**Point of View**

**Toward a New Understanding of the Mechanism and Prevention of Sudden Death in Coronary Heart Disease**

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Sudden death remains an issue of considerable importance in the epidemiology of coronary heart disease despite an overall decrease in its annual mortality. The purpose of this review is to encourage a reexamination of the mechanism and prevention of the events that lead to the lethal electrical disorganization of cardiac contraction. Previous investigation of sudden death has been dominated by paradigms that have limited imaginative research directions and were focused on the suppression of ventricular ectopy. Some of the factors that will be discussed include the importance of ambient ventricular ectopy, myocardial ischemia, and the complex metabolism of the failing left ventricle.

The quest for the mechanism of sudden death long preceded the instruction in the eighteenth century of Pope Clement I to his court physician, Antonio Lancisi, to investigate the rash of sudden deaths that were occurring in Rome at that time. After an exhaustive analysis, Lancisi concluded that a single cause probably could not be identified, because a multitude of disease states were linked to sudden death. Contrary to the conclusions of Lancisi, the era is now ending in which a single cause was long presumed to be the major cause of sudden death—the ventricular premature contraction. The results of the Cardiac Arrhythmia Suppression Trial (CAST) represent a watershed in our thinking in regard to mechanisms and prevention of sudden death and encourage a reassessment of our current attitude in regard to this problem. It had been proposed that the eradication of ventricular ectopy in patients with coronary heart disease could prevent sudden death. The CAST observations suggest that this eradication or suppression of ventricular ectopy at least with two commonly used drugs actually results in an increased mortality rate. Although disappointing in some respects, these observations have provided an opening for the examination of other mechanisms of sudden death in coronary heart disease.

**Definition of Sudden Death**

Investigation into the mechanism of sudden death has required a definition of the event, a definition that has proved elusive. The need for a definition of sudden death is predicated on the hypothesis that there are both arrhythmic and nonarrhythmic mechanisms of cardiac arrest. Therefore, different therapeutic alternatives such as antiarrhythmic or antiischemic drugs should be used for its prevention. In light of current events, such a definition may at least be partially outmoded. Simplistic definitions dependent on events occurring within 1 hour or less have been supplemented by more mechanistically based definitions that depend on the clinical presentation of the event. The attempt to define mechanical and arrhythmic presentation of sudden death has proved difficult, because the occurrence of either event can lead to the other. Because of these difficulties, a definition that includes both time and clinical setting has been proposed. The Cardiac Arrhythmia Pilot Study, using a time- and etiology-based assessment, concluded that sudden death usually equates to arrhythmic death. However, with this approach, approximately 25% of the arrhythmic deaths were associated with myocardial ischemia or infarction. Using the Hinkle-Thaler classification system, Marcus et al observed that 58% of these presumed arrhythmic sudden deaths were preceded by symptoms of myocardial ischemia. It is clear that mechanical dysfunction can occur rapidly, leading to ventricular failure in minutes, just as prolonged periods of seemingly life-threatening arrhythmias, such as ventricular tachycardia, can persist for hours and be manifested by symptoms of left ventricular failure.

**Ventricular Arrhythmia and Antiarrhythmic Therapy**

There is evidence that frequent and complex ventricular ectopy in patients with coronary heart disease is an important predictor of sudden death, particularly in the postinfarction population. Ventricular ectopy occurring in the absence of heart disease,
however, has little or no predictive importance. The specificity of ventricular ectopy for mortality, even in the setting of coronary heart disease, varies greatly relative to the extent of left ventricular function. High frequency ventricular ectopy, greater than 10/hr, occurs in about 10% of patients with preserved ventricular function and is associated with a twofold to threefold increase in mortality. As ejection fraction falls, ventricular ectopy becomes a more common phenomenon. In the setting of advanced ventricular dysfunction, frequent, multiple, and multiform ventricular premature beats occur in almost 50% of the patients and is a poor predictor of total and sudden death. In these disparate settings, the role of suppression of ventricular ectopy is not clear, and a unifying hypothesis is elusive.

The importance of ventricular ectopy as a predictor of both total and sudden death mortality has led to a variety of investigations into the use of antiarrhythmic agents in coronary heart disease. Although limited by relatively small size, none of these investigations, however, demonstrated efficacy. These investigations have taken a number of different forms from the treatment of all patients with ischemic heart disease, regardless of the presence of ventricular ectopy, to the more recent approach of suppression of high-frequency ventricular ectopy in post-myocardial infarction patients. The International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT) study is an example of the former approach and the CAST study of the latter strategy. In the IMPACT study, mexiletine randomly administered to post-infarction patients caused a modest decrease in ventricular ectopy with no effect on mortality and an actual trend toward a higher mortality in the patients without ventricular ectopy. The failure to achieve a benefit was attributed to either the lack of potency of mexiletine or its adverse effect on patients without ectopy. The CAST study, on the other hand, compared encainide, flecainide, and ethmozine with a placebo after ventricular ectopic beat suppression by one of the active agents was demonstrated with Holter recording. The encainide-flecainide arm of the study was prematurely ended because of an approximate threefold increase in mortality in patients assigned to those two drugs despite an 80% suppression of ventricular ectopic beat. In the CAST study, the adverse effect was presumed to be related to proarrhythmic or negative inotropic effect of the drugs. These observations have resulted in a major reassessment of the suppression hypothesis. Although these results can be extrapolated to suppression of ventricular ectopic beats by all antiarrhythmic agents, this conclusion is probably premature.

Numerous studies examined the use of programmed ventricular stimulation techniques to determine drug suppression. These studies have examined patients presumed to be at high risk of sudden death, such as patients who have been resuscitated from a previous cardiac arrest. Suppression of arrhythmia induction with stimulation techniques has been used as evidence of drug efficacy. It has therefore been deemed unethical to withhold that antiarrhythmic drug from the patient once suppression is demonstrated. One randomized placebo control study, however, examined the benefit of class I agents on mortality in postinfarction patients in whom inducible ventricular tachycardia by programmed stimulation was demonstrated. After inducibility had been demonstrated, patients were randomized to receive quinidine, mexiletine, and dypsymamide at doses determined to achieve “therapeutic” serum levels. No benefit was observed in the patients randomized to the active treatment group when compared with the placebo control group.

These observations urge a more imaginative assessment of antiarrhythmic therapy at this time. Most clinical studies have examined the efficacy of antiarrhythmic agents on spontaneous arrhythmias in a relatively stable ischemia-free state. Drugs that suppress arrhythmias in the nonischemic state may become proarrhythmic in the setting of ischemia. The failure of the encainide-flecainide arm of the CAST study may be explained by such a mechanism. The interrelation between ischemia and arrhythmogenesis in humans was reported by Morady and associates during programmed stimulation. They demonstrated that myocardial ischemia evidenced by transmural ischemia-free state was a requirement for electrophysiological induction of ventricular tachycardia in some survivors of cardiac arrest.

Animal models demonstrated that lidocaine and mexiletine, which suppress ventricular ectopy in the ischemia-free state, had little or no antiarrhythmic effect in the setting of ischemia coupled with sympathetic stimulation. On the other hand, propranolol and amiodarone were both very effective in the ischemic and nonischemic setting. Models such as these may provide a different approach to investigating antiarrhythmic therapy. It is possible that pleiotropic drugs like propranolol and amiodarone may have a more important role in arrhythmia therapy.

The importance of arrhythmia control in general, however, is supported by the success of the automatic implantable cardiac defibrillator. Although as yet not investigated with placebo-controlled trials, that device appears to be effective in the prevention of arrhythmia deaths in high-risk patients. It should not be presumed, however, that this supports the premise of arrhythmia suppression in the prevention of sudden death but merely an acceptance that ventricular fibrillation is its major final common pathway. We have been aware for almost three decades of the benefit of early external defibrillation in patients with acute myocardial infarction. It is clear, therefore, that the suppression hypothesis requires more drug- and event-specific information, and it appears that ventricular ectopic beat suppression alone can no longer be viewed as a surrogate for improved survival.
Myocardial Ischemia

Although sudden death is intimately related to ischemic heart disease, the link between ischemia and sudden death has been difficult to document. The observations by Spain and Bradess, and later by Roberts and others suggested that coronary occlusion and infarction were not important factors in sudden death. Our initial investigations of out-of-hospital resuscitated cardiac arrest victims, however, implied a strong role for ischemia and infarction in the pathophysiology of sudden cardiac arrest. This was supported by other studies of resuscitated sudden death victims and patients surviving acute myocardial infarction. It remained for the work of Davies and Thomas to describe the coronary pathology associated with sudden death. Their demonstration of atherosclerotic plaque fissuring, coronary mural thrombi, platelet aggregates, and micro-infarction in patients dying suddenly with acute myocardial infarction established that link. Muller et al. called attention to the potential ability of trigger events, such as circadian rhythmic changes, to precipitate acute ischemic events including acute myocardial infarction and sudden death. They observed that there is an association between those events and the sudden circadian increase in norepinephrine, heart rate, blood pressure, platelet activation, and decreased fibrinolytic activity.

Clinical trials of a number of agents aimed at modulating ischemia and preserving the integrity of coronary blood flow support the ischemia hypothesis. The restoration or improvement of coronary blood flow by coronary bypass surgery was observed to have a special effect on sudden death in the Coronary Artery Surgery Study. The ability of platelet-active agents such as aspirin to decrease sudden death in patients with unstable angina has been reported. Aspirin therapy has also been estimated to reduce the risk of vascular death by 13% and nonfatal reinfarction by 31%. A number of beta-adrenergic blocking agents have been shown to decrease both total and sudden death mortality. Propranolol administered to high-risk post-myocardial infarction patients with a variety of admission arrhythmias including ventricular fibrillation, ventricular tachycardia, and high-frequency ventricular premature beats showed a decrease in sudden death. Muller et al. observed that a salutary effect was observed in patients receiving beta-adrenergic blocking agents on the early morning occurrence of myocardial infarction. These observations were also supported by the effects of propranolol on modifying the occurrence of early morning sudden death in the Beta Blocker Heart Attack Trial. The well-known effect of beta-blockers to limit ischemia has been ascribed to their negative chronotropics and inotropic mechanism. In ischemic animal studies, however, a direct effect of propranolol was observed on mitochondrial salvage and preservation of ATP content. In addition, it has been demonstrated that some beta-blockers can increase the ventricular fibrillation threshold in ischemic animals and decrease the frequency of ventricular ectopy in post-myocardial infarction patients. The specific mechanism by which beta-blockers prevent sudden death, however, remains uncertain, but their efficacy is supported by an expanding volume of basic and clinical investigations.

Ventricular Dysfunction

The mechanisms of sudden death in patients with advanced left ventricular dysfunction and heart failure have a more complex genesis than in those patients dying with acute ischemia or infarctions. The scarred ventricle with its heterogeneity of both depolarization and repolarization is an ideal setting in which ventricular arrhythmias can occur. In addition, the increase in serum catecholamine levels and perhaps other known and yet unknown metabolic substances that occur in heart failure may adversely alter the function and electrical integrity of the heart.

In the setting of ventricular dysfunction, treatment with diuretics with their potential for hypokalemia, and digitalis with its potential for cardiac arrhythmia, may adversely alter the threshold for ventricular fibrillation. Also, subtle degrees of myocardial ischemia may possibly precipitate major arrhythmic events. Because of these possibilities, investigations have considered other forms of therapy, including vasodilators and newer inotropic agents. Although the latter group of agents have not yet emerged as therapeutic alternatives, vasodilators have been effective adjuncts and alternatives to digitalis and diuretics. A previous study with vasodilator therapy with hydralazine and isosorbide dinitrate combination reported a decrease in total mortality, but it did not examine the effect of therapy or sudden death. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial, made up largely of hospitalized patients, the angiotensin converting enzyme inhibitor, enalapril, demonstrated a decrease in total mortality without any significant effect on sudden death. Angiotensin converting enzyme inhibitors, in particular, have been shown to have a salutary effect on ventricular ectopy, norepinephrine, and potassium concentrations in patients with severe heart failure. Animal studies indicate that these drugs can prevent ventricular fibrillation during reperfusion and preserve ventricular function by a direct action on tissue conversion of angiotensin I to angiotensin II.

Beta-adrenergic blocking agents, because they cause down-regulation of myocardial beta-adrenergic receptors in the failing heart, have also been examined in the treatment of heart failure. Initial studies demonstrated that the use of propranolol in high-risk post-myocardial infarction patients characterized by both heart failure and high-frequency arrhythmias resulted in a beneficial effect on sudden cardiac death. A retrospective analysis of the Beta Blocker Heart Attack Trial suggests that in patients with a history of heart failure, propranolol therapy resulted
in a beneficial effect on the incidence of sudden death.

In view of these observations, the uncertainty of the efficacy of antiarrhythmic therapy, and the observed benefits of interventions directed at limiting ischemia and improving ventricular function, we should reconsider the mechanisms and prevention of sudden death without the constraints of previous paradigms. It seems time to examine the interaction between ventricular ectopy, myocardial ischemia and infarction, the failing left ventricle, and sudden cardiac death. Examination of these interrelated disorders may lead to a better understanding of both the maintenance and the degeneration of the heart’s electrical integrity. As we continue to consider the role of antiarrhythmic therapy in sudden death, we must also investigate the importance of ischemia on the action of these agents. Clearly, in the relatively well-preserved left ventricle, ischemia is critical to the development of ventricular fibrillation. In the scarred and uncompensated left ventricle, however, the myocardial substrate for ventricular fibrillation exists, and the role of ischemia is less apparent. Antiarrhythmic agents may have a role in both, but their benefit is yet to be demonstrated. Alternative interventions aimed at modulating the cardiac response to ischemia and the preservation of myocardial metabolic integrity may hold greater promise in the prevention of sudden cardiac death.

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