Electrotonic Interactions across an Inexcitable Region as a Cause of Ectopic Activity in Acute Regional Myocardial Ischemia

A Study in Intact Porcine and Canine Hearts and Computer Models

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SUMMARY. We recorded 60 DC simultaneous electrograms from isolated porcine and canine hearts in the first minutes after coronary occlusion. Ventricular premature beats (VPB) originated from the normal side of the ischemic border, which was frequently separated from the central ischemic area showing delayed activity by a small zone of inexcitable tissue. We attempted in a computer model to generate VPB's at one side of an area showing conduction block. In computer simulations, the presence of elements capable of automatic activity greatly facilitated the induction of VPB's. By coupling automatic elements to nonautomatic elements, overt pacemaking activity could be suppressed. Subthreshold depolarizations transmitted through a zone of conduction block could, when properly timed, trigger the latent automatic elements into overt automatic activity, resulting in single or repetitive VPB's. The ventricular premature beats in the intact hearts with acute regional ischemia may be caused by "triggered automaticity" in which the trigger is provided by the "injury current" flowing from ischemic cells showing delayed repolarization via a segment of inexcitable ischemic cells in the border zone to normally perfused cells with suppressed automaticity.

(RE CIRC 50: 527-537, 1982)

REENTRY is widely recognized as a mechanism playing an important role in the ventricular arrhythmias during the early phase of regional myocardial ischemia. Recent mapping studies in isolated porcine and canine hearts provided evidence that circus movement reentry within the ischemic myocardium occurred in ventricular tachycardia and that fragmentation of the circus movement into multiple reentrant wavelets induced ventricular fibrillation (Janse et al., 1980). However, single premature beats, and the ectopic beats initiating a run of tachycardia, were not caused by large circulating excitations, but were thought to be due to a "focal" mechanism localized in the ischemic border zone.

In the present study, further mapping experiments in isolated porcine and canine hearts are presented, in an effort to analyze the genesis of spontaneous premature beats in the first minutes after coronary ligation. It was frequently found that, in the ischemic border zone, areas of inexcitable tissue were interposed between more centrally located ischemic tissue showing delayed activity and nonischemic tissue showing early activity during premature beats. Therefore, an attempt was made to imitate the situation at the ischemic border zone in a computer model, consisting of an arbitrary number of excitable and inexcitable elements, coupled to each other in various ways (van Capelle and Durrer, 1980). We used the computer model especially to clarify the influence of purely electrotonic currents transmitted through inexcitable elements on the electrical activity of excitable elements which are electrically coupled to the depressed segment.

Special attention will be given to reflection as a mechanism of ectopic impulse generation. In recent studies by Antzelevitch et al. (1980) and Jalife and Moe (1981), the term reflection was used to describe a form of reexcitation in a linear bundle where two excitable ends were separated by an inexcitable segment which was capable of transmitting purely electrotonic potentials only. In a study by Wit et al. (1972) the term reflection was used to indicate reexcitation in a nonbranching preparation by way of micro reentry within the depressed segment.

The results of the present study indicate that purely electrotonic depolarizations, transmitted from the central ischemic area showing delayed activity to normal tissue via a region of inexcitable ischemic myocardium are most likely to induce ectopic activity when some form of latent automaticity is present on the nonischemic side of the border.

Methods

Experiments on Intact Hearts

The methods used have been described in detail elsewhere (Janse et al., 1980). In essence, pigs and dogs of about 20 kg were anesthetized by intravenous sodium pentobarbital. After collection of about 800 ml of blood, the hearts were isolated and perfused according to the Langendorff technique with a 1:1 mixture of blood and modified Ty-
rode's solution, containing dextran. Regional ischemia was produced by clamping the left anterior descending coronary artery (LAD) or circumflex artery close to its origin. Extracellular DC electrograms were recorded simultaneously from 60 epicardial or intramural sites. Multiple electrodes, containing 60 terminals consisting of cotton or silk wicks soaked in isotonic saline, were attached to the anterior surface of the left ventricle in such a way that terminals were located both on ischemic and nonischemic tissue. Intramural wicks (Janse et al., 1979) were, in some experiments, inserted in the left ventricular wall. DC extracellular electrograms at each site were recorded from the subepicardium and from intramural sites at 4 mm and 8 mm, respectively, below the epicardial surface. The saline in each electrode was in contact with a chlorided silver wire which was connected to a buffer amplifier with a high input impedance. A differential input DC amplifier measured the potential at each site with respect to the DC potential of the aortic root. After an initial 20-fold amplification, the signals were led into a high-speed A/D converter (maximal sampling frequency 130 kc/sec) and written into a circular buffer in the memory of a PDP 11-34 computer. During the experiment, signals were monitored. When a spontaneous premature beat occurred, a button could be pushed so that the signals of the preceding 2 seconds were transferred to a high-speed digital tape recorder. An analysis of the data was performed with the same computer, by means of an interactive program whereby the signals were displayed on a Megatek graphic display and moments of activation could be indicated with a joystick. Zero potentials were obtained from control signals, and DC potential values could be obtained at any desired moment in the cardiac cycle.

The Computer Model

We have developed a computer model (van Capelle and Durrer, 1980) which consists of an arbitrary number of excitable elements. The behavior of the individual elements is determined by a set of functions and parameters that can be adjusted to bring about electrophysiological characteristics such as automaticity and duration of the refractory period. In this way, a library of elements with different electrophysiological properties was created, from which elements could be extracted for use in subsequent multi-element simulation studies.

For a simulation run, up to 650 elements can be connected in various ways. Since different types of elements may be present in the same simulation, the interaction of different cell types may be studied. The geometrical arrangement of the elements, together with the values of the coupling resistances between the elements and the size of the individual elements (that is, their membrane area), is specified interactively by means of a graphic screen and a joystick. A simulation may be interrupted at all times to change the configuration, and it may be restarted from an earlier point in time.

Since the differential equations controlling the behavior of the elements must be solved for many elements simultaneously, we had to use a very primitive model for the underlying mechanism. Two voltage-current relations $i(V)$ describe the behavior of the membrane. $i(V)$ has a region of negative chord conductance and is therefore able to generate an action potential upstroke. The other current, $i_n(V)$, is used to carry the membrane back to its resting potential. An excitability parameter, $Y$, which assumes values between 0 (maximal excitability) and 1 (complete inexcitability), determines how much of each current is switched on at a particular time. $Y$ acts simply as a weight factor and the instantaneous voltage-current relation of the complete membrane is thus given by $i(V) = Y i(V) + (1-Y) i_n(V)$. $Y$ itself moves toward a steady state value $Y_{ss}(V)$, an S-shaped curve which corresponds with maximal excitability for values of $V$ which are more negative than the resting potential and with inexcitability for positive values of $V$.

The membrane is now characterized by the two equations:

$$C \frac{dY}{dt} = -Y i(V) -(1-Y) i_n(V) + i_n$$

$$T \frac{dV}{dt} = Y_{ss}(V) - Y$$

where $C$ is the membrane capacitance, $T$ is the time constant of the activation/inactivation process, and $i_n$ is the current entering the element through its connection with other elements.

Results

Experiments in Intact Hearts

In a series of 30 experiments (11 dog hearts, 19 pig hearts) in which spontaneous ventricular premature beats occurred between 2 and 8 minutes after coronary artery occlusion, earliest activity during the ectopic beats was, in all hearts, recorded from the nonischemic tissue close to the ischemic border. This border was defined as the area where the T-Q segment potentials of normally propagated beats became negative. In no instance was there evidence of propagated activity which bridged the gap between delayed excitation of ischemic myocardium during the propagated impulse and early ectopic activity in the nonischemic myocardium. In 21 hearts, the premature impulse occurred after a deep negative "T wave" had been recorded from the ischemic myocardium (8 dog hearts, 13 pig hearts). The average interval between the deep negative "T" wave in ischemic tissue and early ectopic depolarization in nonischemic myocardium in close proximity to the ischemic area displaying "T wave" was 77 msec (range, 27 to 114 msec; standard deviation, 30; standard error of the mean, 9.2 msec).

In 15 hearts (6 dogs, 9 pigs), a zone of inexcitable myocardium was found to be interposed between the ischemic zone in which delayed activity and a deep negative "T wave" was recorded, and the nonischemic tissue where earliest premature activity occurred. An example of this situation is shown in Figure 1, where three selected DC electrograms are shown, recorded from a dog heart in which the circumflex branch was occluded. The first complex is the last beat propagated from the atrium (basic beat); the second is a spontaneous premature impulse. Complex A, recorded from ischemic myocardium, displays a deep negative "T wave" "T wave" during the basic beat. Complex B, also from ischemic myocardium 5 mm from A, is nearly completely monophasic during the basic beat, indicating absence of regenerative activity at the site. Complex C, 3 mm from B, is from nonischemic myocardium, as indicated by the isoelectric T-Q and S-T segment potentials (the horizontal line is the DC potential of the aortic root). The intrinsic deflection at C, representing local activation, is fast, and occurs early during both the basic and the premature beat. The interval
between the moment when in A the deepest point in the negative "T wave" is reached, and the intrinsic premature deflection in C, is in this example 103 msec.

In the maps on the left, representing the epicardial area of 16 X 44 mm from which the 60 DC electrograms were simultaneously recorded (see schematic drawing of the heart), activation patterns of basic and premature beats are shown in the upper two panels. Isochronic lines separate areas activated within the same 10-msec interval (t = 0 is the P wave of the basic beat), and areas of conduction block (monophasic extracellular complexes) are shaded. In the lower two panels, isopotential maps are shown during the T-Q segment of the basic beat, and at the moment when the complex at site A displayed a deep negative "T wave" (indicated by the dotted line in the recordings). The position of the electrical border zone is visible in the T-Q segment potential map as on the area where T-Q potentials became negative, i.e., between the zero and the -4 mV isopotential line (between sites C and B). Note that, between sites C and A (9.5 mm apart), an extracellular potential gradient of 50 mV exists at the moment of the negative "T wave."

During the basic beat, a zone of conduction block is found close to the border zone. The tissue around site A is activated late, 250 msec after the P wave, but the pathways by which activity reached this site cannot be reconstructed. (As shown earlier (Janse and Kléber, 1981), the negative deflection at site A is
FIGURE 2.
and premature beat (lower panel) in a segment of the ventricular zone. T stands for conduction block. Note circumscript area showing earliest recorded activity during premature beat.

The symbol T indicates conduction block. During the basic beat, the ischemic area is invaded from two sites, and activity is blocked in the center. The interval between last propagated activity and earliest ectopic activity is 210 msec. Earliest ectopic activity is recorded at one terminal, on the normal side of the ischemic border, and from that site, both the normal and ischemic myocardium are activated.

In Figure 3, the coupling intervals for 46 spontaneous ventricular beats in 30 experiments are plotted against basic cycle length. The coupling intervals were measured from recordings from nonischemic myocardium in which early ectopic activity was found. It should be realized that these sites are not necessarily the earliest activated sites in the heart during the ectopic beats. It is clear that there is no fixed coupling interval. There is a tendency for the coupling interval to shorten at faster heart rates, but coupling intervals are generally greater than 75% of basic cycle lengths of 400 msec and shorter. At slower heart rates (cycle lengths longer than circa 400 msec), coupling intervals are mostly shorter than 75%.

The results of these mapping experiments can be summarized as follows: (1) In all experiments, earliest activity during a spontaneous premature beat was recorded from the normal tissue, close to the ischemic border, and no activity bridging the gap between late propagating and early ectopic activity was found. (2) In 21 of 30 experiments, the extracellular space of the ischemic tissue had a markedly negative potential some 70 msec before earliest ectopic activity was recorded. In earlier experiments (Kleber et al., 1978; Janse et al., 1980) we demonstrated that, in such a situation, an intracellular current flows from ischemic toward normal cells, tending to depolarize the latter, and that maximal current sources on the normal side of the border are in the order of 2 μA/mm². (3) In 15 of 30 experiments, a zone of inexcitable tissue was found to be interposed between the ischemic area displaying the deep negative potential and the normal area showing earliest ectopic activity. (4) Spontaneous premature beat occurred late in the cardiac cycle when heart rates were fast (cardiac cycle lengths shorter than about 400 msec).

Computer Simulation Studies

We attempted to imitate the situation in the ischemic border zone in the computer model and, in particular, tried to elucidate the influence of purely electrotonic depolarizations transmitted through excitable elements on active responses in adjacent elements.

We concentrated upon the following question. Is it possible to obtain an extrasystolic activation by “reflection” over an area of impaired conduction, using the primitive excitable elements available in our computer simulation? And if so, are we in a position to say anything about the mechanisms involved?

It was not difficult to evoke reflection, using a one-dimensional arrangement of the elements which excluded a priori all forms of spatial re-entrée. There were certain conditions to be fulfilled, however. The
coupling interval (msec)

300 400 500 600 msec

basic cycle length

conduction block had to be unidirectional, blocking impulse transmission antegrade except for the occurrence of local response at the distal end of the cable, but permitting retrograde conduction of action potentials originating from the distal side of the block zone. Furthermore, suppressed automaticity, a concept we shall explain below, was required to be present at the distal end of the block zone.

Unidirectional block was created by reduction of the size of the excitable elements proximal to the block. This impaired antegrade conduction, because less current was available to depolarize the block area. Retrograde conduction was facilitated, on the other hand, because less current had to be supplied from the block zone to carry the proximal elements to threshold. By increasing the severity of the block, either by substitution of larger coupling resistances in the block zone or by augmentation of the amount of inexcitable tissue in the block area, the block could be trimmed until antegrade conduction just failed, while retrograde conduction was not severely hampered.

Conduction block alone was not sufficient to obtain reflection. The case is illustrated in Figure 4 where two identical nonautomatic elements are coupled through a large resistance. One of the elements is stimulated and fires. This activation is, marginally, conducted to the second element in the righthand panel of Figure 4, but it is blocked in the lefthand panel, because the coupling resistance was just too large to permit propagation. The propagation delay shown in the right part of the figure was the largest delay that could be obtained using the present cells. During this delay, the membrane capacity of the second element is discharged by a depolarizing current supplied by the first cell, until threshold is reached in the second cell. The question can be asked whether this latency can be made to outlast the duration of the action potential of the first element. If this were the case, the first element could be re-

FIGURE 3. Coupling intervals of ventricular premature beats in 30 experiments, plotted against basic cycle lengths (abscissa). The dotted line indicates 75% of the basic cycle.

FIGURE 4. Computer simulation of interaction of two excitable elements across a high-resistance gap. In the left panel, the coupling resistance is just too high to permit propagation from the stimulated element 1 to element 2. In the right panel, the longest conduction delay which could be achieved by slightly lowering coupling resistance is depicted. Note that, at the moment of take-off of the action potential in 2, the membrane potential of element 1 is much more positive than that of element 2.
excited by the second one, and that is precisely what we would call reflection. The answer to the question is negative, unless some additional delay generating mechanism is provided.

The reason passive coupling alone is not sufficient is easily understood, when we appreciate the fact that depolarizing current flows from the first toward the second cell during the period of latency. The membrane potential must therefore be more positive in the first element during this time. The larger the coupling resistance, the larger this potential difference must be. Consequently, the second element must fire, if it fires at all, well before the first element has repolarized. In this case, the only effect on the action potential of the first element is a hump during the plateau phase or the early repolarization phase, which lengthens the duration of the proximal action potential.

There was however another way, which was highly successful, to produce reflection. It involved "suppressed automaticity," a concept derived from earlier work with our model.

As explained in greater detail before (van Capelle and Durrer, 1980), the automatic properties of pacemaker elements can be modified when they are connected to nonpacemaker elements. It is intuitively clear that a small pacemaker cell cannot be expected to maintain its automaticity if it is coupled tightly to nonpacemaker elements. It is intuitively negative, unless some additional delay generating mechanism is provided.

FIGURE 5. A and B: action potentials of 4 nonpacemaker elements. Elements 2, 3, and 4 are tightly coupled, but a variable high-resistance barrier is present between 1 and 2. In A, this resistance is high and prevents conduction from 1 to 4; in B, it is slightly lowered to permit conduction with maximal delay. In C, a pacemaker element (5) is added via a low resistance connection to 4. The size of element 5 is small compared to the size of the nonpacemaker elements to which it is tightly coupled, resulting in suppression of its overt automaticity. The coupling resistance between 1 and 2 is the same in panel C as in panel A (no conduction). The subthreshold response in 4 triggers an automatic response in 5, which is conducted back to 1 and leads to an extrasystole. Note the subthreshold afterdepolarization after the action potential in 5.

An example of successful reflection based on this mechanism is shown in Figure 5. The inset shows the configuration of the elements. A nonautomatic element with a rather short refractory period is coupled with a high-resistance connection to a short cable consisting of other nonautomatic cells. A pacemaker element can be attached to the distal end of this cable, using a coupling which is tight enough to suppress its overt automaticity. In panels A and B, this pacemaker element is not connected. Block and marginal conduction over the high-resistance gap are illustrated in these panels: the situation is not very different from the one depicted in Figure 4. Attenuation of the local response along the distal elements can be seen in panel A. In panel B, where the gap resistance was slightly lower, successful propagation of the impulse occurred. The activity of element 2 is reflected in the action potential of element 1 as a hump, and the duration of the action potential is thereby much prolonged. In elements 2 and, to a lesser extent, 3, prolongation of the action potential duration, which is associated with the conduction of the impulse down the cable, can be seen. Element 4 displays an action potential that is typical for collision against the end of a cable; it is short and has a steep upstroke. In panel C, the pacemaker element has been connected to the end of the cable, and the resistance of the gap is high, resulting in impulse block. The activity of the pacemaker element is completely suppressed, as is evident from the stable baseline of element 5 prior to the arrival of the local response which is propagated across the block. It can be seen that this local response is sufficient to initiate a single action potential in the
pacemaker element, and that the delay involved in the propagation of the local response, added to the latency of the pacemaker element before it fires, is sufficient to permit retrograde conduction of the activity across the gap. Note also the subthreshold afterdepolarization following the action potential of the pacemaker element.

It is of interest to note that, in the elegant experimental study of Antzelevitch et al. (1980), the authors were able to demonstrate reflection with two very different types of conduction block. Perfusing the middle compartment of their three-compartment tissue chamber with isotonic sucrose solution, they created a zone of high-resistance block which could be modified by variations of the external resistance between the outer compartment. Reflection was found under those circumstances, but it could also be evoked when the middle compartment was made inexcitable by perfusion with a solution containing a high concentration of potassium. It is convenient to refer to these types of block as high-resistance and low-excitability block, respectively. We wondered whether the results reported above, namely, that an additional delay generating mechanism was required to obtain reflection in our model, would also be true in cases of low-excitability block.

We have tried two ways of diminishing the excitability of the elements in our computer model. The easiest way is to suppress the regenerative current component $i_0 (V)$ (see Methods) in our elements. This results in purely passive elements, which maintain, however, their original resting potential. To mimic the effects of acute damage to the membrane (and here, we think, of acute ischemia), it may be more appropriate to use elements which are not only inexcitable, but also depolarized. Both kinds of elements may act as an inexcitable gap, being incapable of generating an active response but transmitting local responses. The second type has an additional property: it acts as a source of depolarizing current for surrounding elements. Since these elements can be inactivated by this depolarizing current, the effective region where conduction is impaired can, in this case, extend itself considerably beyond the region occupied by the passive elements.

We could readily obtain reflection using nondepolarized passive elements instead of high-resistance connections in the gap region, but, again, only in the presence of a supressed pacemaker element at the distal end of the gap. An example is shown in Figure 6. The left and middle panels show instances of block and of marginal conduction in the absence of a pacemaker element. Conduction through the gap was modulated by changing the size of the inexcitable element, leaving the coupling resistance unaltered. The larger the inexcitable element, the greater the impairment of conduction, until block finally occurs. When this is the case, as in Figure 6A, the passive element tends to bring element 1 back toward its resting potential, hastening its repolarization: it can be seen that the action potential of element 1 in Fig 6A is small and very short. On the other hand, when propagation takes place, the elements across the gap are activated and influence, through the low-resistance connections, the action potential of the proximal element. A second peak therefore appears, and the duration of the action potential is prolonged. When the pacemaker element was connected, resulting in suppressed automaticity at the distal end of the gap, reflections could be obtained (Fig 6C). Its mechanism is the same as in the high-resistance case (Fig 5).

We have also tried to use depolarized passive elements. Reflection could be obtained in gaps containing such elements, but only if high-resistance barriers were also present. If not, the depolarizing current flowing from the passive elements toward the adjoining excitable elements interfered with the repolarization of the latter. As a consequence, the duration of the action potentials and the refractory period of these elements was lengthened to such an extent as to make reflection impossible. Using high-resistance connections, we could protect the "healthy" neighbor elements, but the block was then no longer a pure low-excitability block. Our elements being very primitive, they need not reflect the properties of heart tissue well in this respect, and the situation may well be different in biological preparations.

It is of interest to note that suppressed pacemaker activity adjacent to an area of conduction block can also promote the emergence of extrasystoles in a different way. When subthreshold oscillatory activity occurs after activation of the pacemaker element, a...
local response arriving at the moment of a subthreshold afterdepolarization may be able to cause the element to fire again. An example showing a run of extrasystoles based on summation of a subthreshold afterdepolarization and a subthreshold local response is shown in Figure 7. The arrangement of the elements is shown in the inset. The elements in the box, indicated by a dashed line, form an area of bidirectional conduction block. The block is obtained by inactivation of these elements under the influence of a depolarized passive element. There is also another pathway connecting the two sides of the block zone: impulses may travel in either way through a long loop of excitable elements. The conduction time required to travel through this loop can be varied by changing the resistance of two zones of incomplete high-resistance block in the loop. The tracings in the top panels are from the corresponding elements in the inset. Stimulating the element labeled "stim 2," we see in the upper left part how the impulse is not conducted across the gap zone, only a local response being present in trace 2. Although the pacemaker element (trace 1) is close to being activated, the suppressing influence of the adjacent nonautomatic elements is too large to permit full-blown activity. The impulse travels through the loop, however, and reaches this region somewhat later from the other side, now activating the pacemaker and its neighbors. The block zone is retrogradely invaded, but, again, impulse conduction is unsuccessful here, and only a local response ensues in traces 4 and 5. Note the subthreshold afterdepolarization in the pacemaker element. In the upper right part, element stim 1 is stimulated. Here also conduction through the block zone fails. The impulse travels through the loop (activation of traces 6, 5, and 4) and invades the block zone again. But, now, summation of the local response associated with the failing conduction through the block zone and of the subthreshold afterdepolarization of element 1 is sufficient to initiate an action potential of good quality, which is also conducted along the loop to the other side of the block region. In this way, a run of extrasystoles results. It can be seen, that the first (stimulated) action potential in trace 1 is considerably larger and steeper than the subsequent ones. One reason for this is, that its take-off potential is much more negative than in the next beat, and that much less inactivation of the regenerative inward current has therefore taken place. Another reason is that this element is activated by its neighbor, in the first case, so that it does not have to supply current to the other elements. During the next beats, the activation starts in this element, and element 2 and its neighbors therefore act as an electrical load on the pacemaker. As a consequence, the interval between the stimulated beat and the first extrasystole is less than the subsequent extrasystolic intervals. The synchrony between the subthreshold afterdepolarization and the local response supplied by the block

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**Figure 7.** Triggering of automaticity by current flow through an area of bidirectional block. The block zone consists of a depolarized inexcitable element (inex), tightly coupled to normal nonautomatic cells. Suppressed automaticity is present at one side of the block (element 1, PM = pacemaker). By varying the coupling resistances in the long loop of normal elements, the conduction delay through this loop can be adjusted. In the left panel, a stimulus is applied to element stim 2; the impulse is not conducted across the gap (see local responses in elements 3, 2, and 1). Elements 6, 1, 2, and 3 are activated via the long loop. Note afterdepolarization in the pacemaker element 1. In the right panel, a stimulus is applied to element stim 1. Again, conduction through the gap fails, and now elements 5 and 4 are activated via conduction through the loop. Summation of the local response associated with failing conduction through the gap and the afterdepolarization of element 1 is responsible for the initiation of a run of premature beats.
zone suffers. In addition, the decrease of the quality of the pacemaker action potential may diminish the amplitude of the afterdepolarization. As a result, the tachycardia stops after 3 beats.

Discussion

In agreement with earlier findings (Janse et al., 1980), our mapping experiments did not provide evidence for circus movement reentry as the cause of ventricular premature beats in the acutely ischemic heart. In all 30 hearts in which premature beats occurred between 2 and 8 minutes after coronary artery occlusion, earliest ectopic activity was found on the nonischemic side of the border. In no instance was activity recorded, which bridged the interval between late propagated activity within the ischemic zone and the early ectopic activity in the nonischemic zone. In 21 of the 30 hearts, we found that the ischemic myocardium close to the ischemic border displayed delayed repolarization, as was evident from a markedly negative "T wave" just before the emergence of an ectopic beat. In this situation, an intracellular current in the order of 2 μA/mm² flows from ischemic to normal tissue, tending to depolarize the latter (Kleber et al., 1978; Janse et al., 1980). In 15 hearts, a special situation was found in which an inexcitable zone was interposed between the ischemic myocardium displaying delayed repolarization and the nonischemic myocardium showing earliest ectopic activity. The limitations of our mapping technique, in which recordings from only 60 sites could be made simultaneously, must be taken into account when interpreting these findings. Thus, no guarantee can be given that in all instances the earliest activated site during premature beats was found. Sometimes evidence was found that ectopic activity could arise from more than one site. Our experiments and those of others (Harris, 1950; Janse et al., 1980; Downar et al., 1981) provided evidence that the ischemic border is the site of origin of ectopic impulses in the acute phase of myocardial ischemia. Since this border is large, and only in part covered by our recording electrode, one cannot expect to find in all hearts the very source of ectopic activity. The fact that we found in 50% of the hearts the special arrangement of a zone of inexcitable tissue interposed between ischemic myocardium with delayed repolarization and normal tissue with early ectopic activity, strongly suggests that electrotonic current flowing through an inexcitable area may play an important role in the genesis of ectopic impulses.

The role of a segment of inexcitable, or depressed, tissue producing conduction delay, conduction block, and ectopic activity has been studied extensively in in vitro experiments (Wennemark et al., 1968, 1975; Cranefield et al., 1971; Wit et al., 1972; Wennemark and Bandura, 1974; Antzelevitch et al., 1980; Jalife and Moe, 1981). From these experiments, the concept of reflection as an arrhythmogenic mechanism has emerged.

Reflection

The term reflection has been used to describe a form of reexcitation in a linear bundle where two excitable ends are separated by an area of depressed conduction. In such a segment showing no gross branching or loops, reflection would require the impulse to find a circuitous reentrant pathway within the depressed segment (Wit et al., 1972). In essence, it would be very much like the reentrant model first proposed by Schmitt and Erlanger in 1929. The ischemic border will certainly be inhomogeneous, and, as was the case in our experiments, totally inexcitable areas could be in close proximity to cells in which excitability is only depressed and not abolished. Therefore, reflection by micro reentry, involving pathways of only a few millimeters (Wit et al., 1972) cannot be excluded as a mechanism for ectopic impulse formation. To demonstrate such a mechanism in the intact heart, multiple, preferable intracellular, recordings at a great many sites, separated by distances of 1 mm or less, would be required. If the pathways were located deep in the ventricular wall, chances of demonstrating micro reentrant circuits would be very slim indeed. We have made many extracellular recordings from the border zone in which terminals were separated by distances varying from 1.5 to 4 mm (Janse et al., 1979; Janse et al., 1980) and have never found evidence for local activity bridging the gap between proximal activity (normal tissue), delayed distal activity (ischemic tissue) and premature activity in the normal tissue. We favor the concept that "injury currents" flowing between ischemic and normal tissue through an inexcitable segment in the border zone have an arrhythmogenic effect. Our computer studies provide some assessment of the passive and active properties of cells involved in such a effect.

In the computer model, reflection could easily be evoked. However, the delay between proximal and distal activity provided by purely passive electrotonic transmission through either a high-resistance or inexcitable gap was not sufficient to create extrasystoles. An additional mechanism by which activity in the distal elements was further delayed appeared to be necessary to evoke premature reflected impulses in the proximal elements. In our model, this additional delay was provided by "suppressed automaticity." Electrotonic currents, transmitted through inexcitable passive elements resulted in subthreshold depolarizations, which, when properly timed, could trigger this automaticity so that full-blown action potentials were generated in the distal element at a time when the proximal elements had repolarized. Only then could the proximal elements be reexcited. Other mechanisms providing an extra delay could also be considered. It is well known that a considerable latency may exist between an externally applied stimulus and the resulting response, especially when the stimulus strength is just above threshold. Also, point stimulation of a cable requires a certain area of membrane to
be brought to threshold before a conducted impulse can emerge from the stimulated area (Rushton, 1937; Fozzard and Schoenberg, 1977). The regenerative inward current, which occurs in the activated area, must be large enough to overcome the current loss which is associated with the (still subthreshold) depolarization of the not-yet-activated areas. When only part of the distal elements is brought to threshold by an electrotonically transmitted current, it is conceivable that an additional latency could be associated with the redistribution of charge bringing adjacent fibers to threshold. In this case, the proximal elements could have (partly) repolarized at the moment the majority of the distal elements fire, setting the stage for reflection. We have tried to evoke such behavior in the computer model, but without success.

We realize quite well that computer simulations offer no proof regarding mechanisms occurring in intact hearts. Yet they do point to possibilities which would be very difficult to find in intact hearts. A major point raised by the computer simulations is that automaticity may be latent and therefore not apparent by phase 4 depolarization in normally conducted beats, or even after a short period of asystole. Automaticity may only become manifest by a properly timed subthreshold depolarization. The “current of injury” may well provide such a trigger. The situation depicted in Figure 7 is compatible with the findings in intact hearts after a coronary artery occlusion. In contrast to the in vitro models of reflection, delayed activity in the central ischemic area is due to slow conduction through ischemic myocardium via pathways other than the unbranched structure in which classical reflection can occur. The tissue showing delayed activation is separated from the nonischemic tissue where the premature impulse originates by a zone of bidirectional block in the ischemic border zone. Properly timed currents, transmitted through such zones of bidirectional block, could trigger automaticity in, for example, Purkinje fibers on the normal side of the border. One may speculate that stretch, caused by systolic bulging of the ischemic myocardium, could promote the occurrence of automatic activity (Kaufmann and Theophile, 1967). Cat
catecholamine release may also contribute to the occurrence of oscillatory activity (Vassalle and Mugell, 1981). On the other hand, the extracellular K concentration on the normal side of the border, which was in our experiments 4.5 mm, might counteract the induction of automaticity (Katzung et al., 1975).

It has been shown recently that, in cow Purkinje fibers, catecholamines exert a stimulatory effect on delayed afterdepolarization and that spontaneous extrasystoles may be seen even in the presence of elevated extracellular K+ concentrations (Carmeliet, 1980). Whether the premature impulses in acute ischemia could be due to delayed afterdepolarization reaching threshold under the combined influence of electrotonic current and catecholamine release is difficult to say. One of the characteristics of delayed afterdepolarization-induced premature beats is that they occur late in the cardiac cycle (Rosen and Reder, 1981); in our experiments, this occurred only at relatively fast heart rates. In the range of basic cycle lengths of 340 to 500 msec, the coupling intervals had a rather constant value of about 300 msec. Traditionally, fixed coupling has been regarded as a sign of reentry. Jalife and Moe (1976) have demonstrated that fixed coupling is compatible with a focal mechanism, in which automaticity is altered by electrotonically transmitted subthreshold depolarizations. Triggered premature activity based on early afterdepolarizations (Cranefield, 1977) should be considered as well. Finally, under the influence of DC current, abnormal automaticity at reduced levels of membrane potential can be induced both in Purkinje fibers and myocardium (Hauswirth et al., 1969; Katzung et al., 1975). Whatever the precise mechanism of “suppressed” automaticity, which could become manifest by electrotonic currents, it will be very difficult to prove the reality of the mechanism depicted in Figure 7, since the ischemic border is large, and the area where “suppressed” automaticity may be present could be very small.

That other effects could occur in the ischemic border seems more than plausible, and these could also contribute to the occurrence of arrhythmias. Thus, bidirectional block within the depressed segment need not be complete, and synchronous arrival of two wavefronts may lead to summation and the emergence of a premature impulse (Cranefield and Hoffman, 1971). In certain areas where the impulse is conducted with difficulty into the ischemic zone, proximal action potentials (in nonischemic tissue) will be long; in other areas where conduction fails, they will be short (Mendez and Moe, 1966). Such dispersion in action potential duration will obviously facilitate the occurrence of reentry in and around the border zone. Although circus movement reentry, in which the circuits have diameters of 0.5 to 2 cm, does occur in ventricular tachycardia and fibrillation in the context of acute ischemia (Janse et al., 1980), the findings presented in this study support the concept that the ectopic beats which initiate the arrhythmias, have a focal origin.

We thank Francien Wilms-Schopman and Jaap van Hulst for their expert technical assistance.

This study was supported by a grant from the Wyman M. Pon Foundation, Amsterdam.

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Received October 13, 1981; accepted for publication January 7, 1982.

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Janse and van Capelle/ Premature Beats in Acute Ischemia


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Electrotonic interactions across an inexcitable region as a cause of ectopic activity in acute regional myocardial ischemia. A study in intact porcine and canine hearts and computer models.

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_Circ Res._ 1982;50:527-537
doi: 10.1161/01.RES.50.4.527

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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