Sudden Death Related to Myocardial Infarction

By Thomas N. James, M.D.

SUMMARY

Sudden death as it relates to myocardial infarction (not necessarily acute) is discussed on the premise that most such deaths are due to a lethal electrical disturbance of the heart. The three sections of the first part deal with the rhythm of the heart, conduction in the heart, and neural control of the heart. In these sections consideration is made of those factors which stabilize cardiac electrical performance, and conversely how these factors may be deranged into electrical instability. In the second part a practical discussion is organized to interrelate the principles presented on maintenance and derangement of electrical stability of the heart; the electrical reserve of the heart, some unstabilizing factors, and clinical considerations are the subjects for this integrating synthesis. The entire review is designed to provide the clinical cardiologist a framework of reference in which logical decisions can be made in caring for the patient who has coronary disease and in whom myocardial infarction will be, is, or has been a complication. By a fuller appreciation of principles underlying maintenance of electrical stability of the heart, the risk of dying suddenly from electrical instability may be reduced.

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Those interested in the subject of myocardial infarction today are keenly aware of its close relationship to sudden death. This relationship is illustrated by the similarity of the populations at greatest risk, by the frequent coexistence of myocardial infarction and sudden death, and by the special hazard of sudden death in survivors of acute myocardial infarction. Some examples of sudden death in relation to myocardial infarction are readily understood, such as that due to rupture of the ventricle. Others, such as the development of acute pulmonary edema, are less completely understood, particularly those occasional examples where the volume of damaged myocardium is unexpectedly small. However, it is generally thought that the main cause of sudden death in myocardial infarction is a ventricular arrhythmia. This review will concern itself with the multitude of factors responsible for a lethal electrical disturbance of the heart, especially considering myocardial infarction (not necessarily acute).

Stability and instability of the electrical activity of the heart are two sides of the same coin, the full value of which can only be appreciated by a close examination of both sides. If one understands those factors which serve to make cardiac rhythm and conduction stable under normal circumstances, it simplifies any discussion of how myocardial infarction may derange this stability. Electrical instability of the heart may be major or minor, transient or permanent, innocuous or symptomatic or lethal, reversible or irreversible, expected or unexpected, or various combinations of these descriptive terms. Although the primary focus here will be on lethal instability of the electrical activity of the heart, as related to myocardial infarction, it may be noted that minor forms of instability under some circumstances may assume much more grave aspects,
given other conditions. Similarly, forms of instability which are usually transient may on occasion quickly terminate with death.

This is not the place to catalog all forms of electrical instability. In oversimplified terms one may summarize mechanisms of cardiac electrical instability in three categories: those in which no effective impulse is generated, those in which one is generated but ineffectively delivered or distributed, and those in which the impulse is generated and delivered but the cells fail to respond (so-called electromechanical dissociation). Too little is known about the cellular or metabolic basis of electromechanical dissociation for meaningful discussion here, although its occurrence in the course of myocardial infarction makes it an important subject for further research, including its potential role in sudden death. More is known about the normal rhythm and conduction in the heart, and their neural control. In the sections dealing with the rhythm of the heart, conduction in the heart, and the neural control of the heart, those factors promoting stability and those which lead to its disorganization will be emphasized, all in the context of sudden death related to myocardial infarction.

**Rhythm of the Heart**

The normal function of the sinus node is to provide a stable rhythm for the heart. Perhaps because so many experimental preparations deliberately destroy the sinus node, it is widely assumed to be a relatively unimportant structure which is readily substituted by a number of alternative automatic centers. Whether this is actually the case in man is at the least highly debatable, but there can be little doubt that electrical stability of the heart is facilitated by the normal generation of sinus rhythm. Three immediately apparent reasons why sinus rhythm is so valuable are: (1) Escape rhythms do not always emerge; the clinical significance of this point is being increasingly appreciated from those examples in which sinus-node malfunction or failure leads to syncopal attacks, often in patients with ischemic heart disease. (2) Those escape rhythms which do emerge may be too slow or irregular and are intrinsically less stable than sinus rhythm. (3) During sinus rhythm, the normal sequence of atrial and then ventricular contractions is preserved, with its hemodynamic advantages.

One basis for stability of sinus rhythm is its higher rate of spontaneous rhythmicity than any other automatic center, except under special conditions. Although there are circumstances in which a slow heart rate is advantageous, e.g. in trained athletes, it is rarely beneficial in older subjects, and they are the principal candidates for ischemic heart disease. Slow heart rates require larger stroke volumes in order to maintain any given level of cardiac output, and many patients with ischemic heart disease have insufficient myocardial reserve to increase stroke volume at all. Furthermore, it is now widely recognized that slow heart rates per se predispose to ectopic beats and ventricular or atrial arrhythmias, principally by increasing the dispersion of refractory periods of either ventricular or atrial myocardium.

Two other ways in which the sinus node contributes to electrical stability are by its advantageous anatomic location in the heart and by its exceptionally rich autonomic innervation. The sinus node has a distribution system which is unmatched in physiologic or anatomic efficiency by any other potential pacemaker of the heart. This special system of internodal and interatrial pathways has a large reserve capacity which is not readily disrupted by focal disease such as that occurring in relation to myocardial infarction. Based on stable cardiac performance in patients with electronic pacemakers, it is tempting to assume that eccentrically located foci of cellular automaticity in the heart can be equally effective; however, ectopic biologic pacemakers are usually slow and easily disorganized. The advantages of dual autonomic innervation in the sinus node will be dealt with later.

Ischemia affects the sinus node in three ways: loss of automatic cells, deranged neural control, and impaired distributive function. These three are given in approximately their order of importance. The matter of neural
control will again be dealt with later. In patients dying with long-standing dysfunction of the sinus node, one of the characteristic histologic abnormalities is a decrease in the number of nodal cells and replacement by excess collagen. It is unclear why fewer cells in the sinus node need be a disadvantage, since one might anticipate that its usual and normal rate might be provided by the spontaneous depolarization of any given cell. Possibly the same pathologic process which destroys some automatic cells also impairs the effectiveness of the others, although they may appear histologically normal on a microscope slide. Furthermore, it is not known how the normal sinus node effectively synchronizes the electrical signal which is so efficiently generated and delivered from a myriad of automatic cells which, it may be assumed, do not all have precisely the same firing rate. Perhaps the loss of some critical number of these, or ones in particular locations in the sinus node, disrupts this normal synchrony and thereby leads to a slower rate—and one more easily disorganized.

It was earlier indicated that the distributive system from the sinus node is not easily disrupted by myocardial ischemia, and this is true because of the availability of three alternate internodal pathways. However, during focal ischemia of the sinus node a characteristic lesion develops directly at its junction with the atrium. Such a lesion may have a specific effect impeding the efficiency of sinus impulse distribution. Almost nothing is known of the mechanism of distribution of electrical activity within the sinus node itself, but it may be assumed that some orderly process is involved and consequently that focal disease within the node would alter intranodal conduction, thereby making it a less stable performer.

**Conduction in the Heart**

During normal sinus rhythm the A-V node and His bundle may be considered as one conjoined unit with three functions: triage of atrial signals, momentary delay (0.04 sec) of the sinus impulse, and then rapid delivery of it to the bundle branches and two ventricles. The triage consists of an effective filtering of all electrical signals arriving at the atrial margin of the A-V node and the organization of these into a consistent activation front delivered to the His bundle. Exactly where the normal A-V-nodal delay occurs is uncertain, so that anatomic possibilities for its circumvention cannot easily be defined.

Both the A-V node and His bundle are multicellular complex structures and their internal organization is different in several important ways. The A-V node is composed largely of slender interweaving and interconnecting fibers which are connected to the internodal system of the atria proximally and to the His bundle distally. There is comparatively little collagen matrix in the A-V node and a virtually unlimited number of cross connections between its component fibers. By contrast, the His bundle is composed of fibers arranged in parallel array, with fine collagen septa distinctly separating these into multicellular strands having relatively few crossovers or interconnection. The cells of the His bundle are predominantly of the Purkinje type while those of the A-V node are typical slender transitional cells. In either the A-V node or His bundle, focal disease of the type which often occurs in myocardial ischemia or infarction may partition these structures either anatomically or physiologically and thereby facilitate reentrant rhythms. More extensive damage may either impair or completely block A-V conduction.

It has long been known that a major subsidiary pacemaking activity resides in the A-V junction. Although such an escape rhythm has been loosely referred to as A-V-nodal rhythm in the past, the current trend is to refer to these as A-V-junctional rhythms, including as possible sites of origin the several structures located between the coronary sinus and the proximal portions of the bundle branches. In this region there are most likely a series of potential automatic centers, with the intrinsically more rapid ones being more proximally located. Ischemia can have two opposite effects on such activity. A very early effect may be one of enhanced automaticity.
manifested clinically by A-V-junctional tachycardia. A totally different effect may occur during escape A-V-junctional rhythm, and that is arrest of the escape pacemaker due to the focal effect of more profound ischemia. Although most experienced cardiologists know of one or a few patients with long-sustained A-V-junctional rhythm, it may generally be stated that such rhythms are basically unstable and effectively serve emergency needs only for relatively brief periods of time. Furthermore, even the stable ones are comparatively slow and thereby predispose to more serious disorganization of electrical stability of the heart.

Ischemic heart disease often leads to focal damage in the bundle branches, and there is evidence suggesting that bilateral bundle-branch block is an important cause of heart block. However, lesions in the bundle branches seldom occur in the absence of significant pathology more proximally located in the A-V node and His bundle. If more proximal disease is an accomplishment of bundle-branch disease, then it is difficult to discount the former lesions as the more pertinent ones, given normal antegrade spread of electrical activity of the heart. Furthermore, the size of a lesion necessary to disrupt completely the conduction in the His bundle is much smaller than the two or more required to block conduction in both bundle branches. It may even be reasoned that lesions observed in the bundle branches are there because the patient survived long enough for the histologic process to be identifiable, whereas the onset of a similar process in the His bundle leads to lethal electrical instability so soon that the ischemic influence is not histologically identifiable. Two possible sources of useful information on this question are: (1) more than usually careful assessment of the exact location of lesions in the coronary arteries and their relationship to the origin of nutrient arteries of the conduction system; (2) better methods for recognizing very early effects of ischemia in these special regions. For the sake of the present discussion it is sufficient to state that focal ischemia in the A-V junction has a variety of unstabilizing effects on all possible normal and abnormal functions of the region.

**Neural Control of the Heart**

Although neural influence on the heart includes that on coronary flow and on myocardial contractility, each of which may in turn lead to disorganization of cardiac rhythm or conduction, this section will deal primarily with the effects directly on rate, rhythm, and conduction. Sources of neurogenic effects on the heart may be considered in five categories: (1) the normal regulatory centers of the brain; (2) cardiogenic reflexes; (3) reflexes of extracardiac origin; (4) conscious and unconscious mental processes; and (5) pharmacologic and humoral influences. The categories overlap and will often coincide.

Centers which constantly influence both blood pressure and cardiac electrical activity are known to exist in the midbrain but remain relatively poorly understood in man, particularly as they may affect stability of rhythm or conduction. There is abundant evidence from experimental animals that virtually any disturbance of the electrical processes of the heart may be artificially produced by the introduction of appropriate stimuli into the brain. For this “tonic” or constant influence on the heart, disorganization may occur either at the central end (in the brain), or by disease of the efferent nerves, or by alteration of responsiveness by special sites in the heart. The same may be said of the general character of neural control of the heart.

Reflexes which originate in the heart are intertwined with those originating elsewhere, as in the carotid sinus or aortic arch; e.g., sudden changes in aortic pressure activate both intracardiac and extracardiac receptors. There are two particular cardiogenic reflexes which are associated with myocardial ischemia or infarction and which have opposite results. One is characterized by a hypertensive response with little primary effect on heart rate, while the other is a combination of arterial hypotension and bradycardia. The details of these and similar cardiogenic reflexes need not be dealt with here, but it is...
important to be aware of their existence and potential role in the maintenance of electrical stability of the heart. Similarly, certain humoral influences on neural control may have profound significance; an obvious example is the increase in circulating catecholamines which occurs during acute myocardial infarction\(^{22}\) and similar stress states. Certain commonly used drugs such as digitalis and quinidine also significantly affect neural response by the heart.\(^{23, 24}\) It is now feasible to employ drugs which selectively antagonize either cholinergic or adrenergic responses. An important example is the use of atropine in patients with bradycardia during acute posterior myocardial infarction.\(^{20, 21}\) On the other hand, both the neural and electrophysiologic effects from clinical use of drugs such as reserpine, guanethidine, or beta-receptor blocking agents\(^{25}\) must be considered in evaluating and anticipating developments which may unstabilize cardiac rhythm or conduction in the patient with ischemic heart disease.

In a recent review, Engel\(^{26}\) lucidly discusses the influence of the emotions on the heart, particularly the effects of situations which contain major elements of uncertainty, whether the associated feelings are ones of pain or fright or anger or sadness. Not only do these considerations have broad application in the understanding of cardiovascular function, but in the patient with ischemic heart disease they may be especially important. A fuller understanding of how patients emotionally and mentally respond to events such as acute myocardial infarction will inevitably improve our ability as physicians to cope with such responses. Arousal of emotional responses is manifested in most instances by either a predominant adrenergic (sympathetic) or cholinergic (vagal, parasympathetic) effect on the heart, and these are of opposing nature. While there is no question that either of these opposing influences may disorganize electrical stability, there is suggestive evidence that predominantly vagal responses are more often associated with sudden death.\(^{27}\)

Neural control of the heart, which is normally in a finely tuned state of balance, may be unbalanced in several ways. Disease may affect predominantly one or the other of the two sets of autonomic nerves, either in their central or peripheral location. Disease may also affect selectively one region of the heart or even predominantly one set of autonomic nerve endings in the heart, and thus unbalance the response to what may have begun in the brain as a balanced autonomic discharge. Just as some emotional responses are characterized more by either adrenergic or cholinergic responses, there are probably other conscious and unconscious processes in the brain which may produce a similarly unbalanced autonomic outflow to the heart. Finally, certain drugs and humoral influences indicated previously will facilitate or antagonize selectively either cholinergic or adrenergic neural control.

**Discussion**

The following discussion will be concerned with integrative concepts based on the principles, considered above, as they apply to the question of sudden death related to myocardial infarction.

**Electrical Reserve of the Heart.** In the preceding sections the emphasis was on normal mechanisms and how they may be disorganized. It is important to appreciate that the heart has a large number of adaptive responses which may be thought of as an electrical reserve favoring maintenance of stable performance. Two aspects of pacemaker activity serve to illustrate this matter. First, the sinus node participates in at least two servomechanisms which furnish a modulating influence on its rate of firing. Second, there is an effective subsidiary pacemaker system in the region of the A-V junction.

Servomechanisms which tend to stabilize the function of the sinus node are only beginning to be explored, although Flack\(^{28}\) many years ago emphasized that the regulatory role of the sinus node was probably more important to the efficient function of the heart than was its role as a pacemaker per se.
Experimental evidence has been presented\textsuperscript{25, 29} which suggests that the pulse in the sinus-node artery is a feedback signal closing the loop of a servomechanism modulating the rate of impulse formation. Any disease which alters or distorts this pulse may be anticipated to have some effect on stability of sinus rhythm. Although the magnitude of this effect is probably small under most circumstances, certain examples of sudden death both in man and other animals have been shown to be associated with obliterative disease of the sinus-node artery.\textsuperscript{30–32} It has also been shown\textsuperscript{29, 34} that neural signals generated outside the heart may similarly serve a modulating influence on cardiac rhythm, although again the magnitude of this influence is comparatively small and its subtlety makes it easy to overlook. There are probably a number of other subtle servomechanisms, the cumulative effects of which may well contribute in an important way to the normal stability of the sinus node.

As indicated above, there are multiple pathways for internodal conduction, for transmission through the meshwork of the A-V node, and for rapid conduction through the partitioned His bundle. Although in each case this multiplicity permits the development of unstable events such as circus movement or reentrant tachycardia, this large number of anatomic alternatives also minimizes the likelihood that all pathways could be simultaneously interrupted. In this sense they furnish a safety margin and considerable electrical reserve.

Finally, the special cells of the electrical system of the heart themselves furnish several forms of electrical reserve. For example, both in the sinus node and in the A-V-junctional region there is a plethora of automatic cells, making the significance of loss of some of them (as during focal ischemic damage) less crucial than if there were only a few originally. Both the automatic cells and those dealing primarily with conduction have a metabolism different from that of working myocardial cells, one important feature of which is considerable resistance to hypoxia.

Thus, the electrical apparatus has a reserve margin which permits preservation of its function during myocardial ischemia at least as long as contractile activity is possible. Teleologically, this is a fortunate difference favoring survival of the organism.

\textbf{Some Unstabilizing Factors.} For the further purpose of integrating the preceding concepts and to focus them on the problem of sudden death related (in any way) to myocardial infarction, this section will deal with certain events and processes often observed in patients with coronary narrowing and ischemic heart disease. Both ventricular hypertrophy and ventricular dilatation occur in such patients, and both introduce factors of anatomic geometry which favor electrical instability. For example, it has long been known\textsuperscript{25} that large hearts fibrillate more easily than small hearts and that termination of fibrillation is much simpler in the latter than in the former. There are few cardiologists or cardiovascular surgeons who have not had the painful experience of being unable to terminate ventricular fibrillation in the patient with aortic insufficiency and a very large left ventricle. The electrophysiologic basis for this observation is the increased dispersion of refractory periods and markedly facilitated opportunity for reentry to develop and to be sustained in large hearts.

Slow heart rates also favor electrical instability. When the slow ventricular rate is accompanied by complete heart block, there is the compounding problem of instability of the subsidiary pacemaker. However, it has recently been demonstrated both experimentally\textsuperscript{1, 5} and in patients with acute myocardial infarction\textsuperscript{1} that the slow rate per se is dangerous, being much more frequently associated with premature beats and the development of ventricular arrhythmias. Here again, the electrophysiologic basis is the provision of a wider dispersion of refractory periods when the heart is slow than when it is more rapid.\textsuperscript{1, 5}

It need hardly be added that both sinus bradycardia and heart block are events which are not uncommon in patients with myocardial infarction, but it may be emphasized that
even their transient occurrence may be a reliable harbinger of subsequent sudden death.

In addition to ventricular hypertrophy and dilatation, and slow heart rates, another factor favoring the development of reentrant arrhythmias in patients with ischemic heart disease is focal fibrosis or degeneration. It is rare to see homogeneous distribution of infarction or scar in any portion of the heart as a consequence of ischemia, the more usual result being streaky or patchy fibrosis mixed with viable myocardial cells. This is not only a histologic postmortem observation but has been amply confirmed with biochemical studies36 demonstrating function of such surviving cells in vivo. The variegated nature of myocardial infarction or fibrosis due to ischemia may involve both the working myocardium and the conduction system. It has been indicated earlier how such focal disease in the conduction system may lead to longitudinal partitioning and reentrant tachyarrhythmias. It should also be appreciated that the same reasoning may be extended to electrical events in the distal Purkinje system37, 38 and even in working myocardial cells, although the evidence for the latter is more tenuous.

During the very early stages of acute myocardial ischemia in man, the S-T segment and T waves undergo marked distortion, sometimes reaching grotesque proportions. This electrocardiographic drama has long fascinated interns and house officers who are so often called upon to deal with the very early acute phase of myocardial infarction. This is also the period in which Q-T prolongation is most hazardous, favoring the development of lethal arrhythmias and sudden death.39 There is now wide recognition that a large percentage of the deaths from acute myocardial ischemia, with or without recognizable infarction or histologic change, occur within the first hour after onset of chest pain or comparable symptoms.40 It is usually assumed and has occasionally been demonstrated that such deaths are due to ventricular arrhythmias. There are of course a number of other electrophysiologic developments at that stage of the disease (increased ectopic automaticity, reflex bradycardia, heart block, etc.), but there is a special hazard introduced by marked delay of ventricular repolarization and increased duration of the vulnerable period. Although it is not known whether the Q-T prolongation in such patients is due to generalized prolongation of ventricular recovery time or to a wider range of times in different parts of the ventricles, it is probably some combination of these processes with major participation by the latter.

Certain humoral factors contribute to disorganization of normal electrical stability of the heart during acute ischemic episodes. A paramount example is the increase in circulating catecholamines.42 Whatever the basis for this increase, most of which is probably furnished from the adrenal medulla, there are numerous major electrophysiologic effects. The positive chronotropic influence on the sinus node may be advantageous, working to prevent abnormal slowing. However, this same positive chronotropic effect enhances the automaticity of ectopic centers and may facilitate the development of reentrant rhythms. If the catecholamine level is sufficient to raise blood pressure acutely, certain reflex responses further influence cardiac rhythm and conduction. Although catecholamines serve to illustrate the potential effect of humoral factors on electrical stability, there are a number of less well-understood but equally potent vasoactive substances such as serotonin, bradykinin, angiotensin, and prostaglandin, the possible importance of which has been inadequately considered in the pathogenesis of sudden death related to myocardial infarction. Along with a consideration of various naturally occurring substances, including the recent interest in fatty acids,41 42 it should be kept in mind that many patients with ischemic heart disease receive a variety of drugs having electrophysiologic actions on their hearts, and this is particularly the case in those patients with some chronic disturbance of rhythm or conduction. These patients in turn are ones who are prime candidates for sudden death.
The final set of unstabilizing factors to consider are those dealing with the neural control of the heart. Partial denervation of the heart in patients with coronary disease may be the consequence of focal disease or of pharmacologic therapy. If ischemic fibrosis more particularly involves nerve endings in the region of the sinus node than in the A-V junction, one consequence may be a selectively greater neural influence in the latter area. Such influence may be either excitatory or depressant. Certain drugs interfere with autonomic control, and the vagolytic action of quinidine is a familiar example; more recently drugs which block the adrenergic beta-receptors or interfere with nerve transmission at the effector cell are coming into wide use, particularly in patients with ischemic heart disease. If the blood supply to the heart is focally reduced, as is characteristic in patients with coronary disease, then it may be assumed that the delivery of drugs to the heart will be uneven, at least in the early stages of therapeutic administration. Here, too, there may be an uneven denervating effect, in addition to an uneven direct chronotropic or dromotropic action.

Clinical Considerations. There is no cookbook recipe to prevent sudden death and it is illogical to expect that there will be. If death is by definition sudden, then the therapeutic possibilities are limited. Where there is a clear basis for optimism is in the better understanding of those fundamental mechanisms dealing with maintenance of electrical stability of the heart, and as a logical consequence a better appreciation of how lethal instability develops. It is for that purpose that the entire preceding presentation has been made, written primarily for clinical cardiologists. A full appreciation of mechanisms of normal and abnormal function serves two clinically valuable purposes: (1) It provides the soundest basis for choice of drugs and for the use of monitoring devices and electronic pacemakers at the present time. (2) It also provides the only logical basis for choosing wisely the new drugs and procedures of the future. Furthermore, it is only by the fullest understanding of the current concepts of such mechanisms that we can hope to grasp the new versions of such mechanisms which are sure to come in the future.

At a time when the significance of where a myocardial infarct is located, or of precisely what an occluded coronary artery was perfusing, is assuming great clinical importance, it is rather sad to note that most of the “new” curricula in medical schools are giving anatomy short shrift. There may be something to the concept that practical anatomy can be taught in the clinical years, but such thinking necessarily assumes that we know today what may be of practical years tomorrow. Relative to the present subject of sudden death and myocardial infarction, it is at the very least essential to know where the sinus node, A-V node, and His bundle are located in the heart, which arteries normally perfuse them, and how coronary occlusion producing this or that site of ventricular infarction may be anticipated to have certain electrophysiologic consequences. For too long the development of electrical instability has been vaguely attributed to the ventricular infarction, and indeed this is an important aspect, but one has so much more useful a basis for clinical analysis if one considers additionally whether critically important components of the cardiac conduction system were also involved or spared. This is a far simpler matter than usually assumed, if only fundamental anatomic facts are kept in mind.

Riches sometimes are embarrassing, and the modern coronary care unit may be considered in this context. While there is little doubt that we have learned much about the acute phase of myocardial infarction from such units, and perhaps dealt with associated problems (such as death due primarily to ventricular arrhythmias) more effectively, there is some uncertainty as to how much inroad has been made in overall mortality and morbidity. Figures from different institutions claim varied degrees of success, but along with the possibility of such success there has developed one widely prevalent misconception, and that is that all the problems due to arrhythmias have
been solved. On careful thought, almost no experienced cardiologist would claim that much has been done to reduce the number of arrhythmic deaths outside the hospital (a group embodying most of the population of sudden deaths). It may even be questioned how effectively the several problems of electrical instability have actually been solved on the very best coronary care units. It is misleading, for example, to think that arrhythmias and conduction disturbances do not play a vital role in the pathogenesis of most examples of cardiogenic shock. Why such electrical instability occurred and what might be done more successfully to treat or prevent it are questions which can only be dealt with intelligently after the problem is admitted to exist.

Perhaps the most important clinical point to emphasize in this whole subject is the fact that virtually all aspects of electrical instability of the heart are amenable to therapy. The neurogenic component, any form of bradycardia, the accurate anticipation of particular electrical disturbances in relation to certain specific sites of infarction—all these and related factors discussed in this review are susceptible to effective therapy, some of it of a preventive nature. When we are faced with exceedingly difficult clinical responsibilities such as cardiogenic shock and sudden death, is it not most logical to focus particularly on an improved understanding of those factors of pathogenesis which are most susceptible to modification?

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THOMAS N. JAMES

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