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Vulnerability to ventricular fibrillation

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One of the factors that favors the development of ventricular fibrillation is an increase in the dispersion of refractoriness. Experiments will be described in which an increase in dispersion in the recovery of excitability was determined during brief episodes of enhanced sympathetic nerve activity, known to increase the risk of fibrillation. Whereas in the normal heart ventricular fibrillation can be induced by a strong electrical shock, a premature stimulus of moderate intensity only induces fibrillation in the presence of regional ischemia, which greatly increases the dispersion of refractoriness. One factor that is of importance for the transition of reentrant ventricular tachycardia to ventricular fibrillation during acute regional ischemia is the subendocardial Purkinje system. After selective destruction of the Purkinje network by lugol, reentrant tachycardias still develop in the ischemic region, but they do not degenerate into fibrillation. Finally, attempts were made to determine the minimal mass of thin ventricular myocardium required to sustain fibrillation induced by burst pacing. This was done by freezing of subendocardial and midmural layers. The rim of surviving epicardial muscle had to be larger than 20 g. Extracellular electrograms during fibrillation in both the intact and the "frozen" left ventricle were indistinguishable, but activation patterns were markedly different. In the intact ventricle epicardial activation was compatible with multiple wavelet reentry, in the "frozen" heart a single, or at most two wandering reentrant waves were seen. © 1998 American Institute of Physics. [S1054-1500(98)00201-8]

It has been known for a long time that the normal rhythmic activity of the heart can be upset by applying a single, strong electrical shock to the heart during a short part of the cardiac cycle, the so-called vulnerable period. The ensuing rhythm is called ventricular fibrillation, in which the different parts of the two main chambers of the heart (the ventricles) are rapidly and asynchronously activated so that a coordinated contraction of the heart no longer occurs. This is a lethal condition, unless another strong electrical shock causes this abnormal electrical activity to cease, allowing the normal pacemaker of the heart to resume control and to initiate the normal, regular heartbeat. In this paper the vulnerability to ventricular fibrillation is described in terms of the "dispersion of refractoriness," indicating a time window during which some parts of the ventricles are inexcitable (refractory), others partially excitable, and still others completely excitable. An electrical stimulus delivered during this time window will initially be unable to activate those parts that are inexcitable, but will cause a wave front of electrical activity that slowly travels around the area of inexcitable tissue, exciting it after a delay when excitability has returned, to finally reenter the site of origin. This so-called reentrant activity, which continues to reexcite tissue that just has recovered its excitability, is responsible for fibrillation. The normal heart has a short vulnerable period, but in diseased states, such as acute ischemia when the blood supply to a part of the heart is suddenly stopped, the dispersion in refractoriness, and thus the vulnerability to fibrillation, is greatly increased.

It is likely that the specialized conducting system of the ventricles (also called the Purkinje system) contributes to the dispersion of refractoriness. Its destruction still allows reentrant activity during acute ischemia, but prevents the degeneration to the more complex rhythms of fibrillation. In the intact, "three-dimensional" left ventricle, fibrillation is caused by so-called multiple wavelet reentry, in which many independent wave fronts travel randomly around multiple islets of (temporarily) inexcitable tissue. In experiments in which the left ventricles of isolated hearts were made "two dimensional" by freezing the inner layers until only a thin layer on the surface remained alive, fibrillation was caused by a more simple form of reentrant activity. Either a single wandering reentrant wave with multiple offshoots, or at most two independent reentrant waves maintained the abnormal rhythm.

INTRODUCTION

Single, strong electrical stimuli delivered through a relatively small electrode can, when properly timed, induce ventricular fibrillation in the normal heart, whereas stimuli of low intensity usually do not.¹⁻⁶ Even when two to five successive low-intensity premature stimuli (i.e., stimuli with shorter coupling intervals than that of the basic rhythm) are applied to the normal ventricle, ventricular fibrillation is rarely induced.^{1,5-10} It is likely that a key element, deciding whether or not electrical stimuli applied to the normal heart result in fibrillation, is a certain degree of inhomogeneity in

the recovery of excitability of individual cardiac cells, meaning that at a particular instant some fibers are totally inexcitable (absolutely refractory), others have partially recovered their excitability (relatively refractory), and still others have completely recovered their excitability. It is in this respect noteworthy that in a perfectly homogeneous computer simulation of identical excitable elements coupled to each other via low resistance connections to form a network, sustained repetitive activity could be evoked by applying a special stimulation pattern:¹¹ a plane wave was initiated within a square grid of coupled elements by simultaneous stimulation at five sites at one of the edges, and a low-intensity premature stimulus was applied at a single point in the wake of the plane wave. This stimulus found the elements in front refractory (i.e., inexcitable), but the elements in the wake already partially excitable, resulting in an "antegrade" conduction block, and a propagating "retrograde" wave front. This wave front turned around and downward and finally reexcited the site of premature stimulation. This "reentrant" activity was possible because of the inhomogeneity in excitability that existed for a brief moment and was "unmasked" by the special stimulation protocol. Similar results have later been obtained (but with a single very strong stimulus) in intact hearts¹² and in isolated thin preparations of dog and sheep cardiac muscle,¹³ where unidirectional block and reentry were induced by a similar stimulation pattern. (For an excellent description of the basic characteristics of reentry the reader is referred to the article by Gray and Jalife, appearing in this volume.)¹⁴ A key requirement for the induction of reentry is the presence of unidirectional block. Usually, reentry occurs following a premature impulse, either occurring spontaneously or induced by a low-intensity stimulus. When properly timed, this impulse will be blocked in regions with a long refractory period, and slowly conducted around the zone of block in areas with shorter refractory periods to return to the point of origin resulting in reentrant excitation. The normal ventricular myocardium shows some inhomogeneity in the recovery of excitability, the difference between the shortest and longest refractory period (also called "dispersion in refractoriness") being in the order of 40 ms.¹ Furthermore, differences between the refractory periods of ventricular myocardium and the specialized conducting system (or Purkinje system) are even larger.¹ Still, as already mentioned, it is very unusual for single low-intensity premature stimuli to induce ventricular fibrillation. It stands to reason that the conditions in which the dispersion in refractoriness is increased are associated with a greater likelihood for reentrant excitation to occur. Two of these conditions are enhanced activity of the sympathetic nervous system (that part of the so-called autonomous nervous system that, when activated by, for example, exercise, emotion, stress, results in, among others, an increase in the heart rate and an increase in the force of cardiac contraction) and acute regional ischemia (when sudden occlusion of a branch of a coronary artery results in an arrest of blood flow to part of the ventricles).

In the first section of this paper we deal with dispersion in refractoriness during these conditions. In the second part, experiments will be described, indicating that the Purkinje

system (which adds to the inhomogeneity in refractoriness in the intact ventricles) may be a necessary requirement for the transition of an initial reentrant rhythm to the more complex rhythm of ventricular fibrillation. Finally, the question will be addressed whether ventricular fibrillation can be caused by different patterns of reentrant excitation, by comparing activation patterns in the intact "three-dimensional" left ventricle and a "two-dimensional" left ventricle created by destruction of most of the ventricular wall, leaving only a thin rim of epicardial myocardium intact.

DISPERSION IN REFRACTORINESS

It has been known since 1850 that the normal heart can be made to fibrillate when exposed to strong electrical shocks,¹⁵ and since 1899 that such fibrillating hearts can return to beating normally after similar shocks.¹⁶ These experimental findings became of importance when in the early decades of this century electrical devices were increasingly installed in households, and more and more people were accidentally electrocuted. Electricity companies gave grants to academic centers to study the effects of electrical currents on the heart,¹⁷ and one of these was the laboratory of Dr. Carl Wiggers at Western Reserve University in Cleveland.

Wiggers and Wégria¹⁸ demonstrated in 1940 that normal hearts have a vulnerable period in late systole during which single induction shocks or condenser discharges induce ventricular fibrillation. The vulnerable period is that part of the cardiac cycle "during which some fibers are in and others have passed out of a refractory state."¹⁹ The duration of the vulnerable period in the dog heart is in the order of 10–20 ms.¹⁹ Thus, the normal heart is vulnerable during a small part of the cardiac cycle, albeit only to strong electrical shocks, and this vulnerability was described as inhomogeneities in excitability. It can therefore be expected that an increase in such inhomogeneity would increase the vulnerability. Han and Moe in 1964 were the first to test the hypothesis that "any agency that increases the temporal dispersion or asynchrony of excitability recovery should increase the likelihood of fibrillation."²⁰ They concluded that "those agencies known to favour the development of ventricular fibrillation were found to increase the temporal dispersion of recovery of excitability, whether the average refractory period was reduced (sympathetic nerve stimulation, ouabain intoxication, ischemia) or increased (chloroform, quinidine in high dosage, or hypothermia). The results emphasize the importance of nonuniformity of excitability and conduction velocity during the relative refractory period in the induction of turbulent impulse propagation."²⁰

Sympathetic stimulation is associated with an enhanced risk for ventricular fibrillation,²¹ and it might well be, as stated by Han and Moe, that this is due to an increased dispersion in refractoriness. If indeed there is inhomogeneity in the recovery of excitability in adjacent areas of the ventricles, a premature impulse, originating in the area with the shortest refractory period may be blocked in a zone of longer refractory periods. When the zone of block is large enough, conduction around this zone is slow enough, and refractory

periods proximal to the zone of block are short enough, the stage might be set for reentry.

We have readdressed the problem originally posed by Han and Moe, employing a different method. Since a premature beat influences the refractory period of many subsequent regular basic beats, determination of the refractory period with a 1 ms precision using the classical extrastimulus method at multiple sites takes a long time.¹ Since the effects of sympathetic stimulation are transient, the classical method of determining refractory periods is not suitable to measure dispersion in refractoriness during rapid and short-lived alterations in excitability. We therefore determined spatial dispersion in refractoriness by measuring VF intervals at multiple sites during ventricular fibrillation in dogs on a total cardiopulmonary bypass before and after brief episodes of stimulation of the sympathetic nerves. At each site, consecutive intervals between local depolarization were determined during a 7 s period, and the average was calculated. A validation of the technique was performed by the determination of refractory periods during regular pacing (cycle length 350 ms) using the extrastimulus technique at the same sites where VF intervals were measured. A very good correlation between the two parameters was found ($r=0.95$). In the normal dog ventricle, the difference between shortest and longest VF interval is in the order of 15 ms (the average VF interval being in the order of 100 ms), that between the shortest and longest refractory period during regular driving 30 ms (cycle length of the driving rhythm being 450 ms).²²

Figure 1 shows an example of an experiment where VF intervals were measured at 16 recording sites, located on the circumference of the ventricles, as schematically indicated in the inset. It is clear that in this particular experiment the effects of stimulation of both the left and right division of the sympathetic nervous system [“left and right stellate ganglion stimulation” (LRSS)] are inhomogeneous: a marked shortening of 15–25 ms is found on the anterior wall (electrodes 1–4) and on the posterior wall (electrodes 11–13) of the left ventricle, whereas other sites only show a moderate shortening. Out of a total of 11 hearts, a distinct regional effect of either left, right, or bilateral stellate ganglion stimulation was found in 6 hearts, whereas in the remaining 5 hearts a more diffuse pattern was found, where VF intervals shortened equally at all recording sites. Thus, in some hearts, sympathetic stimulation produces a distinct increase in spatial dispersion of refractoriness, in others it does not.

It must be emphasized that inhomogeneities in refractoriness may not be the primary determinant of inducibility of VF by strong electrical premature stimuli. Winfree²³ noted that the local ventricular response to strong stimulation could be described in terms of an abstract dynamical system involving the premature (S_2) stimulus and the tissue refractoriness, so the whole heart might respond like a spatially extended field of the same kind, which would entail a vulnerable period and reentrant vortices resembling those known in the heart. Later studies^{24–26} showed that when VF was induced by a large premature S_2 applied to a different site than the regular S_1 stimuli, the location and direction of the initial figure-of-eight reentry (where two reentrant circuits, one clockwise, the other counterclockwise, are set up

FIG. 1. In each panel ventricular fibrillation (VF) intervals or the change in VF intervals (upper panel) are depicted for a row of electrodes schematically shown in the inset. Values are given before and immediately after a brief episode of bilateral (left and right) stellate ganglion stimulation (LRSS). Note shortening in some areas and minor effects in other areas (upper panel). The delta values shown in the top panel are much larger than the error bars in the lower two panels (not shown).

around two zones of conduction block, sharing one common “central” pathway) were not determined by inhomogeneities in refractoriness, but that the reentrant wave front arose in a region where a critical value of the S_2 potential gradient field intersected with a critical degree of refractoriness. Still, in “spontaneously” arising VF, e.g., during acute ischemia, inhomogeneities in refractoriness do play a critical role. Studies by Coronel *et al.*²⁷ showed that during acute regional ischemia (produced by ligation of a branch of a coronary artery), single premature stimuli of low strength applied to the nonischemic myocardium only induced VF between 5 and 8 min following coronary artery occlusion. During this time window, extracellular K^+ concentrations had to be within a critical range of 8–13.5 mmol/L in a lateral “border” zone (interposed between normal tissue and the central ischemic zone), which had to comprise between 20%–35% of the total ischemic zone. Since in ischemic tissue, small changes in extracellular K^+ concentrations result in large changes in refractoriness,²⁸ dispersion in refractoriness within this lateral “border” zone may be estimated to be in

FIG. 2. Activation patterns in two epicardial areas of 2×2 cm covered by a multiterminal electrode (120 terminals) during the initial beats of spontaneously occurring ventricular fibrillation in an isolated, Langendorff-perfused pig heart, 5 min after occlusion of the left anterior descending coronary artery. In the ischemic zone, the activation pattern is compatible with multiple wavelet reentry (isochrones are drawn at 10 ms intervals, shaded areas are zones of conduction block, figures are in ms, arrows indicate the general direction of spread of excitation). In contrast, in the adjacent normal myocardium (lower panels) activity proceeds as a single organized wave front.

the order of 150–200 ms. This figure fits well with findings by Kuo *et al.*,²⁹ who created dispersion in refractoriness by cooling certain regions of the heart. It was found that when a critical difference between the longest and shortest refractory period ranging from 95 to 145 ms was reached, premature stimuli delivered at the site with the shortest refractory period induced repetitive, reentrant activity.

IS THE PURKINJE SYSTEM NECESSARY FOR THE TRANSITION OF VENTRICULAR TACHYCARDIA INTO VENTRICULAR FIBRILLATION?

We hypothesized that in the setting of acute ischemia, an intact Purkinje system might be a necessary requirement for the transition of reentrant ventricular tachycardia to ventricular fibrillation.³⁰ In acute regional ischemia, ventricular premature depolarizations arise in normal myocardium adjacent to the ischemic border, most likely caused by reexcitation of normal cells by injury currents.³¹ The premature wave front initiates reentrant wave fronts within the ischemic myocardium. The reentrant circuits are fairly large, in the order of 8 cm, and revolution times are fairly long, in the order of 350 ms. The rate of a ventricular arrhythmia that is determined solely by reentry within the ischemic myocardium would thus be in the order of 170 beats per minute. The rate of ischemia-induced VF is around 400/min (cycle length 150

FIG. 3. The same heart as in Fig. 2, 1 min later when ventricular fibrillation has fully developed. Activation in the normal zone is now also fragmented and intervals between successive activations are much shorter than during the initial beats [compare the 10 and 220 ms isochrones in Fig. 2 (difference 210 ms) with the 140 and 230 ms isochrones in Fig. 3 (difference 90 ms).]

ms), and this implies that the nonischemic myocardium must become involved, which has a shorter refractory period than ischemic myocardium. It is possible that centrifugal wave fronts, emerging from reentrant circuits in the ischemic zone, are conducted rapidly, and at irregular intervals, at constantly changing sites via the Purkinje system toward the nonischemic myocardium. Since this tissue will repeatedly be prematurely excited, its refractory period will progressively shorten.¹ Because of the irregular activation of the nonischemic myocardium, local differences in refractoriness will occur, and areas of a temporal unidirectional block may develop. Eventually, reentrant wavelets will be set up in the normal myocardium, which will be shorter than those in the ischemic zone, because the refractory period after repetitive premature activation will be much shorter in the normal than in the ischemic zone. It has indeed been found that in the initial phase of reperfusion-induced VF (i.e., when blood flow to an ischemic region is suddenly restored), the normal myocardium is rapidly excited by orderly wave fronts emerging from the perfused myocardium.³² In Fig. 2 epicardial activation maps of the first beats of VF, occurring spontaneously after 5 min of ischemia, are shown. In the ischemic zone, the activation pattern is compatible with multiple wavelet reentry, but in the adjacent normal myocardium there is a single, organized wave front. During fully developed VF, 1 min later (Fig. 3), the normal tissue also shows the pattern of multiple wavelet reentry. Note that, in the lower part of the area covered by the multiple-terminal elec-

FIG. 4. Subendocardial electrograms of an isolated dog heart before and after multiple applications of lugol to the endocardial surface. In control conditions a Purkinje deflection precedes the much larger muscle deflection. After the first application of lugol, the interval between the two potentials is prolonged; after the second application there is only a very small Purkinje potential and a very long interval between the P wave and muscle potential. After the third application there was total AV block. The ventricles were paced (the five signals on the left). After stopping pacing, no idioventricular rhythm ensued, indicating selective destruction of the subendocardial Purkinje system.

trode, the interval between successive activations in the normal zone is $220 - 10 = 210$ ms in the initial phase, while 1 min later it is $230 - 140 = 90$ ms.

In support of the hypothesis that an intact Purkinje system plays a role in the transition of VT to VF is the finding that after destruction of the subendocardium by phenol, acute ischemia still induced reentrant arrhythmias in the ischemic zone, but these never degenerated into ventricular fibrillation.³⁰ Some preliminary results of experiments in isolated, Langendorff-perfused canine hearts (in which an artificial system ensured adequate perfusion of the heart via its coronary arteries), in which selective destruction of the subendocardial Purkinje system was attempted by application of lugol, are shown in Figs. 4 and 5. Figure 4 shows an extracellular electrogram from a subendocardial site in which a Purkinje potential precedes the much larger muscle deflection in control conditions. The application of lugol initially only prolongs the interval between the Purkinje spike and muscle deflection, but after three applications (lower trace) no ventricular activity is visible, following cessation of ventricular pacing (the five signals on the left), indicating that the Purkinje system had been effectively destroyed. Figure 5 shows that in the intact heart, the application of three premature stimuli at an intensity of only two times the diastolic threshold (S_2 , S_3 , S_4) to the normal myocardium induced VF, 5 min after coronary artery occlusion. After destruction of the Purkinje system, the same procedure only led to a nonsustained ventricular tachycardia. It must be emphasized that in these experiments no strong electrical shocks were applied, and that regional ischemia was an essential requirement for the occurrence of the arrhythmias. The same premature stimuli did not induce VT or VF in the absence of ischemia. Thus, these results cannot be easily compared to studies in which the effects of chemical ablation on VF

thresholds were studied, one of which reported an increase in VF threshold,³³ the other no effect.³⁴ It may be that the Purkinje system is only important for the transition to VF in the setting of acute ischemia.

FIG. 5. Selected signals from the same heart as in Fig. 4. Upper panels show that three premature stimuli (S_2 , S_3 , S_4) of only twice the diastolic threshold strength applied to the nonischemic myocardium, 5 min after coronary artery occlusion, induce ventricular fibrillation. After destruction of the Purkinje system with lugol (following reperfusion) the same stimuli during a second episode of ischemia only induce a nonsustained ventricular tachycardia.

FIG. 6. Unipolar electrograms from the same electrode during ventricular fibrillation induced by burst pacing before and after cryoablation (reproduced with permission from Ref. 39).

CAN VENTRICULAR FIBRILLATION BE A TWO-DIMENSIONAL EVENT?

In 1914, Garrey demonstrated that a minimal mass of tissue is required to maintain fibrillation.³⁵ In experiments on open-chested dogs, “pieces were shaved from the wall of the fibrillating left ventricle by a cut parallel to the surface, the cut being made so that the cavity of the heart was not entered. These pieces ceased fibrillating at once, although some were two centimeters wide and four centimeters long, and as thick as could safely be made.”³⁵ Winfree^{36,37} has suggested that wall thickness *per se* catalyzes the transition from monomorphic tachycardia to ventricular fibrillation, and experimental findings from Kavanagh *et al.*²⁶ support this. They applied strong premature stimuli to the surviving rim of epicardial myocardium overlying a four-day-old infarct in the

"Three-dimensional VF"

FIG. 7. Activation pattern of the epicardial surface during ventricular fibrillation in the intact left ventricle during an arbitrary 100 ms time window. Six different wave fronts are present (the same heart as in Fig. 6). Areas of block are stippled, numbers are in ms, time zero is arbitrarily chosen (reproduced with permission from Ref. 39).

Two-dimensional VF

FIG. 8. Epicardial activation patterns during 420 ms of ventricular fibrillation in a “frozen heart” (the same as in Figs. 6 and 7). Note the presence of one, or a most two different wandering reentrant waves (reproduced with permission from Ref. 39).

dog heart and found that the initial stable figure-of-eight reentrant circuit only degenerated into VF when the rim was thicker than about 3–4 mm.

We have attempted to create a “two-dimensional” left ventricle by cryoablating all the ventricular tissue except for a thin layer of subepicardial tissue in the free wall of the left ventricle. In essence, we copied the “frozen heart” model developed by Allessie and co-workers for the rabbit heart.³⁸ In isolated, Langendorff-perfused pig hearts, cryoprobes were inserted into left and right ventricular cavities. These probes were filled with liquid nitrogen, coronary perfusion was interrupted, and the heart was immersed in a tissue bath containing Tyrode’s solution of 20 °C. The cryoprobes were left in place for some 10 min and then removed. The heart emerged from the bath and the coronary arteries were perfused with a blood–Tyrode mixture (for details, see Ref. 39). In those frozen hearts in which the surviving subepicardial layer was larger than 20 g, it was possible to induce sustained VF by burst pacing (i.e., applying 10–20 electrical stimuli at very short coupling intervals). As shown in Fig. 6, unipolar electrograms from the same electrode during VF induced in the intact heart (control) and in the frozen heart are indistinguishable from each other. Epicardial activation patterns, however, were markedly different. Figure 7 shows the isochronal map during a 100 ms time window during VF in the intact left ventricle. Six different wavelets are present. Since no intramural recordings were made, some of these might have been offspring of a single intramural reentrant circuit. Still, the overall pattern is compatible with the multiple wavelet hypothesis. After the cryoablation procedure, the activation patterns are much more simple. Figure 8 shows isochronal maps of four successive time windows during sustained VF after freezing (part of the epicardial surface was frozen also, as indicated by the shaded area). In panel (a) (time zero coincided with the beginning of the recording) a single reentrant wave front is present, propagating around a small arc of functional block of about 8 mm. This wave front

continues in panel (b) to end at the edge of the surviving subepicardial layer at 180–190 ms. A second wave of apparent focal origin emerges at 140 ms and reenters at 220 ms in panel (c), continuing at 300 ms in panel (d), and propagating further after 420 ms to the next time window (not shown). Two additional wave fronts appear, one at 220 ms in panel (c), another at 320 ms in panel D. Since the epicardial layer at places was as thick as 7 mm, these “focal” origins could have been an epicardial breakthrough of intramural reentrant circuits, although a true focal origin cannot be ruled out on the basis of these recordings. Still, this experiment (and others—Ref. 39) shows that the characteristic extracellular waveforms of VF can be caused by different forms of reentrant activation, varying from a single reentrant circuit with offsprings, to two independent wave fronts, to multiple wavelet reentry within the order of six different wave fronts. Further experiments not only using epicardial electrodes but also intramural electrodes recording activity throughout the ventricular wall, and extending over longer time periods, are required to determine whether, indeed, reentrant excitation alone is the basis of VF, and if so, what the minimal number of reentrant wavelets is that is needed to maintain VF. So far, our experiments are compatible with the concept that true “two-dimensional” VF does not exist.

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