Electrode Catheter Recordings during Malignant Ventricular Arrhythmia Following Experimental Acute Myocardial Ischemia

Evidence for Re-entry due to Conduction Delay and Block in Ischemic Myocardium

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SUMMARY
In 20 anesthetized opened-chest dogs, plunge wire and electrode catheter recordings of the His bundle electrogram which also showed septal activation, were monitored before and after ligation of the anterior septal artery. The average time to onset of ventricular tachycardia after ligation was 5 1/2 min. The evolution of the arrhythmia was temporally related to progressive fragmentation and delay of the septal potential, resulting in a marked increase in total ventricular activation time (up to 335 msec). In six experiments the fragmented, delayed septal depolarization was inscribed well beyond the T wave of the surface QRS prior to the onset of arrhythmias. Various conduction disorders involving the ischemic septal myocardium were observed which closely correlated to the patterns of conduction disorder in the ischemic proximal His-Purkinje system. First degree block, 2° block of the Mobitz II and Wenckebach types, higher degree block and paroxysmal complete block occurred. The onset of the arrhythmia was characteristically associated with a Wenckebach pattern of conduction delay of a part of the septal deflection. Conduction disorders of the ischemic myocardium were tachycardia-dependent. Bradycardia resulted in recovery of form, duration, and timing of the septal potential with the coincident disappearance of ventricular arrhythmias. The study shows that the basic prerequisites for re-entry do exist during the early period following occlusion of a major coronary artery and can explain the malignant phase of ventricular arrhythmias. Similar disorders in man may be detected by intracardiac electrode catheter recordings.

Additional Indexing Words:
Septal electrogram Tachycardia-dependent block Conduction disorders
Sudden death Ventricular ectopic beats Wenckebach conduction
Prematurity index Ischemic heart disease

SEVERAL PREVIOUS STUDIES have demonstrated slow desynchronized ventricular conduction during experimental myocardial infarction in the canine heart and have suggested re-entry as a possible mechanism responsible for the early malignant phase of ventricular arrhythmias. Recent studies have shown a temporal relationship between progressive delay in activation of local myocardial electrograms and the onset of ventricular arrhythmias. Delays of 215 msec\(^6\) and 320 msec\(^7\) after onset of depolarization were observed, time periods that would allow local activation to be inscribed beyond the T wave of the standard electrocardiogram. In several recent reports, we have studied the time course of ischemic conduction disorders of the proximal His-Purkinje system following acute ligation of the anterior septal artery in dogs. Ligation of the anterior septal artery also leads to two distinct phases of ventricular arrhythmias similar to those described by Harris and Rojas after major coronary artery ligation. The early phase of ventricular arrhythmia is more serious and can degenerate into rapid ventricular tachycardia and ventricular fibrillation. We observed that this early phase of arrhythmia has a distinctly different time course from the conduction disorder of the proximal His-Purkinje system. The arrhythmia seems to be specifically related to a characteristic pattern of conduction disorders primarily involving the ischemic septal myocardium which strongly suggests a re-entrant mechanism. These disorders could be analyzed from both the electrode catheter and plunge wire recordings of the septal electrogram. Analysis of the electrode catheter recordings is of particular interest for it may suggest possible application to similar situations in man.

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Material and Method

Experiments were performed in 20 adult mongrel dogs weighing 10–20 kg and anesthetized with intravenous sodium pentobarbital (30 mg/kg). A Harvard respirator using room air provided mechanical ventilation through a cuffed endotracheal tube. Blood pressure in the femoral artery was monitored through a polyethylene catheter connected to a Statham transducer. A thoracotomy incision was made through the left fourth intercostal space. The bifurcation of the left coronary artery was exposed by retracting the tip of the left atrial appendage and incising the epicardium overlying the proximal portions of the anterior descending and left circumflex arteries. The anterior septal artery was exposed by blunt dissection of the bifurcation and branches of the left coronary artery and a silk ligature was placed around the vessel to be occluded after taking control records.

The left thoracotomy was then closed and the animal turned to expose the heart through a right thoracotomy. One to three pairs of plunge wire electrodes were placed in the His bundle area through a 22 gauge needle 1/2 inches in length containing two teflon-coated stainless steel wires (0.007 inches coated diam.). The cut ends of the wires served as close bipolar pairs. The position of the recording wires was considered satisfactory when late septal depolarization dominated the ventricular deflection and was inscribed coincident with the terminal part of the surface QRS and/or slightly afterward. Invariably, a His bundle deflection and low amplitude atrial activity were also seen on these recordings. Recordings of the His bundle and regular ventricular muscle were also obtained by electrode catheters (5 French with ring electrodes 10 mm apart). The catheters were either inserted into a common carotid artery and advanced to the aortic root or into a femoral vein and positioned in the right side of the heart across the tricuspid valve. An attempt was always made to obtain an electrode catheter recording from the His bundle area that shows — in addition to a sharp His bundle deflection — a ventricular potential with a relatively distinct terminal deflection, reflecting late septal depolarization. In five out of 20 experiments, catheter electrode recordings were only obtained to show that the observed changes after ligation of the anterior septal artery were not altered due to possible traumatic injury resulting from insertion of the plunge wire electrodes.

Two reference electrodes were placed in the lateral free walls of the right and left ventricles at sites approximately equidistant from the ventricular septum. These recordings were achieved by inserting two fine teflon-coated stainless steel wires (0.003 inches diam) into the epicardium through a 25 gauge needle. In addition to the electrograms, two or more standard electrocardiographic leads were recorded, specifically leads II and aVR. All records were obtained on a multichannel oscilloscopic photographic recorder (E for M, DR-8) at paper speeds of 25–200 mm/sec with the filter frequencies of 0.1–200 Hz for ECG leads and 40–200 Hz for electrogram recordings. Some of the recordings were stored on a magnetic tape recorder (Honeywell 5600) and replayed so that selected sections could be transferred to photographic paper for detailed analysis. Measurements were accurate up to ±3 msec at a paper speed of 200 mm/sec.

Atrial pacing (2 msec duration, 180–200 pulses per minute and 2–10 volts) was achieved via two fine stainless steel wires (0.003 inches diam) inserted by a 25 gauge hypodermic needle into the right atrial appendage. Pacing was performed with a Grass S-88 stimulator and SIU 8 isolation unit. For slowing of the heart rate, two silver wires (0.012 inches in diam) were inserted into the distal portion of the right or left vagosympathetic trunk. Vagal stimulation was accomplished by delivery of 0.05 msec square wave pulse of 1–10 V intensity at a frequency of 20 Hz.

Procedures

Control recordings during sinus rhythm, vagal-induced cardiac slowing, and atrial pacing up to rates that produced atrioventricular conduction of the Wenckebach type were obtained in each experiment before the anterior septal artery was ligated. After abrupt one-stage ligation of the anterior septal artery, the recorded electrical activity was continuously monitored for the onset of ventricular arrhythmias. The effect of atrial pacing was assessed at 2.5 min intervals up to 30 min after occlusion. Termination of atrial pacing and/or vagal-induced slowing of the heart were used to interrupt frequent ventricular premature beats or ventricular tachycardia, allowing sinus rhythm to resume. Using this technique it was possible to allow the experiment to proceed without consequent ventricular fibrillation developing. If ventricular fibrillation did occur, the experiment was terminated and defibrillation was not attempted. In all experiments, postmortem dissection was performed to see that the anterior septal artery had been completely occluded, as well as to verify the position of the plunge wires which were used to record the His bundle and septal potentials.

Results

The sequence of changes following ligation of the anterior septal artery was not different in experiments utilizing catheter electrode recordings alone and in those in which both catheter electrodes and plunge wire recordings were obtained. Typical changes up to the onset of ventricular arrhythmias are shown in figures 1 and 2. Recordings from top to bottom include standard ECG leads II and aVr, electrode catheter recording of the His bundle from the left side (Hb(L)), plunge wire recording of the His bundle (Hb(W)) and two bipolar electrograms from the lateral free walls of the right and left ventricles (RVeg and LVeg, respectively). Panel A in figure 1 shows control recordings before ligation of the anterior septal artery. Note that the ventricular potential in the Hb(W) recording consists of initial low amplitude deflections and a terminal sharp biphasic deflection representing the late depolarization of the septal myocardium. The septal potential is coincident with and extends slightly after the terminal part of the surface QRS and has a duration of 30 msec. On the other hand, the ventricular potential in the Hb(L) recording is a multiphasic complex of which the terminal part consists of a sharp biphasic or triphasic deflection simultaneously inscribed with the septal potential on the Hb(W) recording. The total ventricular activation time (VAT) measured on the Hb(L) recording is longer than the surface QRS duration (85 msec and 60 msec respectively). It is possible that simultaneous recording of X, Y and Z leads instead of leads II and aVr would have resulted in a lesser discrepancy...
between the VAT measured on the Hb electrograms and the QRS duration in surface leads. The close bipolar electrograms from the lateral walls of the right and left ventricles are inscribed simultaneously with the second half of the surface QRS and earlier in relation to the septal potential in the Hb(W) recording. Immediately following occlusion of the anterior septal artery and within the first minute, changes are seen in the septal potential in the Hb(W) recording and the corresponding deflection in the Hb(L) recording. These changes consist of decrease in the amplitude, increase in the duration, and the fragmentation of the potential into multiple components. These changes are clearly evident on the Hb(W) recording where the control ventricular deflection is dominated by the septal depolarization. In the Hb(L) recording, the initial portion of the ventricular deflection which corresponds to most of the surface QRS remains unchanged, the changes primarily involve the terminal portion corresponding to septal activation. Figure 1, panels B to D, show a gradual increase in the fragmentation and delay in time of septal activation after the ligation (see the magnified sections encircled). On the other hand, there is no change in the RV and LV electrograms. Proximal His-Purkinje conduction judged from the His bundle potential and the H-V interval also remains unchanged. The increase in the duration of the septal depolarization results in an increase of the total ventricular activation time. The fragmentation and delay of septal activation may be slightly different in one or more of the plunge wire or electrode catheter recordings. However, the electrode catheter recording usually showed the greatest duration of total VAT. The gradual dispersion of septal activation results in more of the ventricular depolarization being inscribed during the ST-T segment of the surface ECG. It should be emphasized that the changes in septal activation are not associated with any appreciable changes in the surface QRS or ST-T complex.

Figure 1

Progressive fragmentation of the septal potential following acute ligation of the anterior septal artery. Traces from above: ECG leads II and aVr, electrode catheter recording of the His bundle from the left side (Hb(L)), plunge wire recording of the His bundle (Hb(W)) and two bipolar electrograms from the lateral free walls of the right and left ventricles (RVeg and LVeg respectively). The control recordings show a sharp biphasic deflection representing late septal depolarization in the Hb(W) electrogram simultaneously inscribed with the terminal part of the ventricular potential on the Hb(L) recording which is a sharp biphasic deflection. Both deflections extend beyond the terminal part of the surface QRS by about 25 msec. Following occlusion there is progressive decrease in amplitude, increase in duration and fragmentation of the septal potential of both the Hb(L) and Hb(W) recordings resulting in gradual increase of total ventricular activation time (VAT) (see magnified sections encircled). No changes in the RVeg and LVeg are seen.
Figure 2 was obtained 6 min after ligation and illustrates the onset of ventricular arrhythmia. The total VAT of the first beat measured from the onset of ventricular depolarization to the end of the fragmented potential in the Hb(L) recording has increased from 140 msec in figure 1, panel D, to 160 msec. This is followed by a beat-to-beat increase in the VAT due to progressive delay in the fragmented septal depolarization (see magnified sections). The third beat, which shows the greatest dispersion of ventricular activation, is followed by the onset of ventricular arrhythmia. Note that the first ventricular ectopic beat has a long coupling interval so that it is inscribed shortly after the onset of the next sinus P wave. The two ventricular ectopic beats show a left bundle branch configuration which is reflected in the LVeg by widening and delayed inscription relative to the RVeg. The Hb(W) recording reveals retrograde His bundle activation shortly after the onset of the ectopic QRS (marked by arrow). Vagal-induced slowing of the heart rate (VS) was applied to interrupt the ventricular arrhythmia. The first sinus beat that follows vagal stimulation has a preceding R-R cycle of 1480 msec. Note that the septal potential shows a lesser degree of fragmentation with significant recovery in form, amplitude, and duration resulting in marked decrease of the total VAT. In all experiments, atrial pacing enhanced the fragmentation and delay of the septal potential as well as the onset of ventricular arrhythmia. Termination of atrial pacing and/or vagal-induced slowing of the atrial rate resulted in prompt reversal of the dispersion of septal activation with decrease of total VAT as well as disappearance of the ventricular arrhythmia. In two experiments, however, vagal-induced slowing of the atrial rate failed to interrupt the ventricular arrhythmia which rapidly degenerated into ventricular fibrillation.

In all experiments, a close temporal relationship was observed between fragmentation and delay of septal depolarization resulting in increase of total VAT and the time of onset of ventricular arrhythmia. Figure 3 is a graphic representation of this relationship in the 20 experiments. The average time for ventricular tachycardia (VT) in absolute terms was 5½ min. The figure shows that the increase in total VAT followed an exponential curve with delay becoming
marked prior to the onset of VT. An increase in total VAT of up to 335 msec was observed. In six instances, the recorded electrograms showed markedly delayed ventricular activation which occurred after the end of the T wave of the standard ECG. The occurrence of maximal delay invariably preceded the onset of VT.

In 12 experiments, the sequence of events leading to VT paralleled those shown in figures 1 and 2 in which fragmentation of the septal depolarization resulted in gradual increase in total VAT. In eight experiments, one or more of the recorded electrograms, usually the electrode catheter recording, showed less diffuse fragmentation with the delay of a discrete low amplitude septal deflection. Alternate inscription of this delayed potential suggested that conduction to the area of delay was completely blocked every other beat. This is shown in figure 4. Note the sharp late septal deflection in both the electrode catheter recording (Hb(L)) and the plunge wire recording (Hb(W)). The large atrial deflection in the Hb(W) recording is probably due to the insertion of the plunge wire at the top of the ventricular septum close to the lower atrium. Four minutes following ligation of the anterior septal artery, the late septal deflection fragmented resulting in increase in total VAT. Both the Hb(L) and Hb(W) recordings show a distinct late septal potential which is inscribed every other beat resulting in alternation of the total VAT between 100 and 125 msec.

In the eight experiments in which a 2:1 block of a discrete late septal deflection was observed, the conduction disorder always preceded the onset of ventricular arrhythmia by a few seconds up to 2 minutes. In five of the eight experiments the onset of ventricular arrhythmia was related to a characteristic pattern of conduction delay of the late septal potential. This is shown in figures 5 and 6 which were obtained from another experiment and illustrate both an electrode catheter recording from the left side of the heart (Hb(L)) and a plunge wire recording from the His bundle area (Hb(W)). Figure 5, panel A, shows control recordings and illustrates a sharp triphasic deflection at the end of the ventricular complex in both the Hb(L) and Hb(W) recordings which represents septal depolarization. The deflection is
Evolution of a delayed septal potential and 2:1 block following acute ligation of the anterior septal artery. Traces from above: ECG leads II and aVR, electrode catheter recording of the His bundle from the left side (Hb(L)) and plunge wire recording of the His bundle (Hb(W)). Control recordings show a sharp triphasic deflection representing late septal depolarization in both the Hb(L) and Hb(W) electrograms. Panel C, obtained 3 1/2 min after ligation, shows a beat-to-beat progressive delay of a late septal potential that terminates by the occurrence of a 2:1 block of the septal deflection. The arrows point to the discrete late septal deflection in the Hb(W) electrogram.

Coincident with and extends slightly after the terminal part of the QRS complex in the surface leads. Figure 5, panels B and C, were obtained 1 1/2 and 3 1/2 min after ligation and show gradual fragmentation of the septal deflection, resulting in significant increase of total VAT. Panel C shows a beat-to-beat progressive delay of a late septal potential which gradually splits from the rest of the ventricular complex. Note that the

Recordings from the same experiment shown in figure 5. Panel A was obtained 5 1/2 min after ligation and illustrates the characteristic pattern of conduction delay of the late septal deflection associated with the onset of ventricular arrhythmia. Panel B was obtained 25 min after ligation and illustrates a tachycardia-dependent paroxysmal complete block of the late septal deflection during atrial pacing (Pi) at a rate of 200 beats/min. S = stimulus. The arrows point to the late septal deflection.
progressive increase in total VAT in the Hb(L) recording is attributed primarily to gradual fragmentation and increase in the duration of the late septal potential and to a lesser extent to actual delay and split of the deflection from the rest of the ventricular complex (see the magnified sections encircled). On the other hand, the Hb(W) recording shows a distinct, relatively sharp late septal deflection which is clearly split from the rest of the ventricular deflection and corresponds only to the late part of the septal potential in the Hb(L) recording. Note that the gain has been increased threefold on the Hb(W) recording relative to the control record to be able to detect the discrete late septal deflection. The second half of panel C illustrates the onset of 2:1 block of the late septal deflection. The conduction pattern of the late septal deflection both prior to and subsequent to the block is reminiscent of the Mobitz type II block. However, as in the case of A-V conduction disorders, the arrangement usually represents a Wenckebach conduction with a few msec increment of conduction delay.

Figure 6, panel A, was obtained 5½ min after ligation and illustrates the characteristic pattern of conduction delay of the late septal deflection associated with the onset of ventricular arrhythmia. Atrial pacing was started at a rate of 150 beats/min. The first half of panel A shows a regular 2:1 block of the late septal deflection associated with a progressive widening and delay of the deflection so that the total VAT increases gradually from 145 to 160 msec. In the second half of panel A, however, the septal deflection, instead of being completely blocked as expected in a regular 2:1 sequence, starts conducting in a 1:1 pattern with a progressive delay resulting in significant prolongation of the total VAT. The beat with the longest VAT of 200 msec is immediately followed by ventricular tachycardia. Note that the first beat in the ectopic run has a very long coupling interval and is actually inscribed shortly after the Hs bundle deflection of the preceding sinus beat. The pattern of conduction delay of the late septal deflection that preceded the onset of ventricular tachycardia is reminiscent of the Wenckebach type of conduction delay.

The early phase of ventricular arrhythmias subsides with time, 15–30 min after occlusion of the anterior septal artery. At that time, rapid atrial pacing fails to induce the arrhythmia contrary to its effect early after occlusion. The fragmented, delayed septal potential does not return to the pre-occlusion pattern. In five experiments high degrees of conduction block of a delayed septal deflection (3:1 and 4:1, etc.) as well as paroxysmal complete block could still be induced by increase of the atrial rate. However, the progressive conduction delay of the septal depolarization which is characteristically related to the onset of ventricular arrhythmia as shown in figures 2 and 6 is no longer seen. This is shown in figure 6, panel B, which was obtained 25 min after ligation. Rapid atrial pacing at a rate of 200 beats/min resulted in long periods of A-V nodal Wenckebach conduction with occasional short periods of 2:1 A-V nodal block. Note that during the periods of fast ventricular response, the late septal deflection is completely blocked. The septal deflection is only inscribed when the ventricular rate momentarily slows during 2:1 A-V nodal block.

In two experiments a temporal relationship was observed between a delayed septal deflection and the occurrence of a certain type of ventricular ectopic rhythm which would suggest that this area of the septal myocardium may be involved in a regular reentrant circuit. This is shown in figures 7 and 8 which illustrate an experiment in which electrode catheter recordings from the left side of the heart (Hb(L)) were obtained. Plunge wire recordings were not obtained in this experiment. Figure 7, panel A, shows the control record and illustrates a discrete sharp biphasic deflection at the end of the ventricular complex which represents septal depolarization. This results in total VAT, measured from the Hb(L) electrogram, of 80 msec as compared to the surface QRS duration of 50 msec. Panels B to D were obtained following ligation and illustrate progressive delay in the inscription of the septal deflection associated with marked decrease in the amplitude of the deflection and an increase in its duration. In panel D a 2:1 block of the late septal deflection developed. Panel E shows that the 2:1 conduction block of the septal potential was a tachycardia-dependent phenomenon. Vagal stimulation was applied at the beginning of the record with gradual slowing of the heart rate. At a critical increase of R-R cycle to 700 msec, the 2:1 conduction block changed into a 1:1 delayed conduction. It is of significance to note the remarkably stable electrode catheter recording, as evidenced by the constant configuration of the A deflection, Hb deflection, and the proximal part of the V deflection. The only dynamic changes involved the late septal deflection.

Figure 8 shows that the onset of ventricular arrhythmia is associated with a characteristic pattern of conduction delay of the late septal deflection similar to that shown in figure 6. The first part of panel A shows a 2:1 conduction block of the septal deflection during a regular relatively slow heart rate of 94 beats/min obtained by vagal stimulation. In the fourth beat, however, the septal deflection, instead of being completely blocked as expected in a regular 2:1 pattern, was markedly delayed and continued to be inscribed well after the end of the T wave of the standard ECG. This was immediately followed by the onset of a short run of self-terminating VT. Note the
long coupling interval of the first ectopic beat (430 msec). The first two beats in the ectopic run have an exactly similar QRS configuration in the standard ECG and both of them are regularly preceded by the septal deflection at an almost constant interval of 170–180 msec (measured from the beginning of the septal deflection to the onset of the QRS). The third ectopic beat has a slightly different QRS configuration.

Figure 7

Evolution of a delayed septal potential and 2:1 block following acute ligation of the anterior septal artery. Traces from above: ECG leads II and aVR, and an electrode catheter recording of the His bundle from the left side (Hb(L)). Note that the Hb(L) recording illustrates a discrete sharp biphasic septal deflection. Following ligation, there is progressive delay in the inscription of the septal potential with marked decrease in the amplitude of the deflection and an increase in its duration. In panel D, the septal deflection is markedly delayed and clearly split from the rest of the ventricular complex. The deflection is only inscribed every other beat suggesting the occurrence of a 2:1 block to this area of septal myocardium. Vagal stimulation, applied in panel E, illustrates that the 2:1 block is a tachycardia-dependent phenomenon.

Figure 8

Recordings from the same experiment shown in figure 7 showing temporal evolution of ventricular arrhythmias. Note that both episodes of ventricular arrhythmia in panels A and B are associated with a characteristic Wenckebach pattern of conduction delay of the septal potential. Vagal stimulation (VS) was applied to interrupt the multiform ventricular tachycardia in panel B.
MALIGNANT VENTRICULAR ARRHYTHMIA

and is not preceded by a discernible septal deflection. The self-terminating run of VT is followed after an R-R interval of 750 msec by an escape sinus beat. The septal deflection of this beat shows much less delay resulting in significant shortening of the VAT. Panel B in figure 8 was obtained 1½ min after panel A and shows another run of VT. The onset of ventricular arrhythmia is preceded by exactly the same pattern of conduction delay of the septal deflection shown in panel A. There is, however, a greater degree of conduction delay of the septal deflection of the fourth beat (total VAT of 335 msec compared to 310 msec in panel A). This resulted in a longer coupling interval of the first beat of the ectopic run (460 msec compared to 430 msec in panel A). The longer coupling interval, in addition to the relatively faster sinus rhythm in panel B, resulted in the inscription of the first ectopic beat shortly after the beginning of the next sinus P wave. The first three ectopic beats in the second run of VT have the same QRS configuration as the first two beats of the first run of VT and each of these beats is similarly preceded by a septal deflection with a constant interval of 165–180 msec. On the other hand, the fourth and fifth ectopic beats in the second run of VT show an abrupt change in the QRS configuration of an opposite direction (a left bundle branch block pattern in the first three ectopic beats and a right bundle branch block pattern in the last two ectopic beats). These two beats are not preceded by a septal deflection. The observed temporal relationship between the delayed septal deflection and the occurrence of a certain type of ventricular ectopic rhythm suggest that this area of the septal myocardium is involved in a regular re-entrant circuit. The occurrence of sudden change in the configuration of the ectopic beats concomitant with failure of the inscription of the septal deflection may suggest that a different re-entrant circuit came into play. Change in the QRS configuration of the ectopic rhythm was observed to invariably precede the onset of ventricular fibrillation, a fact which may suggest the operation of multiple re-entrant circuits leading to marked desynchronization of the ventricular depolarization. This process could be interrupted if vagal-induced slowing of the atrial rate was promptly applied, as was done in this experiment.

During this study it was observed that the majority of ventricular arrhythmias started by a late coupled rather than an early coupled ventricular ectopic beat. Table 1 shows a detailed analysis of the prematurity index of the first beat of an ectopic run in all 20 experiments. The prematurity index was determined by dividing the coupling interval of the ectopic beat (R-R') by the Q-T interval of the preceding sinus beat. In 16 out of 20 experiments (80%), including the two experiments in which ventricular fibrillation developed, the prematurity index was greater than 1. In three experiments runs of VT started with a ventricular fusion beat.

Discussion

Re-entry Due to Desynchronized Local Conduction Delay and Block in Ischemic Myocardium

The present report confirms recent studies conducted following ligation of the anterior descending coronary artery9-8 by showing fragmentation and delay of local electrograms resulting in marked dispersion of the total ventricular activation time as well as a close temporal relationship between local areas of delayed activation and the onset of the early phase of ventricular arrhythmias. This study, however, presents at least three additional features:

1) Ischemia following ligation of the anterior septal artery involves the septal myocardium as well as the proximal His-Purkinje system. The time course of ischemic conduction disorders of the proximal His-Purkinje system has been amply defined and occurs significantly later following ischemia compared to the time course of ischemic conduction disorders of septal myocardium.9-11 Thus, the present study strongly suggests that the early phase of ventricular

Table 1

Prematurity Index of the First Ectopic Beat of Ventricular Tachycardia* (Coupling Interval (R-R') Divided by Q-T Duration)

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<th>Exp. no.</th>
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<th>Q-T (msec)</th>
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*Calculations are made for the first episode of ventricular tachycardia defined as a run of 3 or more ectopic beats.
Arrhythmias following ligation of the anterior septal artery is specifically related to the effects of ischemia on the septal myocardium. On the other hand, ischemia following ligation of the anterior descending artery involves both the subendocardial Purkinje network and the working myocardium. Significant temporary depression of the properties of the Purkinje tissue was shown to develop shortly after ligation of the anterior descending artery in both in vivo and in vitro studies. The contribution of depressed subendocardial Purkinje network to the conduction delay of local intra-myocardial and epicardial electrograms that also rapidly follows the onset of ischemia may be difficult to assess.

2) Almost all previous studies that demonstrated slow desynchronized ventricular conduction during experimental myocardial infarction have utilized local close bipolar recordings. These recordings reflect the electrical activity of a relatively small part of the myocardium. In the present study, delayed and fragmented ventricular depolarization was regularly detected by intracardiac electrode catheter recordings. It is reasonable to assume that a larger area of the myocardium is probably being sampled by the electrode catheter recording. In a recent study of the nature of His bundle recording by bipolar electrode catheters, the recording was shown to represent a composite of the bipolar view (essentially what one could see when the bipolar electrode catheter approaches the heart, i.e., generalized atrial and ventricular activity) superimposed with the localized recording from the electrode actually in apposition to the His bundle itself. This latter recording would indicate some localized atrial activity, the His bundle action potential, and late septal activation.

3) Although in this study as well as in similar studies there is no unequivocal proof that the fragmented potentials actually represent delayed myocardial depolarization, the observed gradual evolution of these changes, their rate-dependence as well as their temporal relationship to the onset and disappearance of the arrhythmia, support this contention. In fact, critical analysis of several of our records strongly suggests that the electrophysiological mechanism underlying the early phase of ventricular arrhythmia is consonant with an irregular conduction disorder of ischemic myocardium which closely simulates the patterns of conduction disorder in ischemic proximal His-Purkinje system. These include delayed conduction equivalent to 1st block (figure 5, panel B, and figure 7, panels B and C), 2nd block with few msec increment of conduction delay simulating Mobitz type II block (figure 5, panel C), 2nd block with marked increment of conduction delay (a Wenckebach type of conduction (figure 6, panel A, and figure 8), high degree block (2:1, 3:1, 4:1, etc., figure 4) and paroxysmal complete block (figure 6, panel B). The onset of ventricular arrhythmia was specifically associated with the Wenckebach pattern of conduction delay. Fragmentation of the septal electrogram probably reflects a desynchronized pattern of activation of different portions of the septal myocardium, which ordinarily depolarizes in a synchronous fashion. The progressive beat-to-beat increment of the fragmented septal potential prior to the onset of the arrhythmia (fig. 2) may be basically similar to the more discrete Wenckebach type of conduction (figs. 6 and 8). The former pattern may also reflect a Wenckebach type of conduction delay of one or more of the late fragmented deflections. On the other hand, the Wenckebach pattern of conduction delay of a septal deflection that terminates with ventricular tachycardia (figs. 6 and 8) bears a remarkable resemblance to previously published records showing a Wenckebach pattern of A-V nodal conduction (A-H intervals) associated with the onset of atrial echo beats and re-entrant atrial tachycardias. This pattern similarly suggests the occurrence of an intraventricular re-entrant arrhythmia. However, caution should be exercised in drawing the analogy between conduction disorders in ischemic septal myocardial and A-V junctional conduction disorders and re-entrant arrhythmia too closely. Thus, in the former situation there is no way to discern whether a progressive beat-to-beat delay of a fragmented late septal deflection represents a progressive conduction delay in the same pathway or that activity proceeds to the same myocardial zone through different pathways and/or local re-entrant circuits. This and similar arguments clearly show that this study falls short of actually delineating a re-entrant pathway. However it demonstrates that the basic prerequisites needed to explain re-entry do exist during the early period following ligation of a major coronary artery.

Effect of Rate on the Early Phase of Malignant Ventricular Arrhythmias

This study shows that the influence of rate has a dual time-course. There is a relatively slower component that starts immediately following occlusion during which high rates are associated with increased fragmentation of the septal electrogram and earlier onset of ventricular arrhythmias. Maintaining a slow heart rate immediately after occlusion could delay both the degree of fragmentation of the septal electrogram and the onset of arrhythmia. Superimposed upon this slower conduction there is an immediate rate effect in which a higher degree of conduction delay and block of the septal potential appears instantaneously with sufficient increase in the rate and dis-
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appears rapidly after the rate is reduced (fig. 6, panel B, and fig. 7, panel E). This late effect of rate shows that conduction disorder in the ischemic myocardium is a tachycardia-dependent phenomenon. On the other hand, slowing of the heart rate regularly causes recovery of the timing, form, and duration of the septal potential with the coincident disappearance of ventricular arrhythmias. The effect of bradycardia on the early phase of malignant ventricular arrhythmias is in accordance with our previous experience following ligation of the anterior descending coronary artery\(^{4,6,17}\) but appears to vary with other reports.\(^{5,21}\)

The observation that vagal-induced slowing of the atrial rate frequently interrupts the ventricular arrhythmia may superficially suggest evidence against a self-perpetuating re-entrant activity. This effect can be, however, explained as follows: In the presence of marked dispersion of ventricular activation, the arrival of the atrial impulse to the ventricle could induce one or a few ectopic beats reflecting a self-limited re-entrant activity. Subsequent atrial inputs to the ventricle could further induce a fresh series of re-entrant activity. The presence of multiple re-entrant circuits can rapidly set the stage for ventricular fibrillation. This process could be interrupted by marked slowing or abolition of the atrial input to the ventricle, with the self-termination of an already started re-entrant activity.\(^{23}\) Conceivably, if a self-perpetuating disorganized re-entrant activity had ensued, atrial arrest would offer little help in preventing the arrhythmia from degenerating into ventricular fibrillation. This situation was actually encountered in two experiments of the present series.

Prematurity Index of Malignant Ventricular Ectopic Beats:
The Vulnerable Period and the R/T Phenomenon

This study has shown that a majority of the malignant ventricular tachycardias following acute septal artery ligation in the experimental animal are initiated by a late coupled ectopic beat and not by one that interrupts the antecedent T wave. This observation is not surprising in view of the suggested electrophysiological mechanism for the early phase of malignant ventricular arrhythmias. The late coupling probably relates not only to the degree of delay of activation of a particular portion of the ischemic myocardium but also to the delayed exit of activation from the ischemic zone. This is suggested by analysis of the onset of ventricular tachycardia in figure 8 where the delayed septal deflection preceded the onset of the ectopic QRS in the surface lead by 170–180 msec. Indeed, it is the very early coupled ventricular premature beat in this situation that requires an explanation. The coupling of the ventricular premature beat will depend both on the degree of delay of the ischemic myocardial zone as well as the recovery time of the rest of the myocardium. In ischemia, there is evidence that areas of delayed activation as well as areas of shortened recovery do exist.\(^{28,29}\) It is possible that the short coupling of the ventricular premature beat depends on the presence of abbreviated recovery of some parts of the myocardium.

The findings of the present study may call for a reassessment of the concept of ventricular vulnerability as originally described by Wiggers and Wegria\(^{20}\) and the R/T phenomenon, which represented a clinical extrapolation of the former concept.\(^{27}\) The R/T phenomenon postulates full recovery of excitability of the ventricles by the end of the T wave of the surface electrocardiogram, a contention unsubstantiated in the pathologic situation as shown in this and similar studies. Thus, although it may be true that in the normal heart the vulnerable phase may be limited to the Q-T interval, in ischemia with marked dispersion of ventricular activation, the vulnerable phase can extend throughout most of the cardiac cycle. As a matter of fact, Moe et al. in their studies took into account the fact that under certain circumstances the vulnerable period could be considerably lengthened.\(^{28}\) In a recent study from this laboratory,\(^{22}\) ventricular ectopic beats induced late enough in the cardiac cycle to cause ventricular fusion could induce ventricular fibrillation when the underlying dispersion of ventricular activation following ligation of the anterior descending coronary artery was great. Several clinical reports seem to substantiate the experimental observations.\(^{29,32}\) These observations do not detract from the clinical significance of early coupled ventricular premature beats but rather point out that the arrhythmogenic potential in acute myocardial ischemia is not exclusively confined to those extrasystoles exhibiting the R/T phenomenon.

Predictability of Malignant Ventricular Arrhythmia in Acute Myocardial Ischemia

The suggested electrophysiological mechanism for the early phase of malignant ventricular arrhythmia would appear to de-emphasize the role of the ventricular premature beat \textit{per se} as a predictor of malignant ventricular arrhythmia in the early phase of acute coronary ischemia. This is apparently at variance with the widely held view.\(^{33}\) Although certain characteristics such as short coupling, multiform configuration, frequency, and occurrence in salvos may be more conducive to the occurrence of ventricular fibrillation, those manifestations are only the characteristics of an underlying pathophysiologic process and are not in themselves the primary culprit. It seems that the primary factor that determines the arrhythmogenic potentiality during acute myocardial

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ischemia is the degree of dispersion of ventricular depolarization. However, detection of areas of delayed desynchronous activation is so far only possible in animals by the use of local intramyocardial or epicardial recordings. This study illustrates for the first time that these areas may also be detected by intracardiac electrode catheter recordings. This raises the possibility that similar disorders in man may be detected by the same procedure. Furthermore, with the recently described noninvasive technique of signal averaging, it may be possible to detect delayed ventricular depolarization from the surface ECG if it could be discerned from the ST-T complex. Such studies are currently under way in our laboratory.

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