THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN SUDDEN CORONARY DEATH *

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INTRODUCTION

The question of the role of the autonomic nervous system in sudden death is of paramount importance because, if fully elucidated, it may give critical insights into the basic mechanisms that lead to ventricular fibrillation and may provide the rationale for prevention.

This article does not intend to review the entire question of the relationship between the autonomic nervous system and sudden coronary death since this subject or part of it has been largely dealt with in recent reviews;[1-5] rather, it aims at providing updated information on recent progress in this area with particular reference to the role of cardiac sympathetic nerves and to the development of appropriate animal models specifically designed for the study of neurally mediated life-threatening arrhythmias.

The cardiovascular effects of autonomic nerves are often studied by using the technique of electrical stimulation, which, although valuable in identifying neural circuits, is limited because it shows the artificial effect of massive activation of all nerve fibers present in the stimulated nerves, a very unlikely event in a system characterized by an extreme degree of specificity.[6] We believe that the importance of the autonomic nervous system in relationship to pathophysiologic events which occur in real life situations, such as sudden coronary death, can be best studied by the use of selective denervation. In this way the resultant effects are due to the absence of the tonic sympathetic or vagal activity physiologically present in the nerves under investigation and it is possible to meaningfully compare what happens when the nerves are present and when they are absent.

An attempt to understand the role of the autonomic nervous system in sudden coronary death requires a knowledge of the neural events associated with acute myocardial ischemia, of the effects of neural activity on coronary blood flow, and of the autonomic effects on cardiac electrical stability in ischemic and nonischemic hearts. It requires also the potential of developing relevant animal models in which adequate manipulations of the autonomic

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nervous system can be performed in order to acquire new information, to test hypotheses, and to develop strategies for prevention.

Neural Events Associated with Acute Myocardial Ischemia

Myocardial ischemia excites both vagal[7, 8] and sympathetic afferent fibers of cardiac origin eliciting a variety of reflex responses. For an extensive analysis of this problem the interested reader is referred to the recent reviews by Brown[9] and by Bishop, Malliani, and Thoren.[10] Here, only those basic aspects potentially more relevant to the problem of sudden coronary death will be briefly reviewed; for this reason the sympathetic component will be discussed in greater detail.

The cardiac sympathetic sensory endings[11, 12] are mechanoreceptors normally excited by mechanical events, but their activity can be further enhanced by chemical substances, like bradykinin,[13] which are known to be released in the ischemic heart. This activation elicits an excitatory cardiocardiac reflex[14] (Fig. 1). This reflex, which takes place within a few seconds of ischemia, plays an important role in the genesis of the early ventricular arrhythmias as shown by the fact that the interruption of its afferent limb by a section of dorsal roots from the eight cervical segment to the fifth thoracic segment is capable of reducing to a major extent the arrhythmias associated with short-lasting coronary occlusion[15] (Fig. 2).

The excitation of cardiac sympathetic afferents not only leads to an increase in efferent cardiac sympathetic activity, but can also reflexly and selectively inhibit the activity of efferent cardiac vagal fibers[16] (Fig. 3). This sympathovagal reflex has the potential of impairing the vagally-mediated maintenance of an optimal heart rate,[17] thus facilitating the occurrence of a dangerous tachycardia.

It is noteworthy that the afferent limbs of most cardiocardiac sympathetic reflexes seem to be preferentially distributed through left-sided nerves, which makes these reflexes dependent to a major extent on an intact left stellate ganglion.

The effects of sympathetic discharges relevant to sudden coronary death are mostly those affecting the electrophysiologic properties of the heart, the coronary circulation, and the level of heart rate.

The observation that in the majority of patients seen within 30 minutes after the onset of acute myocardial infarction there were signs of "autonomic disturbance," namely signs of sympathetic hyperactivity mostly in patients with anterior infarction and signs of vagal hyperactivity mostly in patients with inferior infarction, not only represented a major contribution,[18, 19] but also provided a necessary link between experimental studies and clinical reality.

The relationship between acute myocardial ischemia and sympathetic reflexes has just been discussed. Also vagal reflexes have been observed experimentally after myocardial ischemia, particularly of the posterior wall of the left ventricle.[8, 20, 21]

The role of vagal reflexes during acute myocardial ischemia is still controversial,[3, 15, 22] and both protective and detrimental effects have been claimed. Verrier and Lown have provided ample evidence that the protective result of increased vagal activity is mostly due to an indirect effect obtained by opposing the arrhythmogenic influence of adrenergic activity.[23] In uncontrolled situa-

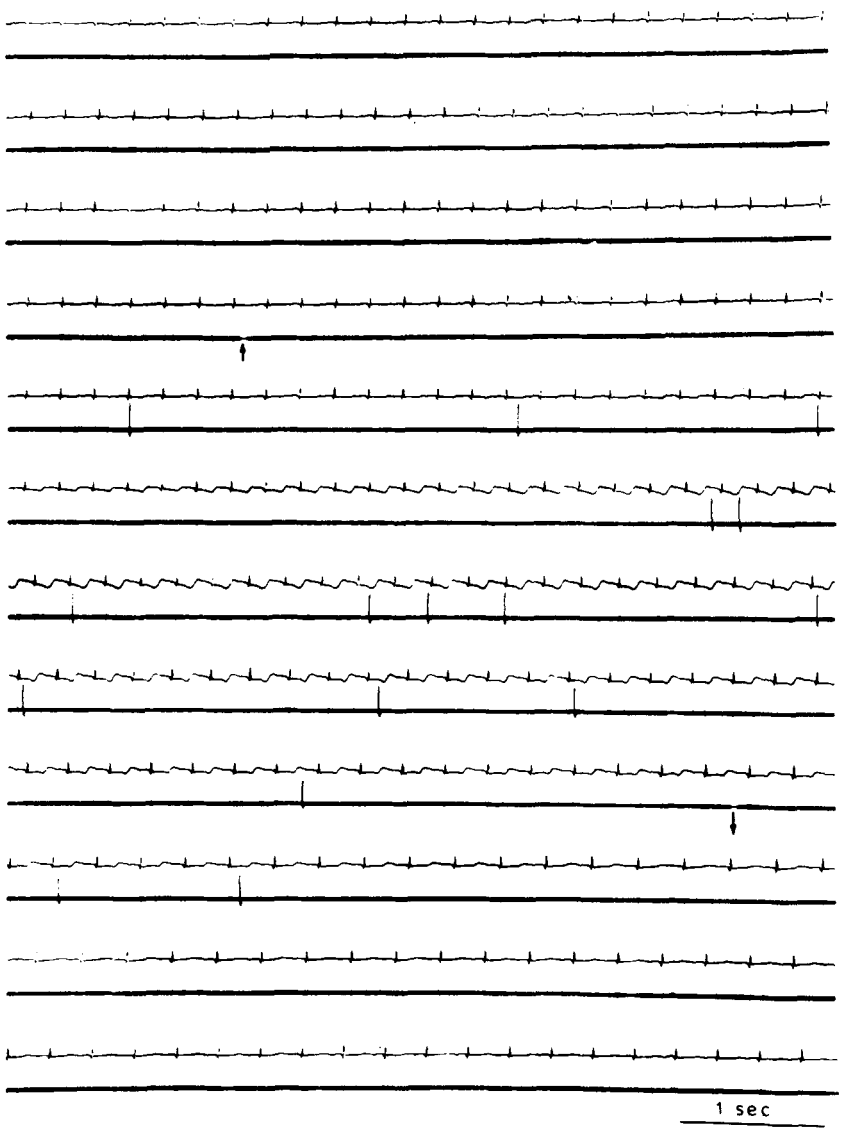

FIGURE 1. Continuous recording of electrocardiogram (*upper trace*) and of sympathetic activity (*lower trace*) in an anesthetized cat. Sympathetic activity was recorded from the left third thoracic ramus communicans (T3) and the Figure shows a single preganglionic sympathetic fiber, spontaneously silent, excited by coronary arterial occlusion. The two *arrows* indicate beginning and end of occlusion. (From Malliani *et al.*[14] Reproduced by permission.)

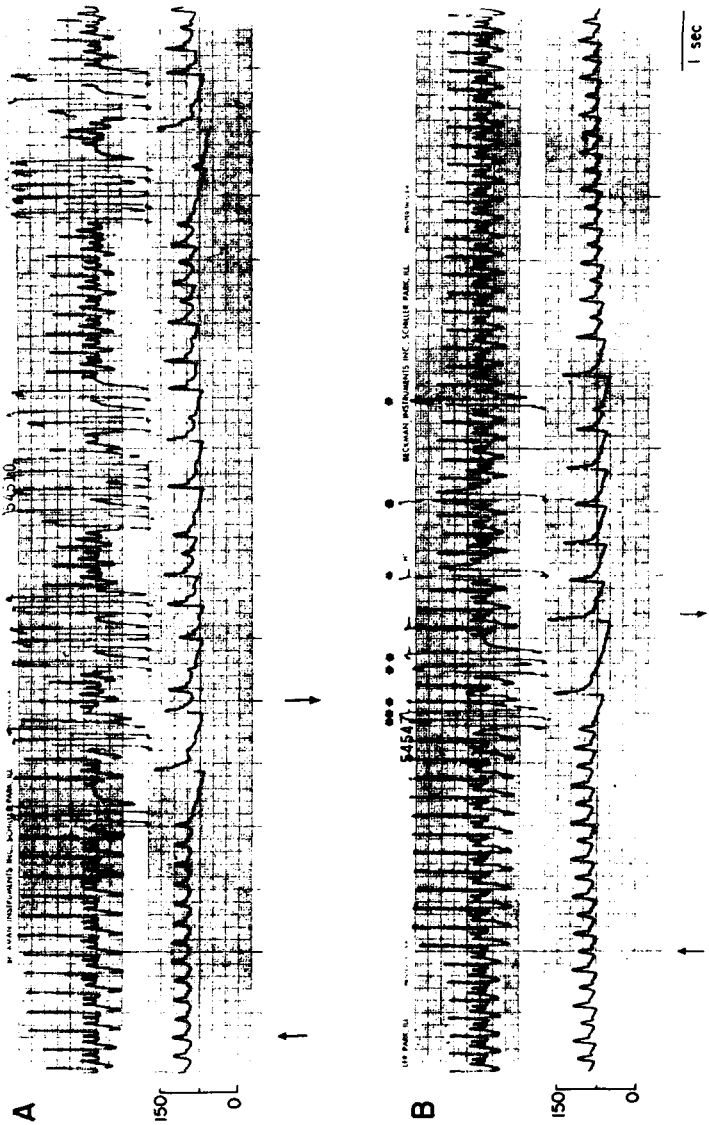

FIGURE 2. Electrocardiogram (*upper trace*) and aortic blood pressure (mm Hg) (*lower trace*) in a vagotomized dog. *Arrows* indicate a 5-sec occlusion of the left descending coronary artery. **(A)** Coronary arterial occlusion during control conditions produces a large number of premature ventricular beats (marked by asterisks), which result in runs of ventricular tachycardia. **(B)** same occlusion after dorsal root section produces only a few ectopic beats. (From Schwartz *et al.*[15] Reproduced by pemission.)

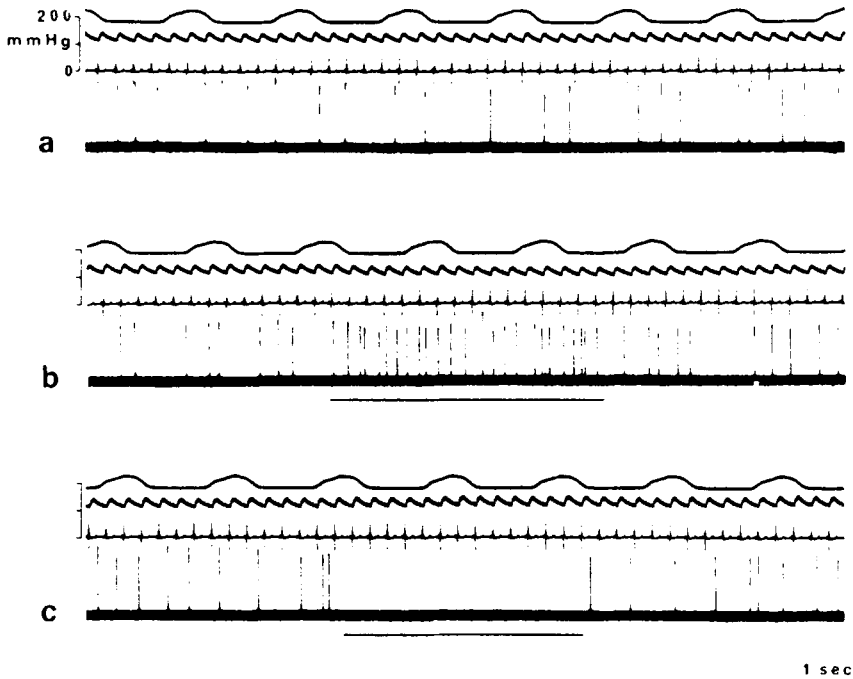

FIGURE 3. Effects of electrical stimulation on the neural discharge of a single right efferent cardiac vagal fiber in a decerebrate, anesthetized cat. **(a)** Spontaneous activity. **(b)** Electrical stimulation (5 volts, 1.5 msec, 30 Hz) of the cut central end of the left cervical vagus (afferent stimulation). **(c)** Electrical stimulation (10 volts, 1.5 msec, 30 Hz) of the cut central end of the left inferior cardiac nerve. The tracings in each section show from *top to bottom:* respiration (positive-pressure inflation is an upward deflection), systemic arterial blood pressure, electrocardiogram, and neural activity. The figure shows that while afferent vagal stimulation reflexly increases efferent cardiac vagal activity, activation of cardiac sympathetic afferent fibers has the opposite effect. (From Schwartz *et al.*[16] Reproduced by permission.)

tions, a major determinant of the effects of vagal reflexes is represented by the attendant changes in heart rate, which makes it difficult to interpret correctly those studies in which the change, or lack of change, in heart rate is not accounted for. As an example, the suppression induced by phenylephrine of ventricular arrhythmias has been initially interpreted[24] as due to the reflex increase in vagal activity, while a subsequent study[25] which in addition employed atrial pacing has shown that the antiarrhythmic effect of phenylephrine is mostly due to the attendant slowing in heart rate.

Some enhancement in vagal tone is beneficial inasmuch as it prevents excessive increases in heart rate, thus preserving underperfused tissue from impending ischemia. However, when the increase in vagal activity is excessive, it may produce hypotension and further reduce coronary flow to the ischemic areas, eventually resulting in either asystole or in ventricular fibrillation, as it can be observed in experimental animals.[26] Why such an overwhelming vagal activity may occur is still unclear. The critical factor may be the existing

level of sympathetic activity. If sympathetic activity is high enough, the vagal reflex may prevent unduly high heart rates without the detrimental effects that may occur if the increased vagal activity is left completely unopposed. The balance between sympathetic and vagal efferent activity may be a key to survival during acute myocardial ischemia.

Neural Control of Coronary Blood Flow

It has been generally accepted that the major factor controlling coronary blood flow is the metabolic demand of the myocardial tissue[27] and the ability of the coronary vessels to autoregulate to meet these demands. The ability of the sympathetic nervous system to cause coronary vasoconstriction was reported by Feigl[28] in 1967, and subsequently coronary vasoconstriction was reflexly elicited through carotid sinus activation.[29, 30] The reflex activation of coronary vasoconstriction, dependent upon the sympathetic nervous system, was shown to be blocked by alpha-adrenergic antagonists and enhanced by beta-adrenergic antagonists. The relationship between the metabolic and neurogenic components of the control of coronary blood flow to the left ventricle was examined specifically and a sympathetic vasoconstriction could be demonstrated when the metabolic demand of the myocardium was elevated in the anesthetized dog.[31] However, the importance and the extent of this mechanism in physiologic conditions in the nonanesthetized animal remained elusive.

Subsequently, in the conscious dog, using the coronary flow response to 10-second occlusions, we found that removal of the left stellate ganglion would increase the reactive hyperemic payback[32] and this result could be mimicked by alpha-adrenergic blockade (Fig. 4). This study clearly showed, for the first time, that a tonic vasoconstrictor tone was present on the coronary vessels and

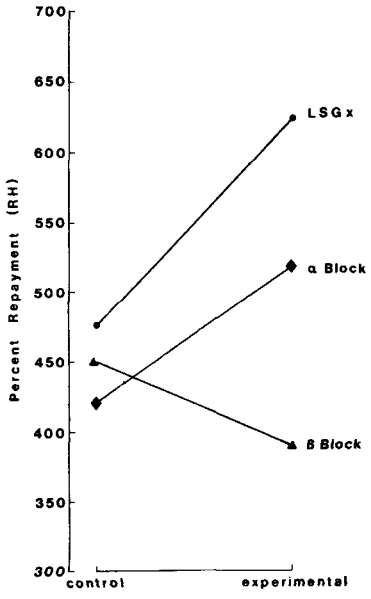

Figure 4. Reactive hyperemia in conscious dogs before and after left stellectomy (LSGx), phentolamine (α-block), and propranolol (β-block). The data points represent the means of 130 trials in 16 dogs. They indicate that left stellectomy and alpha-adrenergic blockade increase reactive hyperemia, a variable that relates to the capability of the coronary bed to dilate, whereas beta-adrenergic blockade has an opposite effect. The same kind of responses were found when heart rate was kept constant by pacing. (After Schwartz and Stone.[32])

that at least brief periods of ischemia were not sufficient to cause a withdrawal of the vasoconstrictor tone despite a significant metabolic alteration as a result of the occlusion. Removal of the left stellate ganglion eliminates the adrenergic fibers that travel down the major left coronary arteries [33] and would be expected to interrupt the tonic vasoconstrictor tone and improve coronary blood flow.

In a further attempt to characterize the role of the sympathetic nervous system in controlling coronary flow in physiologic and clinically relevant conditions, we examined the effect of left stellectomy during submaximal exercise. Left stellate ganglion removal increased coronary flow during exercise and indicated that a tonic sympathetic vasoconstrictor tone can limit coronary blood flow even during the physiologic stress of exercise.[34] Coronary blood flow during submaximal [35, 36] and maximal [37] exercise could also be increased by alpha-adrenergic blockade independent of changes in myocardial oxygen consumption.

It has been recently shown that cyclical changes in coronary blood flow resulting from spontaneous disaggregation of aggregate platelets, at the site of coronary arterial stenosis, were abolished by stellectomy and were enhanced by stimulation of the stellate ganglion.[38] These results probably depend on a catecholamine-mediated fluctuation in platelet aggregability, potentially a phenomenon of high clinical relevance.

In human subjects, Mudge *et al.*[39] measured the reflex coronary vasoconstriction as a result of a cold pressor test and suggested that the vasoconstriction may contribute to the manifestation of ischemic heart disease. If myocardial ischemia or reduced blood flow resulting in tissue hypoxia causes an increase in coronary flow through a purely metabolic mechanism, then coronary stenosis would be expected to result in coronary vasodilation and withdrawal of the tonic vasoconstrictor tone. Recent evidence would suggest that this does not occur and that the ability to constrict the coronary vessels still exists.[40]

A reflex reduction in coronary blood flow can occur, as evidenced by the foregoing discussion, despite an increase in the metabolic demand of the tissue. During myocardial ischemia and with the activation of cardiocardiac sympathetic reflexes, a reduction in coronary blood flow to the marginally ischemic tissue can occur and may be a major factor in the concomitant arrhythmias. The marginally ischemic zone would receive coronary flow from adjacent coronary vessels and from collateral coronary vessels. It appears that the sympathetic nervous system can exert control not only on these adjacent coronary vessels, but also over some of the collateral vessels,[41, 42] which would further increase the extent of ischemia and exacerbate the potential for arrhythmias. This may also explain why infarct size is significantly reduced by left stellectomy.[43]

Autonomic Nervous System and Life-Threatening Arrhythmias

Vagal efferent activity has, in most instances, a protective effect and antiadrenergic interventions, including bilateral stellectomy, also decreases vulnerability to ventricular fibrillation. These topics have been recently discussed in detail.[1-5, 26] This section will only deal with the recent evidence of the effects on arrhythmias of an imbalance in cardiac sympathetic innervation.

Since the pioneering work by Hunt in 1899,[44] many investigators have shown differential effects of right and left cardiac sympathetic nerves on various

aspects of cardiac performance, such as heart rate, ventricular contractility, and ventricular repolarization. In regard to cardiac arrhythmias, the assumption had been made that, since bilateral stellectomy and beta-adrenergic blockade have an antiarrhythmic effect, to remove one part of the sympathetic innervation would at most confer partial protection. Actually, the situation is quite different and while unilateral left stellectomy has indeed a major protective effect, right stellectomy is attended by a paradoxical arrhythmogenic effect.

Our first investigations in this area were the result of our interest in a congenital disease, the idiopathic long Q-T syndrome, which is associated with a high incidence of sudden death and which seems to depend upon a specific imbalance in cardiac sympathetic innervation, namely a lower-than-normal right cardiac sympathetic activity which reflexly results in a higher-than-normal left cardiac sympathetic activity.[45-47]

The first model to be explored was that of coronary arterial occlusion in the dog because it has been studied widely and because it has been clearly shown by many, including Harris in his careful study,[48] that bilateral stellectomy prevents the arrhythmias elicited in that setting. By using a reversible cold blockade, we were able to compare in the same animal the responses to a brief coronary occlusion in control conditions and during functional absence of either right or left stellate ganglion.[49] We found that left stellate ganglion blockade had a protective effect, but that the incidence of arrhythmias was actually augmented by right stellate ganglion blockade. This finding was completely unexpected on the basis of the current knowledge, but has subsequently been confirmed in a variety of different experimental preparations. The next logical step was to investigate whether or not these effects of unilateral stellectomy were present also in nonischemic hearts, and the first study involved examination of ventricular vulnerability to fibrillation. We found that left stellectomy produced a major increase in ventricular fibrillation threshold, while right stellectomy had the opposite effect.[50] The clinical implications of the possibility of decreasing vulnerability to ventricular fibrillation by left stellectomy have been recently discussed.[26] Although these experiments confirmed the opposite effects of right and left stellectomy, they did not illuminate the causes of these differences. Progress was made when, in a study aimed at ascertaining the tonic sympathetic influence on ventricular refractoriness,[51] it was observed that the paradoxical effect of right stellectomy was dependent upon an intact left stellate ganglion. A reflex activation of the quantitatively dominant left stellate ganglion, induced by right stellectomy, is the most likely explanation, as has been discussed elsewhere.[34]

All these experiments had the limitation of having been performed in open chest animals. The effect of unilateral stellectomy was therefore approached in a more physiologic condition, that is, observing the effect of chronic unilateral denervation on arrhythmias induced by exercise.[34] This study was performed in chronically instrumented dogs, and exercise-induced ventricular arrhythmias were found in 8% of the control animals, in 11% of the dogs with left stellectomy, and in 86% of the dogs with right stellectomy. This observation seemed decisive for the acceptance of these strikingly different effects of unilateral stellectomy, but another question had to be answered: are these effects present also in man? In order to reply adequately, in 75 patients stellectomized as a treatment for the Raynaud syndrome (all without cardiac involvement), the incidence of arrhythmias induced by an exercise stress test was compared with that in 25 healthy subjects. The incidence of ventricular arrhythmias was

3% in the control subjects, 5% in the group with left stellectomy, and 21% in the group with right stellectomy.[52] It has to be noted that stellectomy in man produces only a partial denervation, which is at variance with the case in most experimental animals; therefore, our results have actually underestimated the effects of unilateral sympathetic denervation. To achieve in man results similar to those obtained in animals, it is necessary to perform a high thoracic sympathectomy, removing the first four to five thoracic ganglia.[5]

The arrhythmogenic effect of right stellectomy was also found in cats presented with emotional stimuli;[53] under these circumstances both left stellectomy and propranolol had a protective effect. The latter point is of interest because three studies involving stressful stimuli and cardiac arrhythmias yielded somewhat conflicting results about the effectiveness of beta-adrenergic blockade. In these studies different kinds of stressful stimulation were employed (cats wildly attacked by another cat,[53] pigs subjected to coronary occlusion in an unfamiliar environment,[54] dogs shifted from a quiet to a stressful environment,[55] and dogs stressed acoustically with a gun shot [56]); thus, the possibility should not be completely discounted that qualitatively and/or quantitatively different autonomic responses might be elicited under these different circumstances.

Finally, the studies mentioned in this section have demonstrated another aspect of the autonomic nervous system, previously not fully appreciated and quite relevant to the problem of sudden coronary death, namely the major arrhythmogenic potential of left-sided cardiac sympathetic nerves. This concept has already been substantiated by several different investigators [57-61] and is now generally accepted. Examples of ventricular tachyarrhythmias induced by stimulation of left stellate ganglion are represented in FIGURES 5 and 6. Of particular interest is FIGURE 6, which shows ventricular premature beats elicited by just touching with a blunt instrument the left stellate ganglion of a patient who suffered an anterior myocardial infarction 50 days earlier. This observation was made just prior to performing a high thoracic left sympathectomy; the patient is participating in a multicenter clinical trial in which survivors of an anterior myocardial infarction complicated by ventricular fibrillation are randomly assigned treatment with either placebo, beta-adrenergic blockade with propranolol, or high thoracic left sympathectomy.

ANIMAL MODELS FOR SUDDEN CORONARY DEATH

The choice of an appropriate model for sudden coronary death is critical for an attempt to understand the mechanisms involved and for a meaningful assessment of antiarrhythmic interventions. Too often, drugs are claimed to have a major antiarrhythmic effect on the basis of results obtained in conditions far different from those relevant to the clinical problem. The question of animal models for sudden death has been widely discussed.[26, 62, 63]

Two models currently in use in our laboratories will be presented here. They have different objectives and different characteristics. The first aims at providing the opportunity for a preliminary but specific evaluation of antiarrhythmic drugs with an internal control preparation that avoids group comparisons and deals specifically with acute myocardial ischemia and sympathetic hyperactivity. The second is designed in such a way to allow an in-depth analysis of the role of the autonomic nervous system in sudden coronary death taking

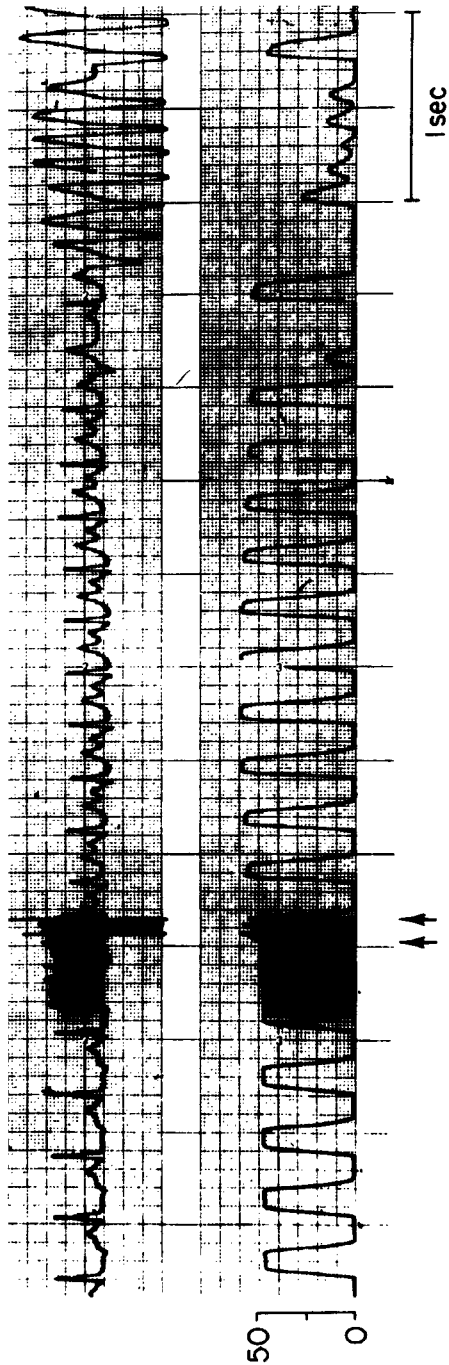

FIGURE 5. Electrocardiographic (*top*) and left ventricular pressure tracings (*bottom*) in an anesthetized dog. The *arrows* indicate the electrical stimulation of the left stellate ganglion, which results in an episode of ventricular tachycardia. After stimulation, the T wave becomes positive and the Q-T interval lengthens. (From Schwartz.[67] Reproduced by permission.)

into account also the association with stress, and a final evaluation, prior to a clinical trial, of an antiarrhythmic intervention already tested in simpler conditions.

The first model involves anesthetized cats in which the left anterior descending coronary artery is occluded for 2 minutes while the left stellate ganglion is electrically stimulated for 30 seconds, starting 1 minute after the beginning of occlusion (FIG. 7). The timing of the two stimuli is such that it is possible to discriminate between arrhythmias induced by ischemia, by ischemia plus sympathetic stimulation, and by reperfusion. In about 65% of experiments the same degree of arrhythmias may be elicited for six to seven consecutive trials; this reproducibility is always evident within the first three trials. If the results are

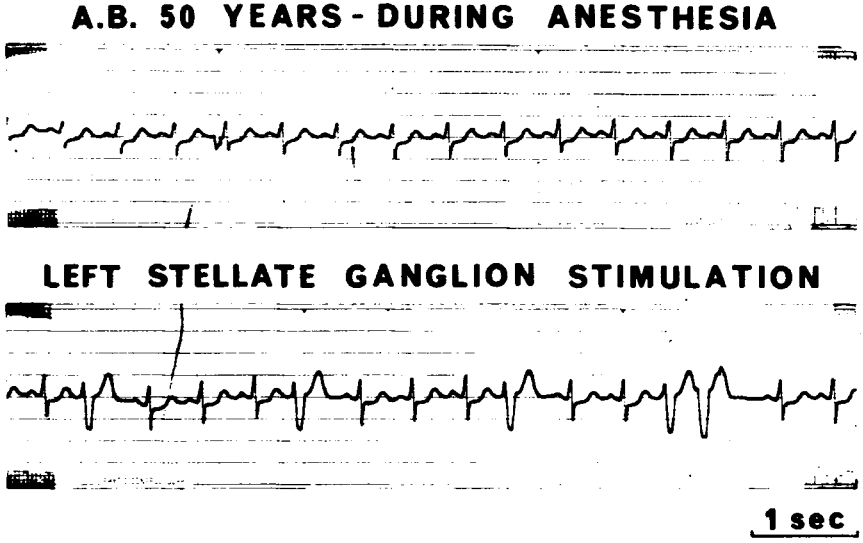

FIGURE 6. Electrocardiographic tracing in an anesthetized man 50 days after occurrence of an anterior myocardial infarction complicated by ventricular fibrillation. The patient was in sinus rhythm until the left stellate ganglion was mechanically stimulated, leading to frequent premature ventricular beats and couplets. Details are given in the text.

consistent they will be reproducibly elicited in the next three to four trials. This allows internal control analysis because if a consistent arrhythmic response is elicited for three consecutive trials, the drug under study may be administered and three additional trials may be repeated. In approximately 45 to 50% of animals, ventricular fibrillation is constantly produced; in the remaining animals, frequent premature ventricular beats or ventricular tachycardia is the usual response. It has to be stressed that once an animal, during the first three trials, responds with a given type of arrhythmia, this response will remain constant throughout the experiment. Preliminary data indicate a major protective effect induced by either verapamil [61] or by creatinine phosphate, while lidocaine and mexiletine do not seem to provide sufficient protection. A likely reason for the reproducibility of life-threatening arrhythmias in this model is the fact that these

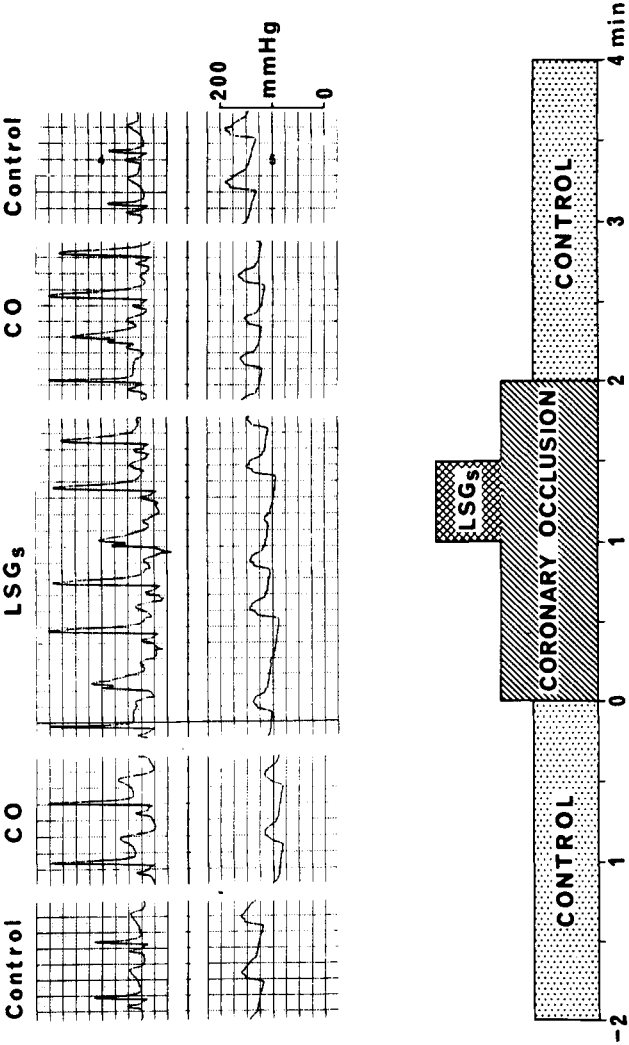

FIGURE 7. Diagram of experimental model with an example of electrocardiographic and blood pressure changes. The *second panel* shows the changes occurring after 1 minute of coronary occlusion (CO) just prior to sympathetic stimulation: blood pressure is lower and classic ischemic changes are obvious. In the *third panel*, electrical stimulation of the left stellate ganglion (LSGs) induced the occurrence of premature ventricular beats and a slight increase in blood pressure; stimulation artifacts are visible in the electrocardiographic tracing. In the *fourth panel*, after cessation of sympathetic stimulation while coronary occlusion is still maintained ventricular premature beats are still present. In the *fifth panel*, a few seconds after release of occlusion both the electrocardiogram and pressure have returned to normal. (From Schwartz and Vanoli.[83] Reproduced by permission.)

ventricular tachyarrhythmias are specifically dependent on the interaction between acute myocardial ischemia and sudden increases in cardiac sympathetic activity. This model seems particularly well suited for the preliminary evaluation, before the study in conscious animals, of drugs potentially protective against the malignant arrhythmias associated with acute myocardial ischemia.

The second animal model involves the interaction of a few clinically relevant factors in conscious animals. Briefly, dogs undergo implantation for chronic measurement of various hemodynamic variables and balloon occluders are placed around the left descending and left circumflex coronary arteries. The dogs are subjected to submaximal exercise on a motor-driven treadmill for 18 minutes. At the 17th minute a balloon occluder is inflated for 2 minutes and acute myocardial ischemia is produced (FIG. 8). Thus, this short-lasting ischemic episode affects the last minute of exercise and the first minute after exercise, and this sequence of events allows separation between arrhythmias dependent on cessation of exercise or on release of occlusion. This protocol begins 3 weeks after initial surgery and is repeated after production of an anterior or inferior myocardial infarction.[65] Grossly, this model resembles what may happen to a patient with a prior myocardial infarction who engages in physical activity and has a brief reduction in coronary flow (spasm?) leading to acute myocardial ischemia, cardiac pain, and arrest of exercise.

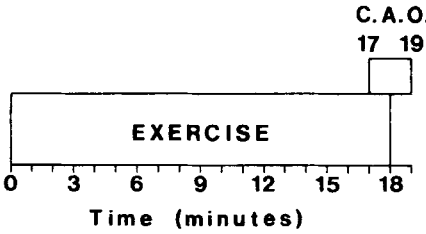

FIGURE 8. Experimental protocol. At the 17th minute of an exercise stress test performed on a treadmill, a balloon occluder previously positioned around one coronary artery is inflated to produce acute myocardial ischemia. Exercise stops after 1 minute of ischemia, which is maintained for an additional minute.

A critical point is represented by the fact that such a brief myocardial ischemia does not induce ventricular arrhythmias at rest; however, when it is coupled with exercise, it results in a high incidence of life-threatening arrhythmias, which are particularly frequent immediately after cessation of exercise. This represents a step forward in comparison with our previous study,[26] in which conscious dogs with a prior myocardial infarction were subjected, while resting, to a 10-minute coronary arterial occlusion, which certainly affected left ventricular function. In this new model, the ventricular tachyarrhythmias depend on the interaction between acute myocardial ischemia, level of heart rate, exercise and its cessation, and vagal and sympathetic reflexes.

Using this protocol, ventricular tachyarrhythmias occurred in 8 of 15 control dogs (53%), culminating in ventricular fibrillation in 6 (40%) (FIG. 9). Ten dogs were studied 3 weeks after production of an anterior myocardial infarction and in this group the incidence of ventricular arrhythmias and of ventricular fibrillation was higher (70% and 60%, respectively). It is noteworthy that most instances of ventricular fibrillation occurred immediately after cessation of exercise. The underlying mechanism for this still unexplained specific temporal relationship is under investigation; in any case, it bears a striking similarity with what happens in most sudden deaths in athletes. Do autonomic interven-

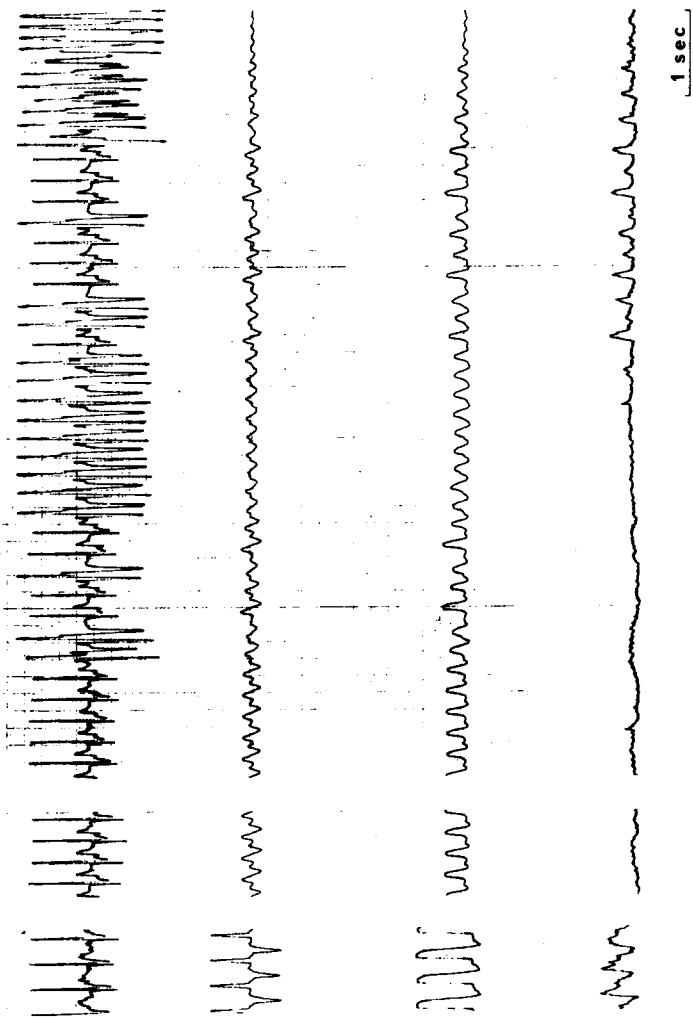

FIGURE 9. Tracings from *top to bottom* are: electrocardiogram, left ventricular dP/dt max, left ventricular pressure, and circumflex coronary flow. **(a)** After 17 minutes of exercise; **(b)** after 1 minute of occlusion of the left anterior descending coronary artery, as treadmill has stopped; **(c)** 15 seconds later onset of ventricular tachycardia that degenerates into ventricular fibrillation. The large decrease in blood pressure within 1 minute of coronary arterial occlusion is an uncommon event in this model.

tions affect the susceptibility to ventricular fibrillation in this setting? Preliminary data suggest an affirmative answer, because in 8 dogs with an anterior myocardial infarction that were studied after left stellectomy, ventricular arrhythmias occurred in only two cases (25%) and ventricular fibrillation in none, despite the fact that heart rate was even higher compared with that of control animals.

The possibility of studying these dogs before they would actually be exposed to a high-risk situation has prompted us to search for possible clues for the identification of subgroups of dogs at higher risk of dying suddenly during the exercise plus ischemia trial. Since autonomic reflexes clearly play a major role in that setting and since some of our preliminary observations in the first group of dogs suggested that vagal reflexes may be protective, we have decided to evaluate in nine dogs with an anterior myocardial infarction the propensity for vagal or sympathetic responses. This was achieved by baroreceptive testing.[66] Blood pressure was increased or lowered by using intravenous infusions of phenylephrine and nitroprusside while heart rate changes were recorded together with changes in aortic blood pressure. The relationship between R-R intervals and the different levels of blood pressure was expressed by a linear regression line, the slope of which would allow distinction between "hypervagal" and "hypersympathetic" responses. Nine animals with prior anterior myocardial infarction were studied: four dogs did not show arrhythmias during the exercise plus ischemia test, while four of the remaining five had ventricular fibrillation and one had ventricular tachycardia. The baroreflex slope was compared between these two groups and was found to be significantly higher (9.3 ± 2.2 versus 4.3 ± 1.6 msec/mm Hg) in the group that showed no arrhythmias. The difference was mostly due to a greater reduction in heart rate in response to phenylephrine; this indicates that the dogs that survived had a greater tendency for powerful vagal reflexes. This finding strongly suggests a protective effect of vagal reflexes when conscious animals undergo an episode of acute myocardial ischemia. If these data are confirmed in a larger series of animals, this finding may have important clinical implications. Baroreceptor testing is a safe, noninvasive procedure that may be performed in patients with a recent myocardial infarction before discharge from the hospital. A prospective study in these patients would reveal whether baroreceptor testing has prognostic implications in man. The early identification of subgroups of patients with ischemic heart disease at higher risk for sudden death remains a critical but still elusive problem. Should the analysis of autonomic responses be found to have significant prognostic value, new and important insights with several therapeutic implications might be gained on the role of the autonomic nervous system in sudden coronary death.

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