrounding area. No surviving epicardial myocardial cells were identified in these nonexcitable areas. The values of maximal epicardial delay during basic and premature stimulation are listed in Table I.

Fig.2. Patterns of epicardial activation sequence during basic and premature stimulation from the right ventricle.

Each epicardial map was aligned parallel to the course of the left anterior descending coronary artery. Numbers in each map represent activation times in milliseconds from the time of stimulation.

Epicardial delay was significantly more marked in types II and III than in type I. Ventricular tachycardia was inducible in 9 of 10 type II or III dogs (90%), but in only 2 of 11 type I dogs (18%) ($p < 0.01$). Namely, inducibility of tachycardia was critically related to the presence of a functional block and marked epicardial delay, both of which satisfied the requirements

for reentry mechanism.

A representative example of possible epicardial reentry is shown in Fig. 3. A mapping electrode was attached to the epicardial surface so that the left side of the electrode was aligned with the course of LAD. Stimuli were applied to the right ventricular outflow tract at a basic cycle length (S_1-S_1) of 300 msec. Two premature

stimuli (S_2 , S_3) introduced at coupling intervals of 160 msec induced monomorphic sustained ventricular tachycardia. The numbers in each epicardial map represent activation times in

milliseconds from the time of stimulation. During S_1 , the entire epicardial recording sites were activated within 90 msec. During the first premature beat (S_2) conduction slowing (crowded isochrones) at the septal border of the infarcted region (left lower portion of the map) became apparent and site C-2 was activated 150 msec after S_2 . During the second premature beat (S_3), an apparent area of functional block developed in the left lower portion of the map. The distal site of this area (B-3) was activated not by a wave front from left to right, but by a wave front travelling in a long pathway in a clockwise direction. During the first beat of tachycardia (E_1), the proximal site of the functional block (A-4) showed the earliest activation, and epicardial activation continued in a similar

	<i>n</i>	max. epicardial delay (msec)		VT induced
		S_1	S_2, S_3	
I FB-	11	83.7 ± 13.8 (56-103) *	110.7 ± 31.3 (58-172) *	2 (18%)
II III FB+	10	120 ± 34.1 (86-180)	166.0 ± 46.0 (102-232)	9 (90%)

★ $p < 0.02$, ☆ $p < 0.01$

Fig.3. A representative example of epicardial reentry as a mechanism of induced sustained ventricular tachycardia.

Epicardial maps during basic (S_1) and premature (S_2 , S_3) stimulation and the first beat (E_1) of sustained tachycardia (SVT) are shown in the middle panels. Numbers in three epicardial maps during ventricular stimulation represent activation times in milliseconds from the time of stimulation (S_1 , S_2 , S_3 respectively). Numbers in E_1 represent activation times from S_3 . Position of mapping electrode is schematically shown in the lower left panel. A dotted line encircles the area of myocardial infarction. Black areas in the schema below maps represent the area of functional conduction block.

Fig.4. Representative bipolar electrograms from 7 recording sites as shown in the epicardial map (same experiment as in Fig. 3).

Continuous activity spanned the entire diastolic interval between the last premature beat (S3) and the first beat of induced tachycardia (E1). Delayed activity at site-f (232 msec after S3) reexcited site-g at 235 msec.

clockwise direction. It is quite likely that delayed activation of site B-3 during S₃ could traverse the area of the functional block in a retrograde fashion and re-excite proximal site A-4, which had recovered its excitability.

Figure 4 illustrates 7 selected epicardial electrograms (a-g) during S₃ and E₁ recorded from the same experiment as in Fig. 3. Location of each electrode is indicated on the epicardial map shown in the upper left corner. Site-a was close

Fig.5. A representative example of epicardial reentry with possible intramural involvement. Note the presence of a "missed" time interval of 90 msec between the latest activation during S₃ (210 msec) and the earliest activation during E₁ (300 msec).

to the pacing electrode and showed the earliest epicardial activation (16 msec after S₃). From this site, continuous activity spanned the entire diastolic interval between S₃ and E₁. At site-g, two electrograms were recorded as a result of a single stimulation (S₃). An initial deflection (18 msec after S₃) represented an excitation produced by a direct wave front from the stimulus and a second late deflection (235 msec after S₃) represented a re-excitation by a circulating wave front. This second electrogram preceded the onset of E₁ on surface electrocardiogram. These observations strongly suggest a two-dimensional reentry mechanism in the surviving epicardium overlaying the infarct. This pattern was observed in 7 of 17 inductions of tachycardia (41%).

In contrast, Fig. 5 demonstrates another example of epicardial reentry, in which the complete sequence of excitation could not be mapped at the initiation of tachycardia. The earliest activation (300 msec after S₃) during the

first beat of tachycardia (E₁) was identified at site D-2, adjacent to site D-3 showing a maximal delay during S₃. However, this activation, although preceding the onset of QRS (E₁), was inscribed 90 msec after the maximal delay during S₃ (210 msec). Namely, the interval of 90 msec could not account for epicardial continuous circus movement. During this "missed" time interval, a wave front might circumvent the epicardial pathway into the intramyocardium to allow site D-2 to recover its excitability (dashed white arrow in the schema of S₃). This type of initiation was observed in 5 of 17 tachycardias.

Figure 6 demonstrates termination of the same tachycardia as in Fig. 5 by rapid ventricular pacing. The first two beats (E₁ and E₂) represent tachycardia and beats 3 to 5 represent capture beats of ventricular pacing at 130 msec intervals (2:1 response). Beat 3 was a fusion between tachycardia and pacing. Cycle length of tachycardia was 300 msec, and a 130 msec missed interval was again noted. On epicardial

TERMINATION OF VT BY RAPID RV PACING

Fig. 6. Change in epicardial activation sequence during termination of ventricular tachycardia by rapid ventricular pacing (same tachycardia as induced in Fig. 5). See text for discussion.

Fig. 7. An example of possible endocardial reentry as a mechanism of induced ventricular tachycardia.

Although a second premature stimulation (S3) produced functional epicardial conduction block, epicardial activation sequence during tachycardia reflected a fast Purkinje activation.

mapping, a similar activation sequence as in Fig. 5 was noted during E₁ and E₂. During beat 3 (S₁), two wave fronts, one from right ventricular stimulation and the other from a

circulating (reentrant) wave collided at the lower left corner (at 20 msec isochrone). Almost the entire epicardium was activated by a wave front from stimulation and a maximal delay of 170

Fig.8. Anatomical correlations of epicardial mapping.
Two cross-sections of the heart (slices 1 and 2) are obtained from the levels indicated in the upper left panel.

msec was obtained at the same site as E_1 and E_2 . However, the next stimulus wave front (S_2) activated the proximal site of the functional block at 14 msec after S_2 , prior to the re-excitation. Sinus rhythm was restored after termination of pacing. This mode of termination provided further evidence for epicardial reentry as the mechanism of this tachycardia.

In 5 of 17 induced tachycardias, epicardial activation sequences during tachycardia mimicked those obtained during left ventricular endocardial pacing. Figure 7 demonstrates one example in which functional block and epicardial delay preceded the induction of sustained tachycardia, but fast epicardial activation during tachycardia suggested a transmitted subendocardial or Purkinje activation sequence. Thus, this type of tachycardia was considered to originate within the Purkinje network, possibly in the infarcted area, since it was never induced in the absence of sizable infarction (see Fig. 1).

3. Anatomical correlates of epicardial reentry

Figure 8 demonstrates the schematic location of a patch electrode with reference to distribution of coronary arteries (upper left panel), epicardial mapping during premature right ventricular stimulation (S_3) (upper right panel) and TTC-stained cross-sections of the heart (lower panel). Sustained tachycardia was reproducibly induced in this preparation. In the schema, the shaded area indicates an area of transmurular infarction, which is surrounded by non-transmurular infarction (indicated by dotted line). Size of the infarction measured as 28.2% of the left ventricle. It becomes evident that the area of functional block as shown in epicardial mapping extended along the septal border of the transmurular infarction. This area corresponded to a transitional zone from non-transmurular to transmurular infarction (electrode sites A to C on slice 1 in the lower figure). A wave front spread towards the apex along the left edge of the

Fig. 9. A schematic diagram of epicardial reentry. Shaded area represents the area of myocardial infarction. See text for discussion.

Fig. 10. A schematic diagram of epicardial reentry with possible intramural reentry pathways. See text for discussion.

transmural infarction. Finally, it traversed the central infarction zone from left to right within a thin layer of surviving epicardial myocardium (sites C to F on slice 2) to reach the distal side of the functional block (site B on slice 2) 156 msec after S_3 .

DISCUSSION

Results of the present study reveal that not only the size^{3,12,13} but also the transmural extension of infarction with a thin superficial muscle layer are important determinants for the occurrence of reentry. The surviving epicardial layer overlaying the transmural infarction varied in thickness from a few cells to a few millimeters⁸ or to about 200 cells⁷ and was the site of a local conduction block or slow conduction. In some of the study dogs without inducible tachycardia, transmural extension was localized only in small areas despite a sizable infarction. Since a functional conduction block developed in the periphery of the transmural infarction (as shown in Fig. 8), a larger area of transmural extension could provide a sufficient length of the area of block necessary for the initiation and maintenance of epicardial reentry.

nance of epicardial reentry.

In approximately 70% of induced tachycardia, the initiating beat (S_3) was associated with development or extension of the area of functional block and markedly slowed conduction. Figures 9 and 10 schematically illustrate the reentry circuit with reference to the anatomical extension of infarction. An excitation wave front from the right ventricle spread subepicardially across the interventricular septum until it reached the border of the transmural infarction. Due to abnormally prolonged refractoriness⁸ of the surviving epicardial cells, a wave front encountered a local conduction block (parallel lines). Another wave front advanced within the normal zone along the edge of transmural infarction and then entered the central infarction area from the opposite side. Conduction of impulses in the infarction area was slow (wavy line) and confined to an essentially two-dimensional plane on the epicardial surface.^{7,8,14} According to Ursell et al.,¹⁴ at 1–5 days after coronary occlusion resting membrane potential, action potential amplitude and upstroke velocity are reduced in these surviving epicardial cells, which may contribute to the observed slow conduction. By 2 weeks after occlusion, an ingrowth of connective tissue distorts the muscle fiber orientation and could disrupt cell to cell coupling.¹⁴ This possibility has also been discussed by Spear et al.¹⁰ as a genesis of slow conduction. Thus, the distal side of functional block (black circle in Fig. 9) is activated late in diastole by a slowly conducting wave front, which is now available to reexcite the proximal side (white circle). Kramer et al.¹⁵ recently analysed intramural activation sequence with a technique of three-dimensional activation mapping in 3–8 day canine infarction. In 71% of induced tachycardia in their study, the reentry circuit was confined to the epicardium as shown in Fig. 9. In these cases, intramural or subendocardial fibers are not a part of the circuit and play a role only in transmitting the reentry impulse to the rest of the ventricle.

In contrast, the schema in Fig. 10 is constructed to explain the mode of initiation, in which the maximal delay in S_3 and the earliest activation in the first induced beat (E_1) are not closely located and a "missed" time interval is present on the epicardial surface. In these cases, the impulse must circumvent the blocked area, which is still refractory, and enter the intramyocardium, eventually emerging on the

epicardial surface (dashed line). This possibility needs further proof from a three-dimensional mapping system.¹⁵

Interestingly, ventricular tachycardia was inducible in the absence of epicardial delay or block in 5 of 17 episodes. None of the 3 episodes of tachycardia rapidly degenerating into fibrillation was preceded by epicardial delay or block. The epicardial activation sequence during tachycardia suggested an endocardial origin (see Fig. 7). Thus, induced ventricular fibrillation and tachycardia degenerating into fibrillation appear to represent different electrophysiological mechanisms from epicardial reentry. The leading reentrant circle¹⁶ where the degree of dispersion of refractoriness plays an important role may facilitate this type of arrhythmia. Triggered activity should also be considered as a cause. Extensive subendocardial mapping may provide informative evidence in this regard.

In summary, the present study presents strong evidence for reentrant mechanisms as a genesis of induced ventricular tachycardia in a 7-day-old canine infarction model. Epicardial mapping with reference to infarct anatomy has re-emphasized the role of a thin surviving epicardial myocardium overlaying the infarct as the main site of reentry. However, further study is necessary to elucidate mechanisms of tachycardia unrelated to the epicardial activation sequence.

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