Localized reentry. Mechanism of induced sustained ventricular tachycardia in canine model of recent myocardial infarction.

H Garan, J N Ruskin

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Research Article

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Localized Reentry

Mechanism of Induced Sustained Ventricular Tachycardia in Canine Model of Recent Myocardial Infarction

Hasan Garan and Jeremy N. Ruskin
Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114

Abstract. This study was undertaken to investigate the mechanism underlying sustained monomorphic ventricular tachycardia (VT) in late experimental canine myocardial infarction. The hypothesis that sustained and "organized" continuous electrical activity (CEA) displaying a reproducible pattern with recurrent components recorded by bipolar endocardial, intramural, or epicardial electrodes in 10 animals during electrically induced sustained monomorphic VT represented reentrant excitation in an anatomically small area of the ventricle, was evaluated in the light of the following observations: Organized CEA always preceded the first monomorphic ventricular complex (QRS) of VT as well as the discrete local electrograms from closely surrounding sites during the initiation of VT. The site of organized CEA corresponded to the site of origin of sustained VT determined by isochronous contour map analysis of activation sequence. Ventricular pacing at rates more rapid than that of VT failed to terminate VT despite ventricular capture unless it transformed CEA into discrete local electrograms. VT could be terminated in three animals, with a single, critically timed premature stimulus delivered at a critically located focus close to the site of CEA, which would result in local capture and interrupted CEA. In six animals, surgical ablation of the site of organized CEA effectively prevented the reinitiation of sustained VT by programmed cardiac stimulation. These data showed that organized CEA and sustained VT were closely associated phenomena and suggested that organized CEA probably represented an important component of the tachycardia circuit.

Dr. Ruskin is the recipient of an American Heart Association Established Investigatorship (81 177). Address correspondence to Dr. Garan.

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Introduction

Recent studies that have investigated the mechanisms underlying ventricular tachycardia (VT),[1] which was induced by programmed cardiac stimulation in late canine experimental myocardial infarction (MI), have suggested involvement of reentrant pathways (1–9). Most of these studies used epicardial mapping techniques, which demonstrated the presence of functional conduction block with subsequent reentrant excitation during the initial complexes of VT, during repetitive ventricular complexes, or during nonsustained VT, that took place in thin layers of surviving epicardial tissue overlying the MI (2, 3, 5, 7, 8). The mechanisms underlying sustained, monomorphic VT, however, have been investigated less extensively (7, 9), with one investigation failing to demonstrate the presence of reentrant excitation during electrically induced sustained VT after experimental MI (7). The purpose of the present study was to investigate the electrophysiologic mechanisms underlying sustained, monomorphic VT, and to seek evidence for reentrant excitation during this arrhythmia in a canine model of experimental MI.

We have recently described the electrophysiologic characteristics of ventricular arrhythmias, which were observed in a canine model of MI that was created by extensive ligation of epicardial collateral vessels around the left ventricular apex in addition to ligation of the proximal left anterior descending coronary artery (10, 11). This technique uniformly resulted in a confluent anteroapical, transmural MI without any epicardial sparing (10). Other techniques of creating experimental MI used previously in various canine models, in which mechanisms of ventricular arrhythmias and reentrant excitation have been investigated, include Harris (12) two-stage coronary artery ligation (1, 4, 7), single stage proximal coronary artery ligation (1, 2, 3, 8, 9), two-stage ligation with reperfusion (4, 6, 7), and coronary artery ligation followed by placing the animals on a protein-deficient diet (5). Despite the histopathologic differences that may exist between our model and these other canine models of experimental MI, reproducible initiation and termination of

1. *Abbreviations used in this paper:* CEA, continuous electrical activity; MI, myocardial infarction; QRS, ventricular complex; NSR, normal sinus rhythm; S_2, S_2S_3, single and double premature ventricular stimuli; VT, ventricular tachycardia.

sustained VT by programmed cardiac stimulation also indirectly suggested reentry as the mechanism underlying the sustained VT that was observed in our model (10). The present report describes the electrophysiologic data that were observed not only during the initiation, but also during the course and at the termination of electrically induced sustained and monomorphic VT as they relate to the hypothesis that this arrhythmia is closely associated with reentry within an anatomically small region at the periphery of the experimental MI.

Methods

The methodologic details by which the experimental MI is created in this model have been described in previous reports (10, 11). Using sterile technique and intravenous pentobarbital (15 mg/kg) and methohexital (5 mg/kg) anesthesia, the heart was approached via a left lateral thoracotomy in the fifth intercostal space. The left anterior descending coronary artery was ligated at a level immediately proximal to the first diagonal branch. All visible epicardial branches in the left ventricular apical area that originated from the left circumflex or posterior descending coronary arteries were also ligated, which thus created a discrete, confluent, transmural anteroapical MI in every animal (10). The thoracotomy was closed and the animals were allowed to recover with meperidine (1.5 mg/kg) analgesia.

Electrophysiologic studies. Electrophysiologic studies were performed in 50 mongrel dogs that weighed 10–15 kg after an average of 26±3 d after experimental MI. Under general anesthesia with pentobarbital (30 mg/kg), the heart was approached via a median sternotomy. Arterial blood gases and serum sodium and potassium concentrations were monitored frequently throughout each experiment. Plasma pH was maintained between 7.35 and 7.45 by adjusting the alveolar ventilation and/or intravenous administration of sodium bicarbonate. Potassium chloride was administered intravenously as required to maintain the plasma potassium concentration above 3.5 meq/dl at this pH range. After the heart was suspended in a pericardial cradle, pairs of teflon insulated, 0.005 in.-diameter stainless steel plunge electrodes with barbs, 0.5–1.0 mm in length at the exposed ends, were inserted and anchored to the endocardial surface with the use of 25-gauge needles at 24 evenly spaced areas of the right and the left ventricular free wall, shown schematically in Fig. 1, for recording and electrical stimulation. These initial recording sites were the same for every dog, with ~1.6–2.2 cm between the adjacent electrode pairs, which depended on the size of the heart. Location of the transmural experimental MI was confined within the shaded area also shown in Fig. 1. On the epicardial surface, the points of insertion of the two insulated plunge wires that constituted each bipolar endocardial electrode at a given recording site were 2 mm apart. No attempt was made to control the orientation of the 0.5–1.0-mm-long barbs, which hooked onto the endocardial surface. Thus, on the endocardial surface, the interpolar distance of a bipolar endocardial electrode could vary from 0.5–1.0 to 3.0–3.5 mm.

The proximal terminal of the plunge electrodes were connected to a multichannel recorder and oscilloscope (VR-16; Electronics for Medicine, Pleasantville, NY) via a switchbox. The input from each bipolar recording electrode was amplified using an input impedance of 22 MΩ and a frequency response range of 0.03–2.5 kHz. All local electrograms were initially recorded at an amplifier gain setting of 1.0 mV/cm. Normal values for the amplitude and the duration of local bipolar electrograms in our laboratory had been determined using the data recorded from the same preselected recording sites displayed in Fig. 1, by using bipolar

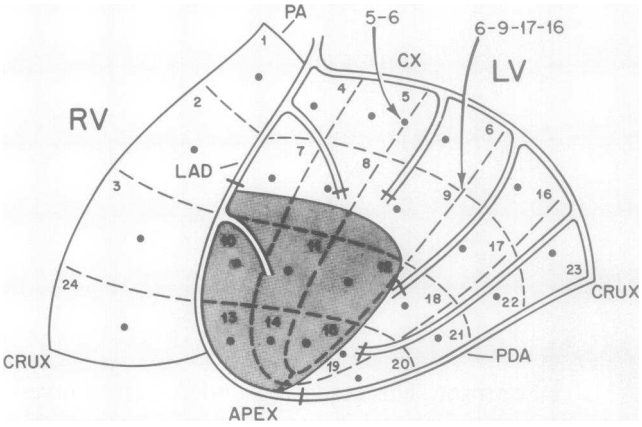


Figure 1. The schematic diagram for the free walls of the two ventricles. The interventricular septum is not represented. The heart was cut open using an incision extending from the crux to the apex along the posterior interventricular groove. The approximate sites of coronary ligation are also shown. The shaded area is the region where transmural MI was located in every animal. The heavy dots represent the centers of the areas that are outlined by interrupted lines and are the sites of 24 endocardial electrodes. Two examples illustrate how this numbering scheme was used to identify additional recording electrodes, which were positioned later during the course of the experiments at sites along, or at, the intersection of the interrupted lines. RV, right ventricle; LV, left ventricle; LAD, left anterior descending artery; CX, circumflex artery; PDA, posterior descending artery; and PA, pulmonary artery.

electrodes with fixed, 2 mm interpolar distance in 10 noninfarcted, anesthetized animals. These normal values for the amplitude and the duration of the left ventricular endocardial electrograms were 10.6±3.3 mV (mean±SDM) and 38±6 ms, respectively. The normal left ventricular endocardial electrogram amplitude ranged from 2.8 to 21.5 mV and the normal left ventricular endocardial electrogram duration ranged from 22 to 48 ms. The corresponding values were 8.8±3.8 mV and 42±7 ms for right ventricular endocardial electrogram amplitude and duration; 13.0±5.5 mV and 28±6 ms for left ventricular epicardial electrogram amplitude and duration; and 11.5±4.5 mV and 30±5 ms for right ventricular epicardial electrogram amplitude and duration.

In the present study, the signal amplitudes of electrograms recorded from the regions that were noninfarcted by post mortem examination (right ventricular free wall; basal, lateral, and diaphragmatic walls of the left ventricle) varied from 1.8 to 17.5 mV, whereas signal amplitude of electrograms recorded from the region that contained the MI ranged from 0.3 to 8.0 mV. A "fractionated" local bipolar electrogram that was recorded from a site at or adjacent to the infarcted area was defined as a signal with an amplitude <1.8 mV (the lowest amplitude recorded from a noninfarcted wall segment in these animals), which had a total duration of at least 60 ms (longer than any of the local electrogram durations recorded from a noninfarcted segment), during which time the slope of the signal changed from positive to negative (or vice versa) more than three times. Continuous electrical activity (CEA) was said to be present at a recording site when the local bipolar electrogram showed activity throughout the entire cardiac cycle without any quiescent diastolic interval (Fig. 2). The amplitude of CEA ranged between 0.3 and 0.6 mV. CEA, which manifested at least three and usually more

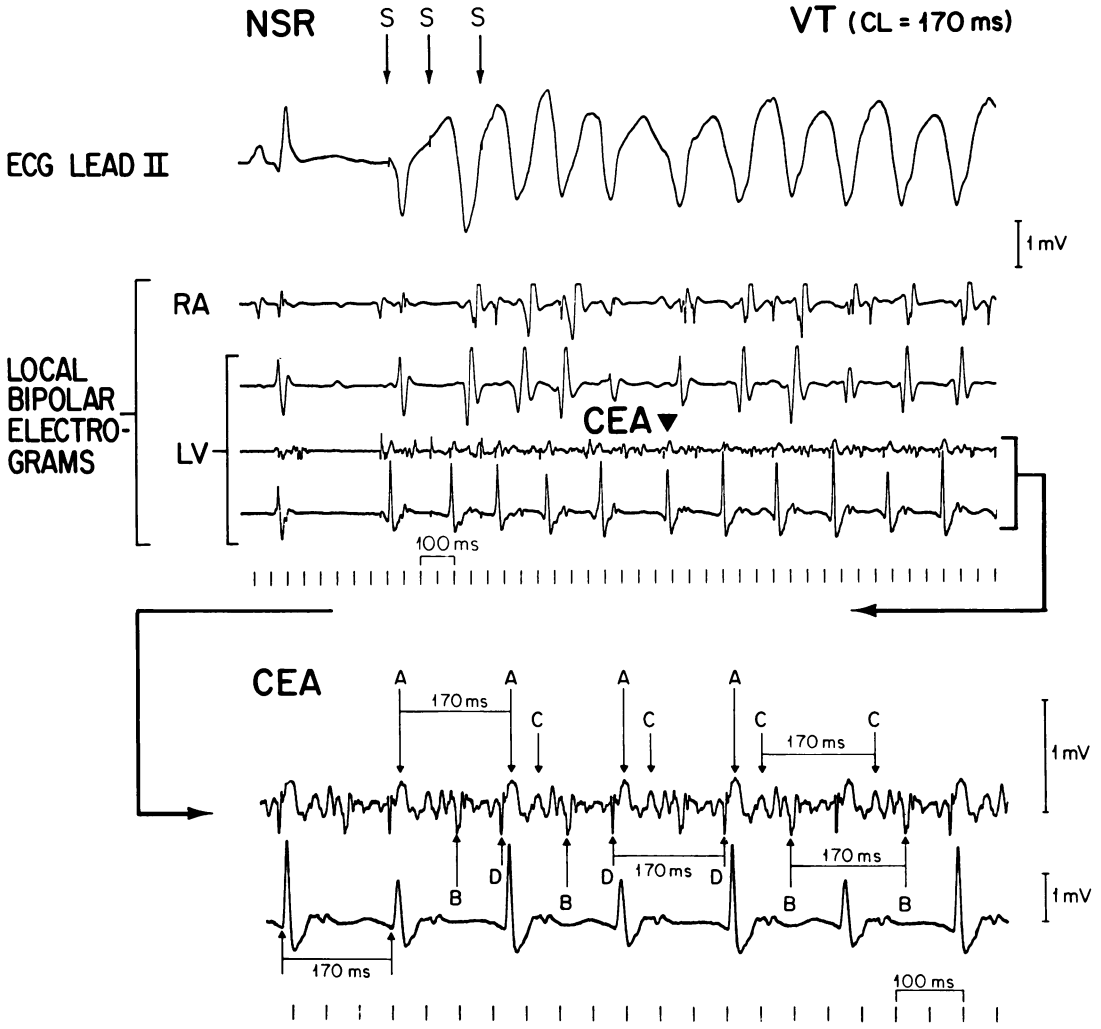


Figure 2. The top panel shows the initiation of sustained VT with a cycle length (CL) of 170 ms, during which time a local bipolar left ventricular (LV) electrogram demonstrates the presence of organized CEA. The lower panel shows the same channel, showing CEA at a higher gain setting, later during the course of the same episode of VT. Five recurrent components of CEA were identified (A–D). Note that the frequency of recurrence was the same for all components. RA, right atrial recording.

consistently identifiable components that recurred with every cardiac cycle, was called "organized" CEA (Fig. 2); otherwise, it was called disorganized CEA. High as well as low frequency wave forms (Fig. 2) were observed in the recurrent, reproducible pattern of organized CEA. The absence of the most of the high frequency wave components of organized CEA in recordings obtained during VT from sites located within 1 cm of the site of CEA, and most importantly their absence during ventricular pacing at cycle lengths comparable to the VT cycle lengths, in recordings obtained from the sites that had manifested CEA during VT, argued against the possibility that these high frequency components represented motion artifacts and suggested that these components more likely represented electrical activity in close vicinity of the recording electrodes.

Local electrograms were displayed simultaneously with surface ECG leads I, II, and V_1. Electrophysiologic data were stored on FM magnetic tape (A. R. Vetter, Inc., Rebersburg, PA). The systemic arterial pressure measured at the left subclavian artery and the left atrial pressure measured via a polyurethane cannula that was inserted through the left atrial appendage were recorded with Statham P323D6 pressure transducers (Statham Instruments, Inc.) on a multichannel Sanborn model 350 oscillograph (Hewlett-Packard Co., Inc, Palo Alto, CA).

24 consecutive post-MI animals in whom sustained, uniform VT was reproducibly initiated by programmed cardiac stimulation, were included in this study. The remaining 26 animals, in whom the predominant response to programmed cardiac stimulation was nonsustained polymorphic VT or ventricular fibrillation, or those in whom no ventricular arrhythmia could be initiated, were excluded. The methods of initiation of VT in this model have been described previously and included programmed single (S_2), double (S_2S_3), or triple premature ventricular stimuli during fixed rate ventricular pacing at two different cycle lengths,

and brief (4–8 beat) bursts of rapid ventricular pacing during normal sinus rhythm at decreasing cycle lengths (300–150 ms) (10, 11). The stimulus strength was maintained at twice diastolic threshold for each site of stimulation. Single and double premature ventricular stimuli or bursts of rapid ventricular pacing at cycle lengths shorter than the cycle lengths of VT were used to terminate sustained VT. Additional 0.005 in.-diameter endocardial plunge electrode pairs (also 2 mm between points of insertion of the two electrodes that constituted a pair) were then placed in and at the periphery of the MI zone in order to create a denser grid of bipolar recording electrodes, with a minimum distance of 5 mm and a maximum distance of 8 mm between the epicardial points of insertion of adjacent electrode pairs. As with the previously placed plunge electrodes, no attempt was made to control the orientation of the 0.5–1.0-mm-long barbs at the tip of the electrodes, which were hooked onto the endocardium. Therefore, in this area of the dense electrode grid, the minimal endocardial interelectrode distance could vary from 3.5–4 to 6–6.5 mm (rather than measuring 5 mm) and the maximal interelectrode distance could vary from 6.5–7 to 9–9.5 mm (rather than measuring 8 mm). Bipolar epicardial electrogram recordings were obtained from epicardial sites that were immediately adjacent to the point of entry of every endocardial plunge electrode, and from other additional epicardial areas during normal sinus rhythm (NSR) and during sustained VT with the use of a hand-held exploring probe, which was a plastic mounted bipolar electrode with an interpolar distance of 2 mm. All of the animals also had bipolar subepicardial recordings that were obtained via 8–12 subepicardial plunge electrodes (teflon-insulated 0.005 in.-diameter wires with 0.5–1.0 mm exposed tips), which were positioned below the epicardial surface in areas 7–19 (Fig. 1). The exposed tips of these recording electrodes were found to be located 1.5–2.5 mm deep, to the epicardial surface, by postmortem examination. The local endocardial or epicardial activation time (taken to be the instant when rapid intrinsic deflection of the local electrogram, ≥ 5 mV/10 ms, crossed the base line [5]) for each recording site, which demonstrated biphasic or triphasic local electrograms with clearly defined rapid deflections, was determined manually. Local activation times were not assigned to recording sites that manifested fractionated local electrograms or CEA. The beginning of the ventricular complex (QRS), during VT, which was determined from a surface ECG lead that manifested a clearly identifiable point of onset, served as zero time reference. When such a clearly defined point of onset of the QRS could not be identified in any of the surface ECG leads, the earliest local bipolar electrogram recorded from the right or the left ventricle was used as zero time reference. Using these data, computer-generated isochronous contour maps were obtained using the method of bivariate linear interpolation of the electrode coordinate set onto a rectangular grid within a boundary defined by the left ventricular outline, followed by use of the GCONTR program, which was adapted to the VAX with minimal alterations (13, 14).

Total cardiopulmonary bypass. Five animals manifesting organized CEA from an endocardial site during VT were placed on total cardiopulmonary bypass. 3,000 ml of heparinized blood from donor dogs were used to prime a cardiopulmonary bypass pump (Cardiovascular Instrument Corp., Wakefield, MA). Each animal received an additional 2,000 U of intravenous heparin sulfate. The azygos vein was ligated and the superior and the inferior venae cavae were cannulated using 20 French Versi-Cath catheters (National Catheter Corp., Argyle, NY). The systemic venous return was diverted into the cardiopulmonary pump, as was the coronary sinus blood, via another cannula with multiple side holes advanced into the right ventricle through a right atriotomy after the main pulmonary artery was ligated. A disposable membrane blood oxygenator (Temptrol) was used to oxygenate the blood that was pumped into the systemic circulation via both femoral arteries. A left ventricular vent was also placed via a left atriotomy. The cardiac output was adjusted to maintain the mean arterial pressure at 90 mmHg, and ranged from 1.4 l/min to 3.3 l/min. The temperature of the blood in the reservoir was kept at 38°C. When hemodynamic stability was achieved on total cardiopulmonary bypass, VT was initiated by the same methods of programmed ventricular stimulation as previously described.

In two dogs, a transmural left ventricular incision that completely encircled the bipolar plunge electrodes that recorded CEA, and were located in the border of the MI, was performed while on total cardiopulmonary bypass during normal sinus rhythm and under normothermic conditions. The isolated transmural tissue, ~ 1 cm $\times$ 1 cm in size, was then resutured using felt support. Programmed cardiac stimulation was repeated, using all available pacing sites, according to the protocol described above. In three other animals, a similar method of ablation was carried out at two other separate control sites, which were located at the periinfarction zone, and manifested fractionated local electrograms or disorganized CEA, but not organized CEA, before the ablation of the site that manifested organized CEA. The ablative procedures were carried out one at a time, and each separate ablation was followed by programmed cardiac stimulation. In a sixth animal, a 0.5-cm nontransmural incision 3 mm deep (confirmed by postmortem examination) was performed between the two subepicardial electrodes that manifested CEA activity during VT. Cardiopulmonary bypass was not employed. This wedgelike incision was then closed using a continuous suture with felt support, after which programmed cardiac stimulation was repeated as described above.

Postmortem studies. While excising and opening up the heart along the posterior interventricular groove (Fig. 1), care was taken not to perturb the position of the endocardial and subepicardial recording electrodes that were labeled for identification according to the numbering scheme described above. The endocardial and subepicardial location of the recording electrodes were confirmed. Except for a rare plunge wire that was found to be embedded in a papillary muscle, all endocardial electrode pairs were observed to be hooked securely onto the endocardial surface with randomly oriented barbs that did not make contact with each other. The data recorded by the endocardial plunge electrodes that were embedded in a papillary muscle were not used for analysis of endocardial activation patterns. The relation of the electrode location to the distribution of MI (in, peri, or outside MI zone) were determined by examining 0.5-cm thick transverse sections of the LV.

Results

In 24 of the 50 animals, sustained monomorphic VT with the same cycle length could be reproducibly initiated and terminated from the same left or right ventricular endocardial pacing site, using similar modes of programmed ventricular stimulation. The modes of initiation and termination and surface ECG characteristics of the VT observed in this canine model have been previously described in detail (10).

Transient, disorganized CEA at the initiation of VT. In every animal there were at least three (up to seven per animal) endocardial and/or epicardial recording sites, located at the periphery of the MI, which manifested fractionated (minimum duration 60 ms) local electrograms during NSR. During premature ventricular stimulation, several, but not all, of these recording sites displayed disorganized CEA due to a combination

of increasing delay from stimulus artifact to the electrogram, and increasing prolongation of local electrogram duration (Fig. 3). The delay from stimulus artifact to the onset of the local electrograms could be as long as 120 ms, and was influenced by the distance between the pacing and the recording sites, as well as by the direction of pacing. Local electrograms with duration <55 ms during NSR were not transformed into CEA during premature stimulation or during repetitive ventricular beats, even in the presence of artifact to local electrogram delay. In the fractionated local electrograms (>60 ms), which ultimately revealed disorganized CEA, the extent of progressive prolongation was 80–140 ms before transformation into CEA. Transient disorganized CEA could be reproducibly induced from at least two nonadjacent recording sites by two programmed premature ventricular stimuli over a wide range of coupling intervals (first interval 210–150 ms, second interval 160–110 ms), or by rapid ventricular stimulation over a wide range of cycle lengths (210–150 ms) in all animals. In each case, stimulation was repeated at least twice at the same coupling intervals to confirm the reproducibility of the findings. Although the presence of disorganized CEA was a reproducible finding over these ranges, the delay and the prolongation of the local electrograms and the duration of disorganized CEA were different at different coupling intervals. In each animal, there were also recording sites which despite manifesting fractionated local electrograms with durations >60 ms during sinus rhythm did not reveal CEA during programmed premature ventricular stimulation; electrogram duration either became prolonged by a small amount (<40 ms) or did not change, or rarely actually became shorter.

When programmed cardiac stimulation accompanied by transient, disorganized CEA also resulted in sustained monomorphic VT, transient disorganized CEA never extended beyond the initial complexes into the uniform phase of sustained VT and was replaced either by fractionated but discrete local electrograms (Fig. 3) or by organized CEA that was sustained and displayed a distinct pattern with reproducible recurrent components during VT as defined in Methods (Fig. 4).

Sustained, organized CEA coexistent with monomorphic sustained VT. In contrast to the transient, disorganized CEA, organized CEA, defined in Methods, was recorded during sustained VT in only 10 of 24 animals. The mean cycle length of VT observed in these 10 animals was 185±20 ms (mean±SDM), and was not significantly different from the mean VT cycle length observed in the remaining 14 animals with sustained VT (181±17 ms). Regardless of the method of programmed cardiac stimulation used to initiate VT, organized CEA always preceded the first monomorphic QRS of sustained VT, (Fig. 5) and once initiated, it was temporally coextensive with sustained monomorphic VT, persisting in its original pattern as long as VT persisted (Figs. 4 and 5). In each of the 10 animals that manifested organized CEA during sustained VT, three of the consistently identifiable, recurrent components of the organized CEA were used by the investigators to determine the cycle lengths with which these CEA components recurred without knowledge of the cycle length of VT determined from surface ECG. In each case, the cycle lengths determined from each of the recurrent components of organized CEA, and from the surface ECG, were either identical or differed by 3–5 ms. The same analysis carried

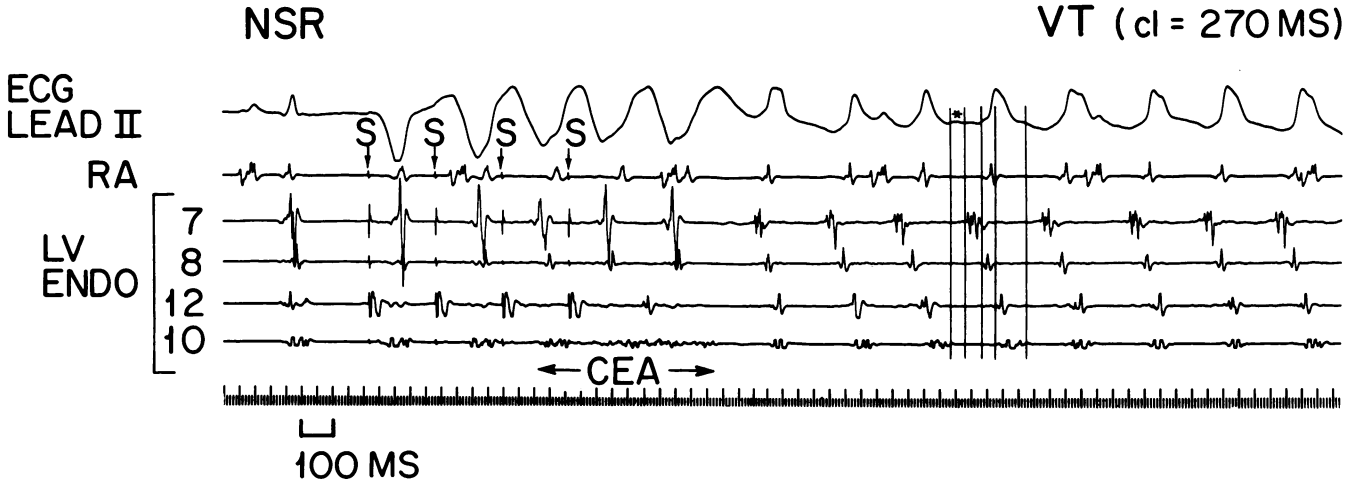


Figure 3. Transient disorganized CEA early in VT. Sustained uniform VT with a cycle length (cl) of 270 ms was initiated by four ventricular premature stimuli (S) that were introduced during NSR. Left ventricular (LV) pacing site is adjacent to endocardial (ENDO) area 12, and all four recording sites (7, 8, 10, 12) were located at the margin of the infarction. Successive ventricular stimuli caused increasing delay of conduction, which culminated in nonsustained disorganized CEA, recorded from area 10, which terminated before sustained monomorphic VT. The vertical lines mark the onset or the offset of local electrograms at recording sites in display. Note that there is electrical activity during all the time intervals except the one marked with the asterisk. See text for further explanation. RA, right atrial recording.

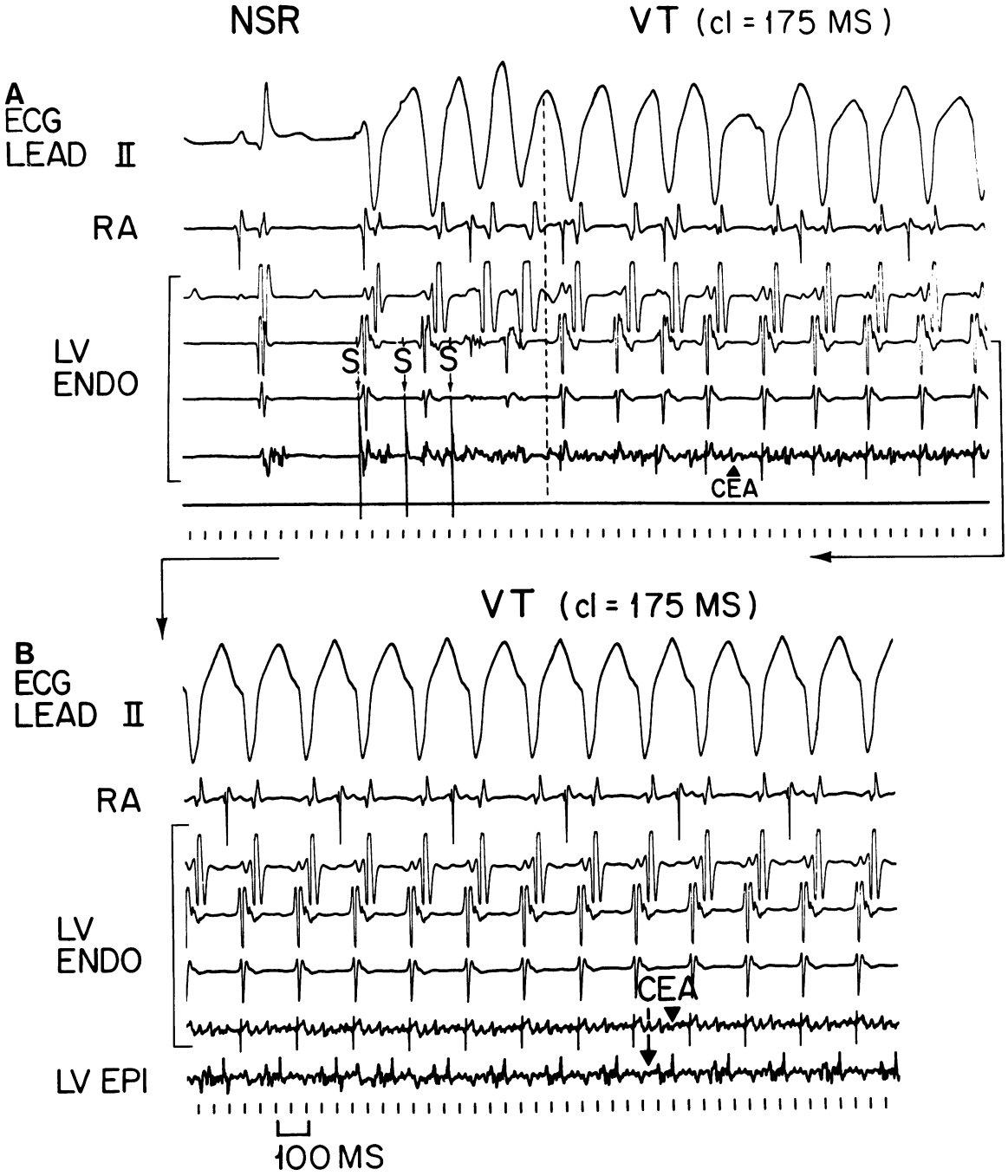


Figure 4. Sustained, organized CEA during sustained monomorphic VT. (*A*) VT was initiated by three premature ventricular stimuli (S) during NSR. Note that the disorganized CEA ceases before the organized sustained CEA, with a recurring pattern, appears (-----). The onset of CEA precedes the local electrograms, which were recorded from surrounding sites. Nothing is being recorded on the last channel during the initiation of VT. (*B*) A bipolar recording obtained from a subepicardial area (LV EPI) immediately overlying left ventricular endocardial (LV ENDO) site manifesting CEA, simultaneous with the endocardial recording channels, has been added to the display during the same episode of VT. The subepicardial recording also shows CEA with recurrent components but with a pattern different from the one observed at the subjacent endocardial recording site. RA, right atrial recording.

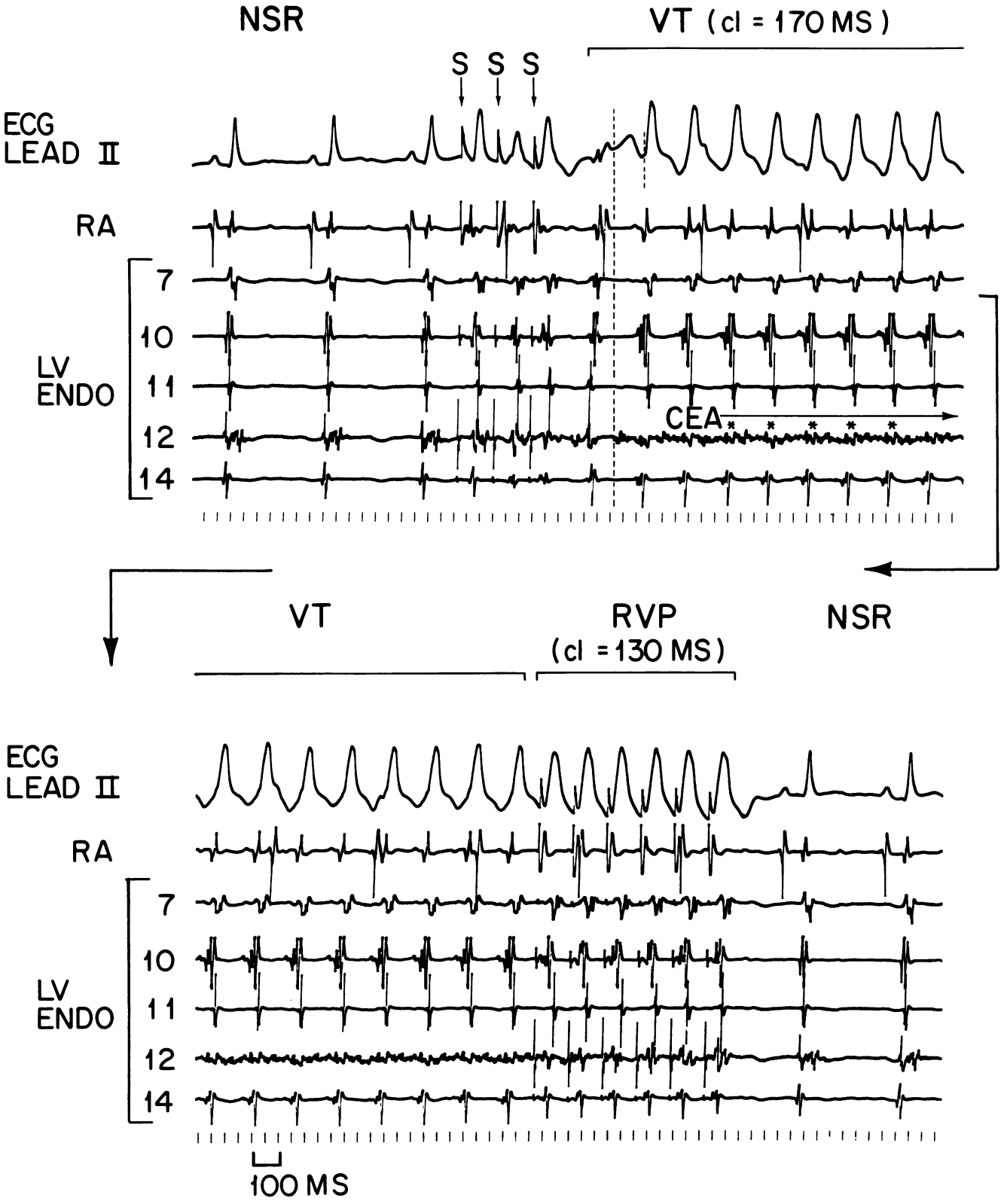
out in each animal during two other instances of the same episode of VT separated by at least 100 complexes yielded the same results. Furthermore, the phase differences between the three recurrent CEA components during the same VT remained invariant throughout the entire course of the VT.

Sustained, organized CEA and endocardial/epicardial activation sequences. Organized CEA was recorded from only a single circumscribed endocardial area in 7 of the 10 animals in whom it was observed. Bipolar recordings that were obtained from neighboring endocardial sites <1 cm away in different directions from each of these circumscribed areas that displayed organized CEA always manifested discrete local electrograms, with quiescent intervals between successive electrograms. Subepicardial recordings obtained from sites 4–6 mm (location confirmed by postmortem examination) superficial to the endocardial recording site manifesting CEA also showed discrete local electrograms in these seven animals. Taking 3.5 and 9.5 mm as estimated minimal and maximal interelectrode distances between two adjacent bipolar electrodes, and using these estimations as radius size for a cylindrical volume with 6 mm height, CEA was probably limited to a volume that could vary in size approximately from 0.3 to 1.7 cm^3 in these animals. A technically adequate isochronous contour map of the endocardial activation sequence during sustained VT could be constructed in six of these seven animals. The data points used to construct these isochrones did not include local electrograms, which displayed fractionated electrograms or CEA (see Methods). In each case, the recording site displaying organized CEA, to which no local activation time could be assigned, was located <8 mm (~6.5–9.5 mm on the endocardial surface) away from the recording site of earliest endocardial activity, with the spread of excitation progressing away from this site during VT (Fig. 6). The site(s) of earliest epicardial activation during VT were located 1.5–3.5 cm away from the endocardial recording site of organized CEA, and the earliest endocardial activity preceded the earliest epicardial breakthrough by 8–25 ms during VT in these six animals. In another animal, organized CEA was recorded from only a single subepicardial site located 2 mm beneath the epicardial surface (location confirmed by postmortem examination of the electrodes). In the remaining two animals, organized CEA was recorded simultaneously from both an endocardial site and from the overlying subepicardial site 6 and 8 mm away. In these latter two animals, the recordings obtained from the endocardial and overlying subepicardial sites that displayed organized CEA were similar but not identical (Fig. 4), and the volume of myocardium that contained CEA could be larger than the one previously estimated. Isochronous contour maps of endocardial and epicardial activation during VT in these two animals showed early endocardial and epicardial activity at sites located <1 cm away from the recording site that displayed organized CEA (Fig. 7).

Interruption of CEA and termination of sustained VT. Rapid ventricular pacing was carried out in every animal from multiple pacing sites including all the electrodes of the dense grid adjacent to the electrode pair recording CEA, during at least two different episodes of the same VT, at progressively decreasing cycle lengths, using a stimulus strength of twice diastolic threshold for that particular site. Rapid ventricular pacing was started in each animal using a cycle length identical to that of the VT. In every animal there was at least one endocardial pacing site, adjacent to the area displaying CEA, from which pacing at cycle lengths 20–60 ms shorter than the cycle length of VT terminated VT reproducibly (Figs. 5, 8, and 9). Rapid ventricular stimuli, which captured the ventricles and terminated VT, had a predictable effect on organized CEA. Before VT was terminated, organized CEA was transformed by ventricular extrastimuli into discrete but fractionated local electrograms with short quiescent intervals in between the electrograms (Figs. 5, 8, and 9). In three animals, rapid ventricular pacing was attempted systematically using the same cycle length range, and the same current strength from four separate endocardial sites 5–10 mm away from the site of organized CEA and located in four different directions 90° apart: organized CEA (and therefore VT) could be reproducibly terminated by pacing from two of the four pacing sites in two animals, and from only one of the four sites in the third animal. Thus, the general direction, and the distance of the pacing site in relation to the site of organized CEA, as well as the cycle length of pacing, could all be important determinants of the outcome of ventricular pacing during VT.

Rapid ventricular pacing at cycle lengths that resulted in ventricular capture without terminating VT had two different effects on organized CEA. In four cases, there were cycle lengths at which the morphologic pattern of CEA changed during rapid ventricular pacing with ventricular capture, with disappearance of certain recurring components, but CEA was not transformed into discrete electrograms; the same CEA pattern with the identical cycle length observed before ventricular pacing became established as VT resumed immediately after the cessation of rapid pacing (Fig. 8). In all these cases, whenever rapid ventricular pacing failed to interrupt CEA, it failed to terminate VT even if it modified CEA transiently without interrupting CEA. On closer examination with high amplitude gain, no examples of entrainment or resetting of the individual CEA components could be documented during rapid pacing, which modified organized CEA. In these four animals, organized CEA was modified by pacing over a reproducible cycle length range (150–130 ms). In the remaining six animals, the CEA pattern was unaffected and no resetting of the repeating cycle was observed during ventricular pacing at all cycle lengths that did not result in transformation of CEA into discrete electrograms, despite local capture of the recording sites adjacent to the CEA site (Fig. 9). The individual CEA components could be observed to march through rapid pacing interval without alteration in periodicity (Fig. 9).

The longest cycle lengths of ventricular pacing that were required to interrupt organized CEA (133±7 ms, mean±SDM)


NSR
VT (cl = 170 MS)
S S S
ECG
LEAD II
RA
7
10
LV
ENDO
11
12
14
CEA
VT
RVP
(cl = 130 MS)
NSR
ECG
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RA
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LV
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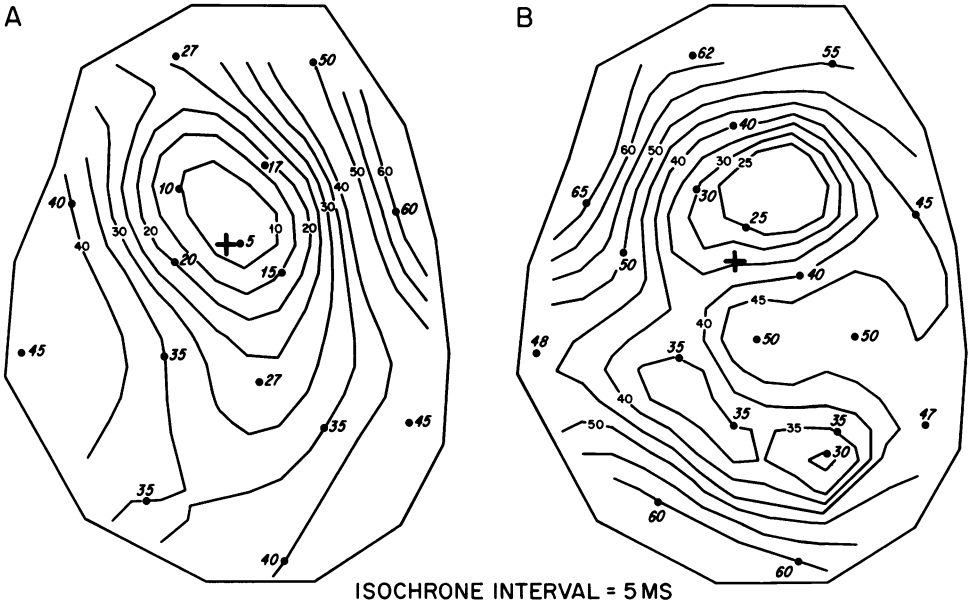

Figure 6. Endocardial and epicardial activation sequences during VT. Isochronous contour maps depict the endocardial and epicardial activation sequences during uniform sustained VT. Only the anteroapical wall, which contains the MI and the periinfarction regions, are shown. The dots represent actual data points, but not all data are shown to avoid crowding. The numbers represent milliseconds relative to the earliest endocardial activity taken arbitrarily as zero time. The cross depicts the endocardial site where CEA was recorded. Note that this site corresponds to the site of the earliest endocardial breakthrough of activation.

were uniformly shorter than the longest cycle lengths of ventricular pacing that were required for ventricular capture without termination of VT (148±11 ms). Thus, when pacing cycle lengths in between these values were used, the site displaying organized CEA appeared either to be protected from any penetration by paced stimuli (Fig. 9), or to be transiently altered, perhaps with partial penetration, but ultimately not transformed (Fig. 8).

The effects of programmed double and single ventricular extrastimuli, scanning the entire cardiac cycle, on organized CEA and sustained VT were investigated in every animal. VT was reproducibly terminated by programmed S_2S_3 in five of the ten animals in whom organized CEA was recorded. As in the case of rapid ventricular stimulation, VT was terminated only when local organized CEA was interrupted by two successive ventricular stimuli. Similarly, when CEA was only transiently altered but not interrupted by double stimuli, VT continued along with the resumption of the previous CEA pattern. In two of these five animals, and in one other animal, local capture with an S_2 interrupted organized CEA without capturing the entire ventricle (Fig. 10). In the example shown in Fig. 10, the programmed ventricular premature stimulation was applied at an endocardial pacing site <1.0 cm away from the site displaying organized CEA, 85 ms after the onset of the surface QRS of VT, a time in cardiac cycle with no possibility of capturing the ventricles at twice diastolic threshold. Yet the premature impulse interrupted local CEA and altered the activation of adjacent sites, as seen in the first local electrogram. Although a reproducible phenomenon at coupling intervals between 80 and 90 ms, termination of organized CEA could not be accomplished with an S_2 of the same strength at coupling intervals outside this range. Furthermore a single premature stimulus at twice diastolic threshold using coupling intervals longer than 145 ms and shorter than 190 ms captured the ventricles without interrupting CEA or VT. The site of stimulation and the lengths of the coupling intervals were similarly critical in terminating VT using an S_2 in the remaining two animals. In two animals in whom an S_2 terminated CEA, attempts to reproduce this finding using the same stimulus strength and the coupling interval range, from equidistant pacing sites located in different directions, were unsuccessful. Resetting of the recurring components of organized CEA by an extrastimulus that captured the ventricles without terminating VT was never observed in any of the animals.

Ablation of the site of CEA. Five animals in whom a well-defined endocardial recording site manifesting organized CEA was identified, were placed on total cardiopulmonary bypass. In order to assess the possible effects on inducibility of the changes in hemodynamics or those in the geometry of the heart on cardiopulmonary bypass, programmed ventricular stimulation was performed from the same LV endocardial sites as those used before total cardiopulmonary bypass. The same sus-

Figure 5. CEA during initiation and termination of sustained VT. Sustained monomorphic VT was initiated by three premature ventricular stimuli (S) and terminated by rapid ventricular pacing (RVP). The transient disorganized CEA (left ventricular endocardial 12) produced by premature ventricular stimuli was separated from the sustained, patterned CEA by a brief quiescent period. The latter was not present during the initial QRS of VT but preceded the first monomorphic beat of VT by 80 ms. RVP from a site 1.0 cm away from the site of CEA at a cycle length (cl) that was 40 ms shorter than that of VT resulted in fragmented, but discrete local electrograms with short quiescent periods between them which replaced CEA before VT was terminated. RA, right atrial recording.

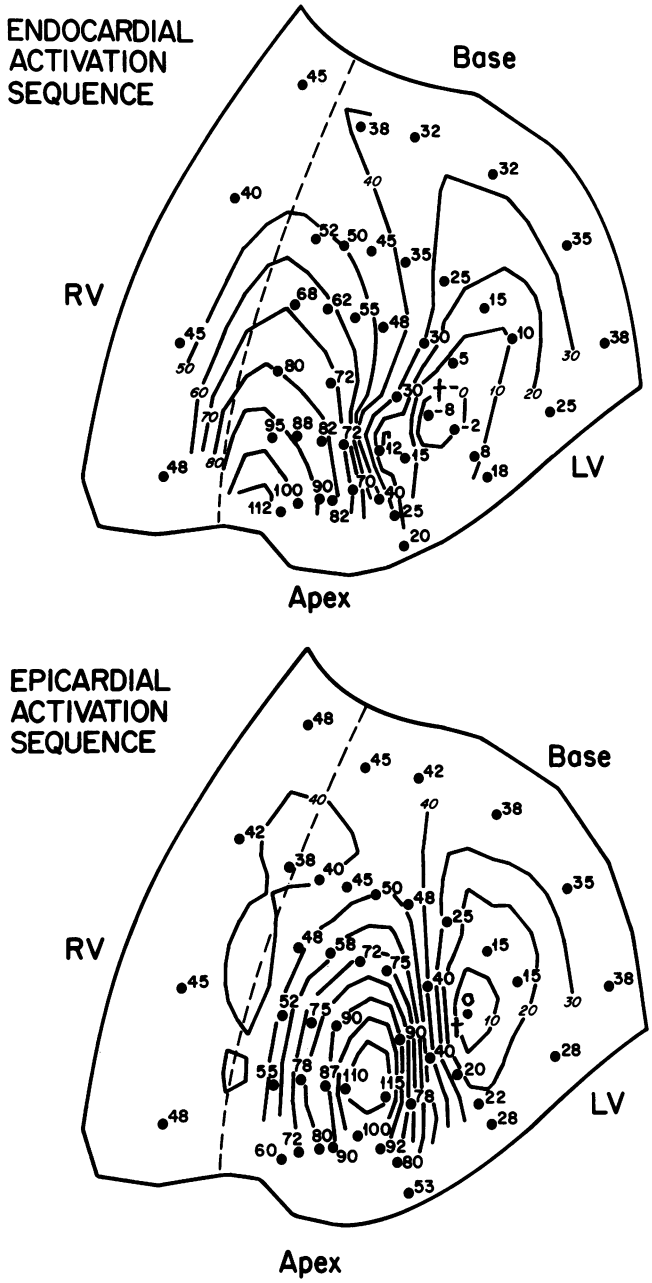

Figure 7. Endocardial and epicardial activation sequences during sustained monomorphic VT in an animal manifesting CEA that was recorded from an endocardial and the overlying subepicardial recording sites. The schematic shown in Fig. 1 is used to represent the free walls of the ventricles. Isochrone interval was 10 ms. The numbers adjacent to the dots depict the local activation times. The clearly identifiable onset of QRS during VT in a surface ECG lead was taken as time zero; local activation times preceding this instant were assigned negative values. Not all data points are shown. The endocardial and the subendocardial recording sites manifesting CEA are labeled with a cross. Note that the site of CEA is located adjacent to the sites of both endocardial and epicardial breakthrough of activity.

tained VT was initiated by stimulation from these sites, and the recording sites that manifested organized CEA during VT before cardiopulmonary bypass displayed the same local electrical activity when sustained VT was initiated during total cardiopulmonary bypass. In two animals, after the encircling transmural incisions (described in Methods), which were performed while the animals were in sinus rhythm, programmed cardiac stimulation was repeated. In both animals, programmed VT could not be induced despite the use of all previously employed modes of programmed cardiac stimulation from all available stimulation sites. In three other animals, in addition to the endocardial recording site located in periinfarction area manifesting organized CEA, two other endocardial recording sites, one displaying discrete local electrograms during VT and another displaying fractionated local electrograms or disorganized CEA, were identified in the periinfarction zone. The same surgical ablation technique was applied to these two additional sites also during sinus rhythm. Morphologically similar sustained VT could still be initiated by programmed cardiac stimulation after ablation of these sites (Fig. 11). In contrast, as in the case of two animals described above, sustained VT could not be induced after a similar ablative procedure was finally applied to the site manifesting organized CEA in these three animals (Fig. 11). Analysis of the signals from all of the previously available recording sites demonstrated that although the morphology of the local electrograms recorded from adjacent recording sites could be altered, none of these sites manifested CEA. Specifically, all the sites previously displaying disorganized nonrepetitive CEA continued to show the same disorganized CEA and were never observed to display organized CEA after surgical ablation.

In a sixth animal, which manifested organized CEA that was recorded from a subepicardial site during VT, a 0.5-cm long nontransmural incision, penetrating 3 mm into myocardium, performed during VT between the two subepicardial electrodes that comprised the bipolar recording electrode pair displaying organized CEA, resulted in termination of VT. Subsequent attempts to reinitiate the same sustained VT were unsuccessful, and resulted only in nonsustained episodes of polymorphic VT regardless of the site and mode of stimulation employed.

Discussion

The present study provides electrophysiologic evidence that supports the presence of localized reentry in a small area of the left ventricle during sustained monomorphic VT, which is initiated by programmed cardiac stimulation in a canine model of experimental MI. The characteristics of organized CEA recorded by closely spaced bipolar electrodes observed during the initiation and especially during the termination of VT by programmed ventricular stimulation in this model support the hypothesis that this pattern of local electrical activity is closely associated with reentrant excitation that takes place throughout the entire cardiac cycle in a small area of the left ventricle rather

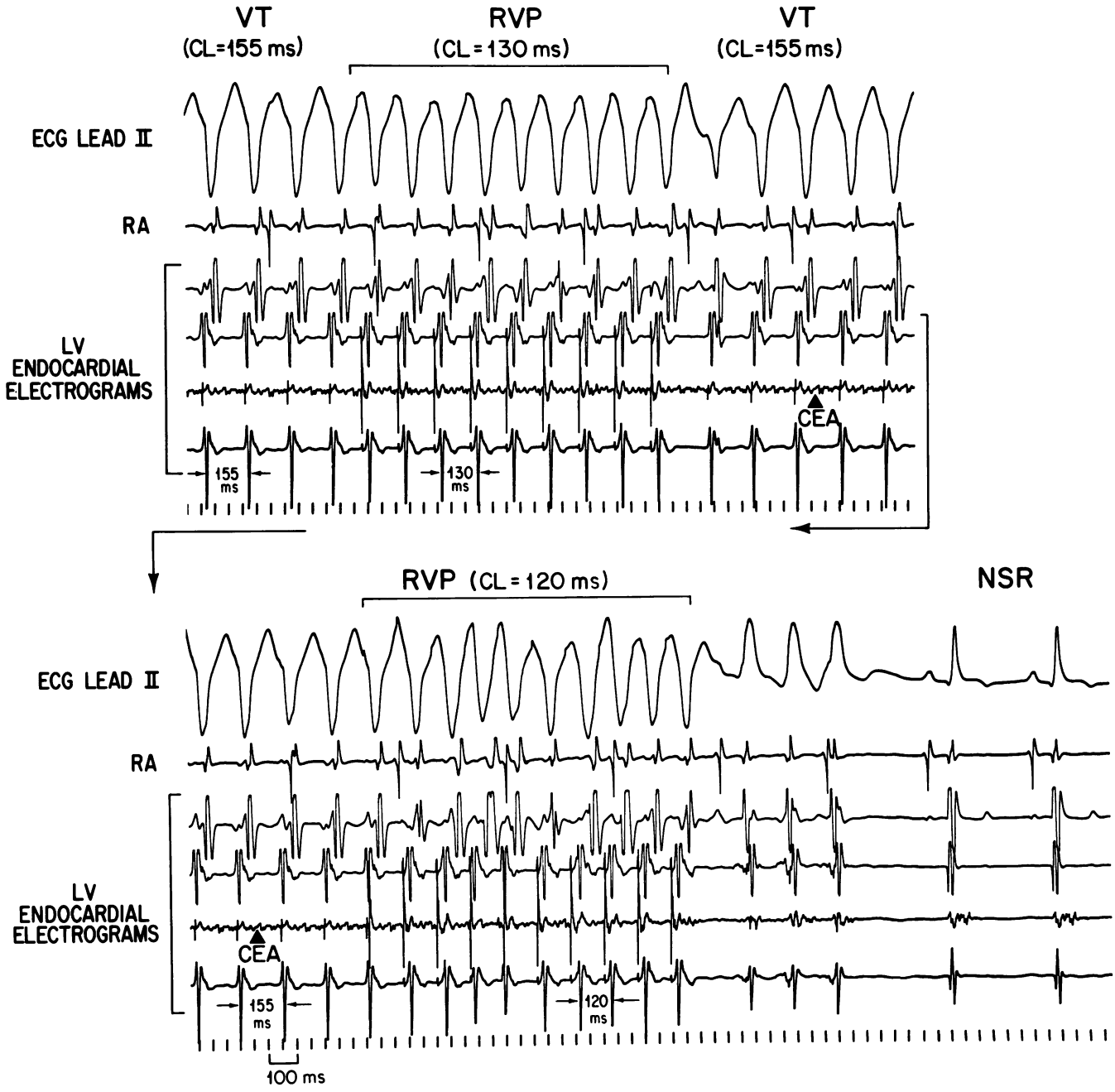

Figure 8. Termination of VT by ventricular pacing. The upper panel shows rapid ventricular pacing (RVP) with a cycle length of 130 ms, which captured the ventricle and altered the CEA pattern with disappearance of certain components, but failed to interrupt CEA. Upon cessation of RVP, the previous CEA pattern was resumed along with VT. A second burst of RVP with slightly shorter cycle length (CL) converted CEA into fragmented but discrete local electrograms and resulted in termination of VT. RA, right atrial recording.

than representing multiple different impulses that originate in remote areas and arrive asynchronously at the recording site. The observations that organized CEA was recorded at the site of origin of VT as determined by isochronous contour maps, and that it was always temporally coextensive with the episodes of sustained monomorphic VT, further support this hypothesis. Finally, the elimination of inducible VT by the ablation of the site where organized CEA was recorded from, and the failure

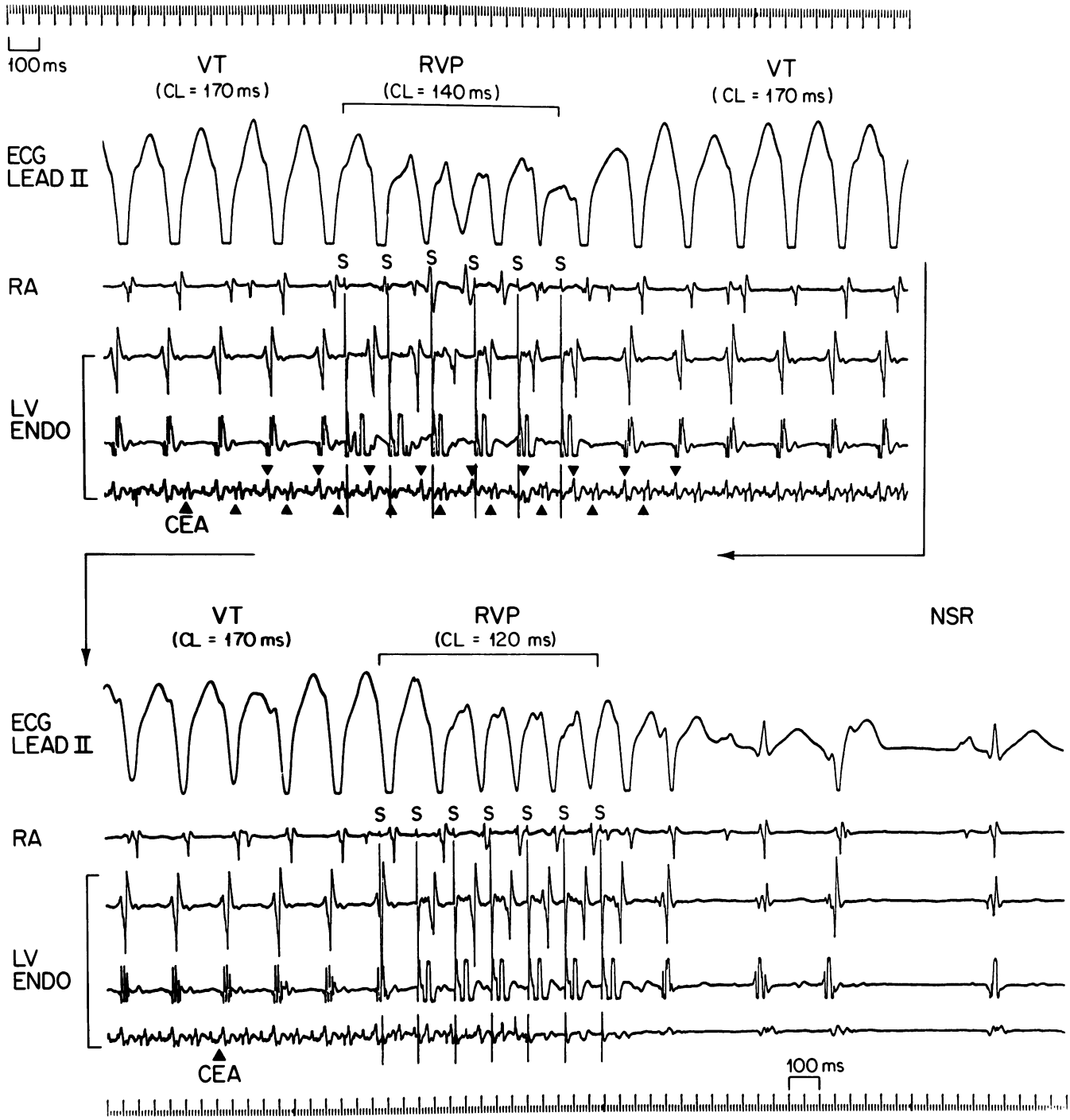

Figure 9. The upper panel shows sustained uniform VT during which organized CEA was recorded from a local left ventricular endocardial (LV ENDO) recording site. Rapid ventricular pacing (RVP) resulted only in local capture during the first extrastimulus and, with the subsequent stimuli, all recording sites shown, except the one demonstrating CEA, manifested evidence of local capture. RVP, however, did not reset or alter in any way the pattern of organized CEA, which suggested entry block. Note that the two labeled (dark arrows) CEA components marched through RVP without a change in periodicity. After RVP, VT continued unaffected. In the lower panel, RVP, using a shorter cycle length (CL), which was applied during the same episode of VT, penetrated the site of CEA, as evidenced by the changing pattern of CEA, which ultimately transformed CEA into fractionated discrete electrograms, and interrupted VT. RA, right atrial recording.

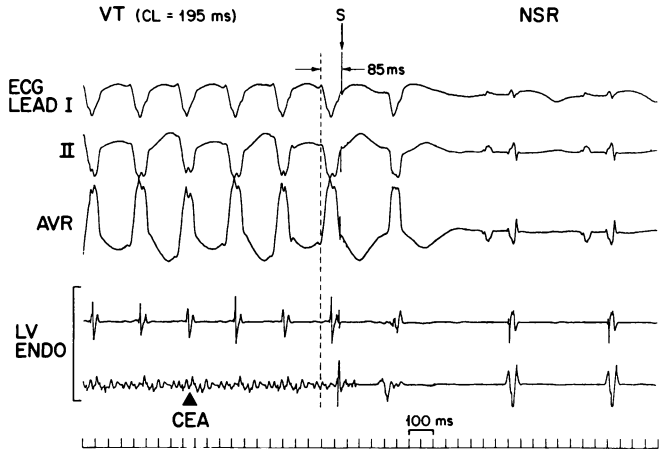

Figure 10. Termination of CEA and VT by a single ventricular premature stimulus. A single, critically timed programmed premature stimulus, 85 ms after the onset of VT surface QRS, delivered to the endocardial site displaying organized CEA, immediately modified the pattern, and interrupted CEA. An early, fragmented, but discrete local electrogram followed, which corresponded to another ventricular beat, after which NSR was resumed. LV ENDO, left ventricular endocardial.

of the same ablative procedures applied to control sites to achieve the same result, suggested that organized CEA might represent an essential part of the mechanism underlying sustained monomorphic VT.

The accepted criteria for the direct demonstration of reentrant excitation, described by Mines, include the presence of a unidirectional conduction block with return of an impulse to its site of origin before the onset of next cardiac cycle, and also the elimination of the impulses that are expected to arise from reentrant activity by physical interruption of the pathway (15, 16). When a wave of excitation satisfying these criteria proceeds along a large pathway at least several centimeters in diameter (macro-reentry), its presence can be detected by examining the local electrograms that are recorded by electrodes positioned in the area containing the pathway (7, 8, 9). However, if reentrant excitation is confined to a smaller area, for example, 1 cm^3 vol (microreentry), direct demonstration of these criteria may not be possible within the resolution of the recording system. The detection of CEA during extrastimulus-induced ventricular ectopic beats was initially proposed as an alternate and valid method to demonstrate the presence of reentrant excitation (2, 3). However, it has been demonstrated that CEA can be recorded during slow depolarization of the surviving epicardial cells overlying MI by the use of a composite electrode in the absence of any evidence of reentry (17, 18). In contrast, when closely spaced extracellular bipolar electrodes are used to record activity over excitable tissue, in which the fundamental bioelectric event consists of depolarization followed by repolarization, activity is recorded when the wave of excitation reaches the tissue immediately underlying one of the electrodes, and the local electrogram represents the instant of activity contained in an anatomically small area between the two terminals (19–21). Such closely spaced extracellular bipolar electrodes were used in our study to record CEA that was composed of recurrent reproducible components, recorded over a wide filtering range. However, CEA, even when sustained, manifesting an organized pattern with regularly recurring reproducible components, and recorded from closely spaced bipolar electrodes, should not be equated with reentrant activity unless other confirmatory electrophysiologic phenomena are shown to be present. Extensive degree of fractionation of a bipolar electrogram into multiple asynchronous spikes during pacing has been reported and interpreted as marked desynchronization of activation within a region comprised of heterogenous fibers (1, 22). Furthermore, the resolution of the recording system and the range of filtering used in our study do not allow an incisive electrophysiologic and geometric interpretation of the individual components or patterns of organized CEA. For example, even at 30 Hz cutoff level, relatively slow wave forms may represent repolarization and not just depolarization. Thus, an organized pattern of CEA may be recorded in the absence of reentry if impulses arising from a distant focus arrive asynchronously at an area, resulting in an asynchronous but relatively fixed sequence of depolarization and repolarization waves, producing a pattern which remains unchanged from one cardiac cycle to the next.

However, our study showed that during sustained, monomorphic VT, the activation spread to the rest of the myocardium away from the site of organized CEA and not from a distant site towards the site of organized CEA. Unlike disorganized CEA, organized CEA was always recorded from a site immediately adjacent to the site of earliest endocardial or epicardial activation during VT, not supporting the interpretation that CEA represented asynchronous wave fronts arriving from a distant focus. In contrast, disorganized transient CEA was recorded from sites farther away from the site of earliest activity and was always preceded by progressive prolongation of fractionated electrograms. Although this phenomenon might occur secondary to further slowing in linear conduction, it could also be the result of further desynchronization of activation by multiple wavelets and cannot necessarily be related to reentry. Similarly, the pacing induced changes in fractionated electrograms might result from more exaggerated slowing of linear conduction or occur as a result of a change from nonlinear to linear conduction secondary to block in one direction, or as a result of the combination of the two phenomena, and should be interpreted with caution.

Even when recorded from the site of origin of VT, it is not simply the presence of a recognizable, repeating pattern, but the presence of other associated electrophysiologic phenomena that support the close relationship between CEA and reentry. These associated electrophysiologic phenomena were best demonstrated during the termination of sustained VT in our canine model. The critical nature of both the timing and the site of application of double and single programmed premature ventricular stimuli, which interrupted organized CEA and termi-

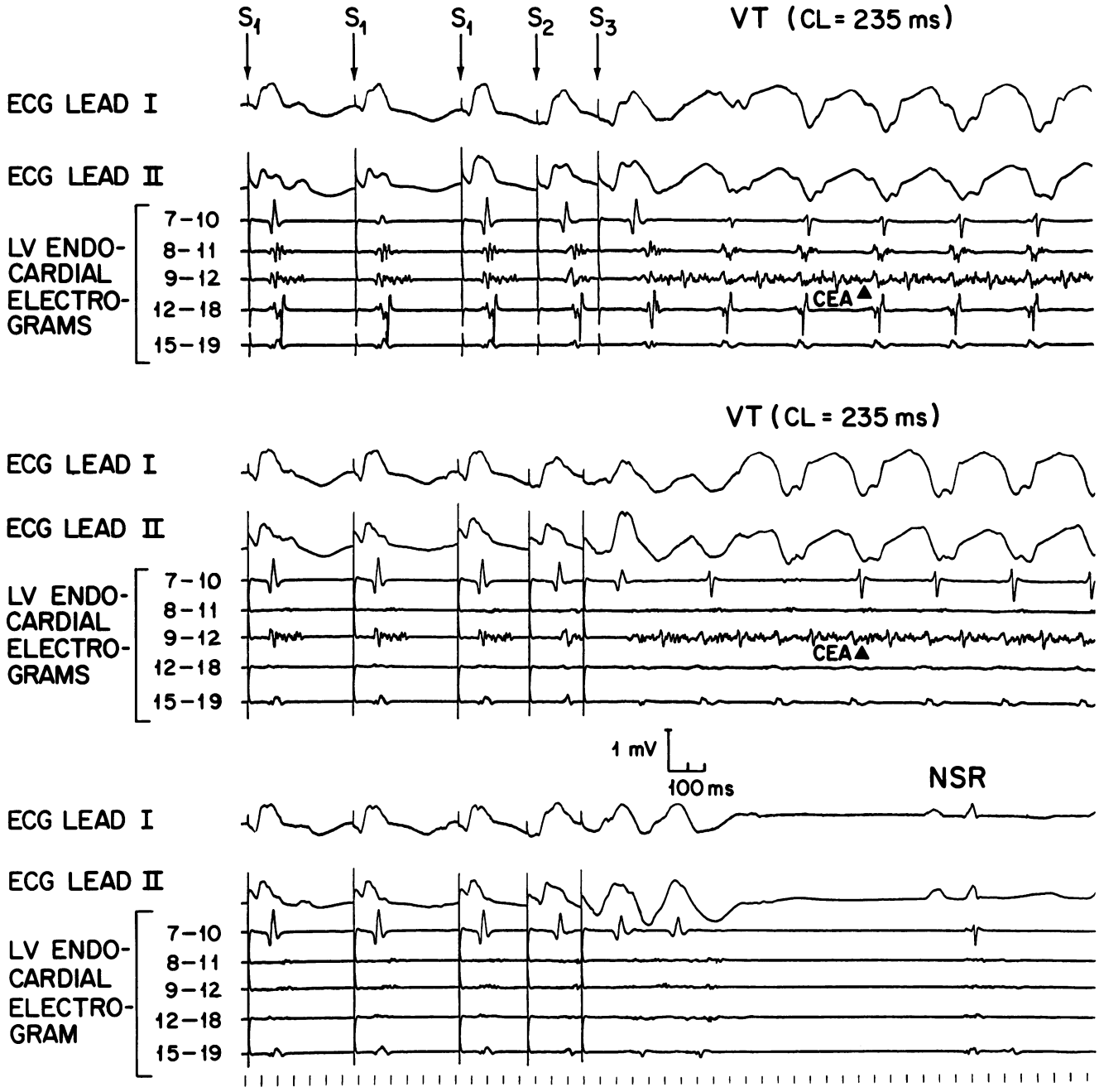

Figure 11. The top panel shows sustained VT that was initiated by programmed cardiac stimulation using two ventricular premature stimuli (S_2S_3) during ventricular pacing (S_1). Local electrograms from five periinfarction zones (Fig. 1) are displayed. Note CEA in channels numbered 9–12. The second panel shows the initiation of the same VT with the same mode of programmed stimulation, albeit using shorter coupling intervals, after surgical ablation was applied to sites 8–11 and 12–18. Note that CEA persisted during sustained VT. After the ablation of the site 9–12 (*bottom panel*), however, all attempts to reinitiate VT were unsuccessful, regardless of the coupling intervals used. LV, left ventricular; CL, cycle length.

nated VT in this model, suggested a reentry mechanism. Probably the strongest evidence in support of a close association between organized CEA and local reentrant excitation was provided by the examples of three animals, in whom a single, properly timed ventricular stimulus applied at a unique ventricular site in close vicinity of the site manifesting organized

CEA, interrupted CEA, and VT (Fig. 10). Equally important was the fact that this phenomenon was reproducible over a narrow range of coupling intervals. A small reentry pathway might be protected from penetration by premature extrastimuli as a result of enhanced refractoriness in surrounding tissue. This type of protection was suggested in our study by examples of ventricular pacing, which resulted in local capture of the recording sites in close vicinity of the site of CEA, without causing any alteration in CEA (Fig. 9). This phenomenon might account for the rarity with which CEA and VT were successfully terminated with single extrastimulus in our model. When multiple stimuli are used, however, the first few stimuli may alter refractoriness in the tissues interposed between the reentry pathway and the site of stimulation, and thereby facilitate penetration of the reentry pathway by the subsequent stimuli, provided that one of the latter stimuli encounters an excitable gap. Such a mechanism may explain the phenomenon shown in the lower panel of Fig. 9. This mechanism may also explain the greater efficacy of multiple extrastimuli in interrupting CEA and VT when compared with single or double extrastimuli introduced over a wide range of coupling intervals. However, since both the proximity and the direction of the site of stimulation appear to be critical in interrupting CEA, inability to terminate VT in every animal using double or single extrastimuli may also be due to the limitations of the techniques used, and to the difficulty in identifying the critical pacing sites required to penetrate the tachycardia circuit. To achieve reproducible interruption of organized CEA with a single subdiastolic threshold stimulus delivered directly into the site of continuous electrical activity, not attempted in our study, would further strengthen this argument, since an appropriately timed subthreshold stimulus that encountered an excitable gap could theoretically interrupt reentrant excitation without capturing any other part of the ventricle.

In general transformation of CEA into discrete fractionated electrograms during rapid ventricular pacing might occur on the basis of more than one mechanism. If CEA represented asynchronous activation of diseased tissue by impulses arriving from a distant site, then interruption of CEA might occur, due to intermittent entry block into this tissue during rapid pacing, and would not necessarily mean that penetration of a site of reentry took place. In that case, resumption of CEA might be expected during the subsequent few cycles of VT that ensue after the cessation of ventricular pacing. This phenomenon was not observed in the case of organized CEA in our study. Instead, every time organized CEA was transformed into discrete fractionated electrograms by ventricular pacing, sustained VT was interrupted and the cessation of pacing was followed by further discrete fractionated electrograms which were recorded from the site manifesting CEA during VT. These observations were compatible with, although did not directly prove the hypothesis that organized CEA represented reentry and that transformation of CEA into discrete fractionated electrograms by rapid ventricular pacing occurred as a result of penetration and interruption of reentry circuit; in that case, after the interruption of organized CEA, subsequent extrastimuli would be expected to capture the site of CEA, resulting in fractionated but discrete local electrograms, precisely the phenomenon observed in our study (Figs. 5, 8, and 9). The examples, which demonstrated no alteration in CEA pattern by ventricular pacing during VT, might be explained by the presence of entrance block into the tissue manifesting CEA (Fig. 9). Ventricular pacing-induced modification of CEA pattern without interruption of CEA (Fig. 8) was harder to explain. This phenomenon might represent partial penetration of the circuit with transient alterations in the pathways, without actual interruption due to inability to encounter an excitable gap, an explanation which, although highly speculative, was indirectly suggested by the observation that CEA was transiently modified without interruption by pacing at critical cycle lengths just longer than the cycle lengths that finally interrupted CEA. However, similar phenomena might also arise from pacing-induced changes, which take place only at critical cycle lengths in the conduction and refractoriness of the tissue lying between the site of recording electrodes and a nearby site of reentrant excitation.

The elimination of electrically induced VT by ablation of the site of organized CEA further showed that organized CEA and sustained monomorphic VT were closely associated phenomena. Although changes due to surgery such as changes in wall tension, alterations in geometry, etc., might affect the induction of sustained VT by their nonspecific effects on the left ventricle, further demonstration of the failure to eliminate inducible sustained VT by similar ablation of other ventricular sites suggested that ablation of the site of organized CEA was a specific intervention. With the techniques used it was not possible to conclude whether CEA represented the entire circuit, or a particular component of the tachycardia circuit. The results of the ablation of CEA site suggested that organized CEA probably represented an essential component of the tachycardia circuit, even if not the entire circuit.

Organized CEA coexistent with sustained monomorphic VT and displaying the electrophysiologic characteristics described above was observed in a minority (42%) of animals in whom sustained VT was reproducibly induced. The difficulty of localizing small areas of reentrant excitation in animals with inducible VT might result from the limited numbers of plunge electrodes used in each study. The uniformity of the model and the electrophysiologic characteristics of the VT observed did not suggest the presence of different underlying mechanisms. However, in the absence of direct evidence for organized CEA during monomorphic VT in every animal with inducible VT in this study, the possibility of other mechanisms, e.g. macroreentry over pathways larger than the ones suggested in our discussion, underlying sustained VT in at least some animals not manifesting organized CEA cannot be excluded.

The electrophysiologic data in our study are consistent with the previous reports, which have provided indirect and direct evidence for reentrant excitation underlying induced ventricular arrhythmias in late canine myocardial infarction (1–10). Our study shows that reentry does not have to be confined to the

epicardium or to the endocardium but is usually observed in the periinfarction zone of the transmural infarction. It suggests that organized, sustained CEA, recorded during sustained VT from a small, and possibly, but not necessarily, unique site of the ventricle, and disorganized, nonsustained CEA, recorded during programmed ventricular stimulation and during repetitive, polymorphic ventricular beats from multiple recording sites, represent different electrophysiologic phenomena. Finally, our study underscores the point that reentry and CEA should not simply be equated, and it proposes several electrophysiologic criteria that can be used to test the association between CEA and localized reentrant excitation.

Acknowledgments

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References

1. Scherlag, B. J., N. El-Sherif, R. Hope, and R. Lazzara. 1974. Characterization and localization of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Circ. Res.* 35:372–384.

2. El-Sherif, N., R. R. Hope, B. J. Scherlag, and R. Lazzara. 1977. Reentrant ventricular arrhythmias in the late myocardial infarction period. 1. Conduction characteristics in the infarction zone. *Circulation.* 55:686–702.

3. El-Sherif, N., R. R. Hope, B. J. Scherlag, and R. Lazzara. 1977. Reentrant arrhythmias in the late myocardial infarction period. 2. Patterns of initiation and termination. *Circulation.* 55:702–719.

4. Karagueuzian, H. S., J. J. Fenoglio, Jr, M. B. Weiss, and A. L. Witt. 1979. Protected ventricular tachycardia induced by premature stimulation of the canine heart after coronary artery occlusion and reperfusion. *Circ. Res.* 44:833–846.

5. Klein, G. J., R. E. Ideker, and W. M. Smith. 1979. Epicardial mapping of the onset of ventricular tachycardia initiated by programmed stimulation in the canine heart with chronic infarction. *Circulation.* 60:1375–1384.

6. Michelson, E. L., J. F. Spear, and E. N. Moore. 1980. Electrophysiologic and anatomic correlates of sustained ventricular tachyarrhythmias in a model of chronic myocardial infarction. *Am. J. Cardiol.* 45:583–590.

7. Wit, A. L., M. A. Allessie, F. I. M. Bonke, W. I. M. Lammers, J. Smeets, and J. J. Fenoglio, Jr. 1982. Electrophysiologic mapping to determine the mechanism of experimental ventricular tachycardia initiated by premature impulses. *Am. J. Cardiol.* 49:166–185.

8. El-Sherif, N., R. A. Smith, and K. Evan. 1981. Canine ventricular arrhythmias in the late myocardial infarction period. *Circ. Res.* 49:255–265.

9. El-Sherif, N., R. Mehra, W. B. Gough, and R. H. Zeiler. 1982. Ventricular activation patterns of spontaneous and induced ventricular rhythms in canine one-day-old myocardial infarction. *Circ. Res.* 51:152–166.

10. Garan, H., J. T. Fallon, and J. N. Ruskin. 1980. Sustained ventricular tachycardia in recent canine myocardial infarction. *Circulation.* 62:980–987.

11. Garan, H., J. T. Fallon, and J. N. Ruskin. 1981. Nonsustained polymorphic ventricular tachycardia induced by electrical stimulation in 3 week old canine myocardial infarction. *Am. J. Cardiol.* 48:280–286.

12. Harris, A. S. 1950. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. *Circulation.* 1:1318–1328.

13. Akima, H. 1978. Algorithm 526. Bivariate interpolation and smooth surface fitting for irregularly distributed data points. *ACM Transactions on Mathematical Software.* 4:160–164.

14. Snyder, W. V. 1978. Algorithm 531. Contour plotting. *ACM Transactions on Mathematical Software.* 4:290–294.

15. Mines, G. R. 1913. On dynamic equilibrium in the heart. *J. Physiol. (Lond.).* 46:350–383.

16. Mines, G. R. 1914. On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation. *Trans. R. Soc. Can.* 8:43–52.

17. Worley, S. H., G. H. Bardy, W. M. Smith, and R. E. Ideker. 1982. Continuous fractionated electrical activity from the composite electrode during slow orderly epicardial depolarization. *Am. J. Cardiol.* 49 (Pt. 2):946. (Abstr.)

18. Moore, E. N., J. F. Spear, M. B. Simson, and E. L. Michelson. 1980. The composite cardiac electrogram: fact or artifact: *Am. J. Cardiol.* 45:417. (Abstr.)

19. Durrer, D., J. P. Roos, and J. Buller. 1965. The spread of excitation in canine and human heart. *In* Electrophysiology of the Heart. B. Taccardi and G. Marchetti, editors. Pergamon Press Inc., Elmsford, New York. 203–214.

20. Scher, A. M., A. C. Young, A. L. Malmgren, and R. R. Paton. 1953. Spread of electrical activity through the wall of the ventricle. *Circ. Res.* 1:539–547.

21. Scher, A. M., and M. S. Spach. 1979. Cardiac depolarization and repolarization and the electrocardiogram. *In* Handbook of Physiology, Vol. I. R. M. Berne, editor. American Physiological Society, Bethesda, Maryland. 9(Sect. 2):357–392.

22. Elharrar, V., P. R. Foster, T. L. Jirak, W. E. Gaum, and D. P. Zipes. 1977. Alterations in canine myocardial excitability during ischemia. *Circ. Res.* 40:98–105.