

## TIPS Reviews

# Sudden coronary death: pharmacological interventions for the prevention of ventricular fibrillation

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*Sudden coronary death in patients with coronary artery disease remains a major medical problem in most industrialized nations and in most instances is associated with the unexpected development of ventricular fibrillation. Despite the development of new anti-arrhythmic drugs, few, if any, are suitable for long-term prophylactic application and none were developed specifically for the prevention of ventricular fibrillation. This article discusses the importance of the preclinical phase of drug development in an attempt to focus on those electrophysiological mechanisms which superimpose upon a vulnerable myocardium thus leading to the onset of lethal arrhythmias. It is against this background that potentially useful pharmacological interventions must be assessed if specific therapy for the prevention of sudden coronary death is to become a reality.*

## What seems to be the concern?

The morbid statistics for the United States alone would suggest that there are 400 000 victims each year who succumb to sudden coronary death. The very suddenness of, and the electrocardiographic observations prior to or accompanying the fatal event, lead to the assumption that cardiac arrhythmias are the cause of death, either ventricular arrest or ventricular fibrillation, with the majority of patients having underlying heart disease. Mobile coronary care units and rapid response emergency systems have been developed as an approach to aiding victims of out-of-hospital ventricular fibrillation and the results of such efforts at resuscitation have demonstrated that many individuals can be returned to a productive life, although the continued presence of their underlying coronary artery disease make them vulnerable to a subsequent event in which lethal arrhythmias may develop suddenly and unexpectedly. There is sufficient clinical evidence to indicate that the majority of episodes of ventricular fibrillation are 'primary' dysrhythmic events and not secondary to acute myocardial infarction.

There is a strong association between certain angiographic and functional abnormalities and the development of ventricular fibrillation and recurrent ventricular fibrillation. In recent years, medical attention has been focused upon identifying patients who are vulnerable to the development of life-threatening arrhythmias. Thus, survivors of myocardial infarction and that identifiable segment of the asymptomatic population with an ominous risk profile are demonstrably at very high risk of sudden death with at least two-thirds of the deaths occurring in the first hour.

If an impact is to be made upon the high mortality due to sudden coronary death, it must depend upon the recognition and treatment of those at risk, with the goal of preventing ventricular fibrillation by a prophylactic therapeutic regimen.

## Present status of pharmacological therapy

A comprehensive review of the pharmacological, electrophysiological and clinical applications of many of the newer, potentially useful, anti-arrhythmic agents has appeared recently<sup>1</sup>. Despite

extensive clinical studies, it is not possible to demonstrate that one or more of the newer agents possesses any promise as being the ideal agent for the prevention of sudden coronary death. Recent studies with amiodarone<sup>2,3</sup>, however, provide reason for optimism in view of the interesting results obtained in patients at high risk of sudden coronary death. Despite its reported efficacy, amiodarone is limited in its widespread and long-term application by the development of undesirable cutaneous, neural, ocular and hormonal side-effects. It may be advantageous to explore potential therapeutic benefits of closely related derivatives of amiodarone in an attempt to achieve similar electrophysiological effects without the toxic effects noted previously.

A number of recent studies have demonstrated that the administration of  $\beta$ -adrenergic receptor blocking agents could reduce the incidence of post-hospital sudden coronary death in patients who had experienced a myocardial infarction. In the  $\beta$ -Blocker Heart Attack Trial (BHAT) supported by the National Institutes of Health, 3 837 patients were randomized to therapy with either 40 mg propranolol or placebo, three times daily, starting at a mean time of 13.8 days from the time of myocardial infarction. After 30 months, the control group had a 9.5% mortality as compared with 7.0% among propranolol-treated patients, thus supporting the concept that mortality in the post-myocardial infarct patient can be reduced with the institution of appropriate therapy. An earlier, Norwegian Multicenter Trial with the  $\beta$ -receptor blocking agent, timolol, demonstrated a potential benefit in reducing the rate of reinfarction and the incidence of sudden death in patients in the post-hospital phase of myocardial infarction.

At present, it is safe to conclude that there is uncertainty regarding the mechanism by which  $\beta$ -adrenergic receptor blocking drugs exert their anti-arrhythmic effects in the ischemically injured heart and whether or not these agents can decrease the incidence of sudden coronary death in all patients at risk of experiencing a lethal arrhythmic event.

The potential implications of these studies are significant in that they indicate that pharmacological interventions can protect the ischemic heart against the sudden onset of ventricular fibrillation, thus allowing more time for

the institution of medical assistance. However, the interruption of adrenergic support to the heart may not be without hazard in those patients who require a degree of cardiac inotropic and chronotropic stimulus during the acute phase of myocardial infarction. Such patients may be subjected to a higher incidence of cardiogenic shock and bradyarrhythmias. Furthermore,  $\beta$ -adrenergic receptor blockade might preclude the successful use of inotropic agents, such as norepinephrine, dopamine, dobutamine, etc. Other limitations to the use of  $\beta$ -adrenergic receptor blocking agents would be in those patients with obstructive airway disease and in those with heart failure.

Those post-myocardial infarction patients who are not considered to be suitable candidates for the administration of  $\beta$ -receptor blocking agents could have other available anti-arrhythmic drugs administered but, unfortunately, they too are limited in their application because of toxicity associated with their long-term use. An important fact to recognize is that, despite their demonstrated efficacy as anti-arrhythmic drugs, currently available agents and many of the newer drugs under clinical investigation have not been shown to be effective in the prevention of sudden coronary death. Furthermore, the effectiveness of a chronically administered drug in protecting the ambulatory patient from sudden coronary death can not be predicted from short-term observations made on hospitalized patients with acute myocardial infarction, since there are no reasons to believe that the electrophysiological disturbances leading to ventricular fibrillation are the same in both situations.

May *et al.*<sup>4</sup> recently reviewed the results of 14 clinical trials involving 3 625 patients with documented myocardial infarction who were treated with one of four anti-arrhythmic drugs: quinidine, procainamide, disopyramide or lidocaine. Despite the fact that each agent has been reported to suppress ventricular arrhythmias in the acute phase of myocardial infarction, and lidocaine may reduce the incidence of in-hospital ventricular fibrillation, not one of the trials has demonstrated that suppression of ventricular premature beats is accompanied by a statistically significant reduction in overall mortality.

#### **Electrophysiological testing procedures for the clinical evaluation of anti-arrhythmic agents**

Electrophysiological abnormalities can

be demonstrated in a large majority of patients who have survived an episode of out-of-hospital cardiac arrest not associated with acute myocardial infarction. Programmed electrical stimulation is capable of eliciting ventricular tachycardias in most of these patients, suggesting the continued presence of an electrically unstable myocardial substrate. On the other hand, electrically inducible ventricular tachycardia is rarely, if ever, observed in patients who do not have structural heart disease, thus illustrating the importance of a vulnerable substrate for the development of a re-entrant tachyarrhythmia.

The provocative testing procedure of programmed electrical stimulation has been applied to the evaluation of drug treatment regimens in patients with recurrent ventricular tachyarrhythmias. The use of an electrophysiological protocol for drug selection is based on several assumptions: (1) the tachycardia produced in the laboratory by programmed stimulation is identical to the clinical tachyarrhythmia; (2) the response to drug therapy in the laboratory predicts the clinical response; (3) the ability to prevent an electrically induced ventricular tachycardia by drug treatment predicts the inability of the heart to develop ventricular fibrillation, especially if an ischemic episode is superimposed upon a vulnerable substrate. Thus, one is not certain that the prevention of electrically-induced arrhythmias by drug therapy is synonymous with the prevention of sudden coronary death. Whereas the first and second assumptions may have been established, the third has not, since an acute ischemic episode is not part of the testing procedure and the true efficacy of a drug intervention can only be determined by looking at its potential to prevent sudden coronary death; an end-point seldom achieved during provocative testing procedures. It may also be true that a drug which fails to prevent the initiation of tachyarrhythmia by programmed electrical stimulation may still successfully prevent a spontaneous recurrence. This would be especially true of those agents which accumulate in myocardial tissue over time and show little correlation between concentration of drug in the plasma and therapeutic efficacy, e.g. amiodarone, propranolol and bretylium. Furthermore, the failure to recognize the formation of active metabolites as participating in the overall pharmacological and electrophysiological effects of an intervention could cast additional doubt on the value of a 'therapeutic

plasma concentration' as a guide to adequate therapy unless one is familiar with the metabolic products and has appropriate means of quantitating them in plasma.

#### **What needs to be accomplished?**

The previous discussion was intended to emphasize the importance of the problem of sudden coronary death and to suggest that a pharmacological approach may make a significant impact upon the mortality rate, if indeed ventricular fibrillation constitutes the terminal electrophysiological event. In reviewing the results of long-term suppressive therapy for the prevention of sudden cardiac death, Lovell<sup>5</sup> stated that 'non-specific long-term prophylactic use of existing drugs holds less promise than appeared at one time to be the case. It may be that tolerable drugs which are highly effective in inhibiting ventricular fibrillation when given long-term will be developed, and this is a worthwhile aim'.

Despite the world-wide need for a truly antifibrillatory drug, there has been relatively little effort directed towards this end. At present, the anti-arrhythmic drugs available in the USA for chronic management of patients with life-threatening arrhythmias are quinidine, procainamide, disopyramide, propranolol, timolol, metoprolol, and phenytoin. None is considered entirely suitable for long-term prophylactic use in the prevention of sudden coronary death. Of the new agents, namely amiodarone, aprindine, betanidine, tocainide, mexiletine, encainide, mebentine, flecainide, and pirmenol, none is known specifically to prevent ventricular fibrillation in either the experimental animal or in man. Furthermore, it is most disappointing to note that the newer anti-arrhythmic drugs were not developed specifically for the problem under consideration. There are limited animal data available with respect to these agents and already several are proving to have serious toxic effects associated with their long-term use. This is especially true of amiodarone, which, despite its clinical efficacy as an antifibrillatory agent, has produced significant side-effects, so as to limit its use to the most seriously ill patients.

The approach to finding an effective antifibrillatory drug in contrast to an anti-arrhythmic drug for the prevention of sudden cardiac death has been one of mere chance alone, and it is doubtful that this 'hit-and-miss' method will ever prove successful. The fact that several pharmacological interventions have

been shown both experimentally and clinically to exert an antifibrillatory effect<sup>6-9</sup> should cause cardiovascular pharmacologists to exert greater effort towards the development of more useful and acceptable agents for the prevention of sudden coronary death. Therefore, if substantial progress is to be made, it will require a greater emphasis upon the preclinical development of pharmacological agents, which, on the basis of *in-vivo* and *in-vitro* electrophysiological studies, provide evidence for possessing activity which could allow them to be classified as being antifibrillatory.

#### Where can one start?

A major problem in designing therapeutic approaches to sudden coronary death has been the limitation of appropriate animal models. The bulk of the available data on the electrophysiological properties of current anti-arrhythmic drugs was derived from *in-vitro* studies on 'normal' cardiac muscle from a variety of animal species. Within recent years some effort has been made to employ ischemically injured myocardial tissue in electrophysiological studies *in-vitro*.

The description of the mechanisms for arrhythmias and conduction disturbances observed in intact hearts has been based primarily on electrophysiological data obtained in isolated heart muscle or in intact hearts studied many hours or days after ischemic injury or in intact animal preparations in which cardiac arrhythmias are induced through the administration of digitalis glycosides or other cardiotoxic-arrhythmogenic agents. Several methods have been developed for producing animal models with chronic myocardial ischemic injury in which ventricular arrhythmias develop spontaneously or in response to programmed electrical stimulation<sup>10-13</sup>. However, these models do not provide an opportunity to examine the electrophysiological events preceding the development of ventricular fibrillation or to study pharmacological interventions for the prevention of life-threatening arrhythmias. In considering the problem of sudden coronary death, it would be advantageous to employ a chronic animal model in which a previous myocardial infarction has left the heart susceptible to the development of re-entrant ventricular tachyarrhythmia and in which ventricular fibrillation will occur in response to a new, albeit transient, ischemic insult, insufficient to produce myocardial infarction, but which results in sudden coronary death.

The ideal animal model for the study

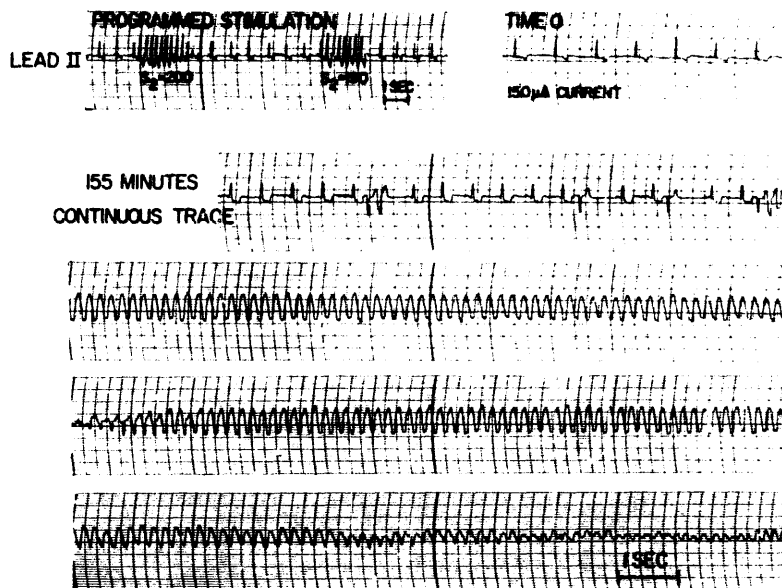


Fig. 1. The lead II electrocardiogram as recorded from a conscious dog four days after the surgical induction of acute myocardial infarction as a result of temporary occlusion (120 min) of the left anterior descending coronary artery. The tracing in the upper left hand corner shows the induction of two runs of a non-sustained ventricular tachycardia in response to electrical premature ventricular stimuli ( $S_2$ ) delivered 200 and 190 ms after the preceding normally conducted impulses. Thus, the canine heart with a previous myocardial infarction is susceptible to the induction of ventricular tachycardia by programmed electrical stimulation.

The subsequent tracings illustrate the electrocardiographic responses which occur when a 150  $\mu$ A anodal d.c. current is applied to the intimal surface of the left circumflex coronary artery. The resulting intimal injury leads to the development of platelet thrombi and transient episodes of regional ischemia as evidenced by the appearance of ST-segment depression 155 min after applying the anodal current. The continuous electrocardiographic tracing shows the development of ventricular premature complexes, ventricular tachycardia and finally, ventricular fibrillation. The lethal arrhythmia occurs spontaneously in response to ischemia superimposed upon a vulnerable myocardium and in some ways replicates what one sees in patients who experience sudden coronary death.

of pharmacological interventions for the prevention of life-threatening arrhythmias should be based on the knowledge that the incidence of primary ventricular fibrillation is maximal in the first few minutes after an acute ischemic event and thereafter decays exponentially, and that the majority of patients have ventricular fibrillation because of coronary artery disease, but without acute myocardial infarction as the precipitating event.

Our laboratory has recently described a conscious canine model<sup>14</sup> which is susceptible to the induction of ventricular tachyarrhythmias by programmed electrical stimulation and which possesses the characteristics stated above so that ventricular fibrillation (sudden coronary death) develops in response to a transient ischemic event which is superimposed on a ventricular myocardium with a previous history of ischemic injury (Fig. 1). We have been able to demonstrate that disorganization of the cardiac rhythm and the development of ventricular fibrillation in response to transient regional ischemia is unlikely to

occur in the absence of previous myocardial ischemic injury, suggesting that disorganization of the cardiac rhythm is more likely to occur in a ventricle which serves as a proper substrate for initiating and maintaining a rhythm capable of degenerating into ventricular fibrillation.

The model permits one to demonstrate the existence of conduction defects in the epicardium of the infarcted myocardial region, suggesting that a re-entrant mechanism is responsible for the tachyarrhythmias which occur in response to programmed electrical stimulation. Thus, the animal model in which the heart has been subjected to a previous infarction exhibits many similar electrophysiological characteristics to the human post-infarcted heart. It is susceptible to the induction of ventricular tachycardia by provocative electrical stimulation and it can develop ventricular fibrillation as a result of a superimposed transient ischemic event (Fig. 1). In our laboratory, untreated control animals have a 90% incidence of 'sudden coronary death'. Pretreatment with bretylium<sup>15</sup>, pranolium<sup>16</sup>, amiodarone,

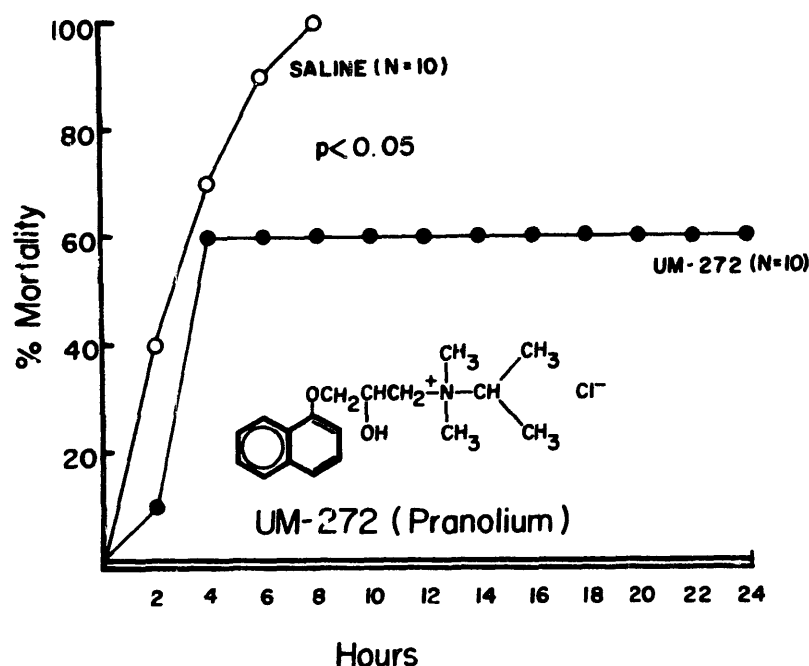


Fig. 2. Two groups of animals were subjected to the test procedure described in Fig. 1. The control group treated with saline displayed a 100% development of ventricular fibrillation within 8 h of application of the anodal current to the intimal surface of the circumflex coronary artery. The animals pretreated with UM-272 had a 60% mortality rate, with the remaining animals surviving up to the end of the study protocol, at which point they were sacrificed and examination of the circumflex coronary artery showed a totally occlusive thrombus in the left circumflex coronary artery. Thus, pretreatment with UM-272 allowed 40% of the animals to survive despite extensive ischemic injury to the left ventricular myocardium. The animal model of sudden coronary death may serve as an important approach to the preclinical assessment of anti-inflammatory drugs.

or nadolol<sup>17</sup> provides significant protection (40–80%) from ventricular fibrillation in animals subjected to the test procedure (Fig. 2). Quinidine, however, given in dosages which achieved plasma concentrations equivalent to those used clinically, was without a protective action<sup>16</sup>. Furthermore, we could not demonstrate a correlation between the ability of a drug to prevent ventricular fibrillation and to suppress induction of ventricular tachycardia by programmed electrical stimulation. This was particularly true with respect to amiodarone. On the other hand, quinidine prevented the induction of ventricular arrhythmias by programmed electrical stimulation, but was without benefit in preventing ventricular fibrillation in our animal model of sudden coronary death.

We recognize the difficulty in extrapolating from the animal experiment to the clinical situation of sudden coronary death in man. However, it has become obvious that most anti-arrhythmic drugs have been, or are evaluated using *in-vitro* or *in-vivo* models which have little, if any, relationship to the clinical pathophysiological situation associated with

sudden coronary death. Thus, animal models such as the one being used in our laboratory should provide a new approach to the preclinical assessment of pharmacological interventions intended specifically for the prevention of ventricular fibrillation and the prevention of sudden coronary death. The final analysis of a drug's potential worth will depend, as usual, upon appropriate clinical testing in patients who are at risk of developing sudden and unexpected life-threatening arrhythmias and/or ventricular fibrillation, rather than employing the more expedient and less dependable approach of evaluating new agents for their ability to reduce the frequency and/or complexity of ventricular premature depolarizations.

Substantial progress has been made in recent years with respect to identifying subsets of patients who are at risk of sudden coronary death. Both surgical and electrical means of preventing sudden coronary death in the most difficult-to-manage patient groups have been attempted with impressive results. However, there continues to exist a need for an increased priority to the development

of more reliable and effective therapeutic agents capable of preventing ventricular fibrillation. The challenge is formidable, but one which can be met through the use of relevant animal models for the pre-clinical testing of potential therapeutic interventions and appropriate end points to determine clinical efficacy in a patient population known to be at an increased risk of sudden coronary death.

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