# Sudden Death: Strategies for Prevention

This is the eighth in a series of Research News articles examining recent developments in research on heart disease.

Each year in the United States, almost 700,000 deaths are attributed to heart attacks; two-thirds of the victims die before they reach a hospital. Many of these sudden deaths are due to ventricular fibrillation, a condition in which the ventricles or large muscular chambers of the heart contract in such a chaotic and uncoordinated manner that the heart stops pumping and cardiac arrest ensues. One of the major lessons emerging from the operation of specialized coronary care units is that prompt treatment of cardiac arrest can restore the heartbeat and pull the patient back from the brink of death. Moreover, many of those resuscitated can live at least as normally as persons who have had heart attacks without ventricular fibrillation.

Ventricular fibrillation is caused by disturbances in the electrical impulses that normally regulate the heart's beating. The likelihood that the disturbances will occur increases with the size of the infarct (dead tissue) that results when blood flow to a portion of the heart is drastically reduced by blockage of one or more of the coronary arteries. This is one of the principal reasons for devising strategies to limit infarct size (*Science*, 10 December 1976, p. 1147). But another lesson being learned, according to Leonard Cobb of Harborview Medical Center in Seattle, is that many persons who experience ventricular fibrillation show no evidence of a recent infarct. Cobb, who is medical director of Medic I, a Seattle community program for delivering emergency medical aid outside the hospital, says that this is true for more than half of those resuscitated in their program. However, most of the patients do have dead cardiac tissue as a result of heart attacks that occurred months or years earlier. And the coronary arteries of almost all are blocked sufficiently to reduce the supply of blood and oxygen to the heart even though tissue may not have actually been killed.

Cardiologists think that it should be possible to lower the high toll now being taken by ventricular fibrillation. Strategies being investigated include community emergency programs, the use of drugs to control dangerous arrhythmias that may lead to ventricular fibrillation, and surgery to destroy abnormal tissue that gives rise to the arrhythmias. More effective methods for preventing cardiac arrest may also follow from studies of how stress increases the susceptibility of the heart to ventricular fibrillation. The studies are providing a mechanism that helps to explain the oft-postulated association between stress and sudden death.

Saving lives by intervening only after cardiac arrest begins presents formidable problems both because of the number of people involved and the time factor. Therapy must be started within 5 minutes because irreversible brain damage occurs if the brain's blood supply is cut off for longer times. Heart attack victims who survive long enough to reach the hospital are placed in coronary care units where their hearts are continuously monitored; any abnormal rhythms that presage ventricular fibrillation can be treated as soon as they occur. But getting prompt help to the person who goes into cardiac arrest at home, work, or on the street is a chancy proposition. One way to improve the chances is by instituting community programs as exemplified by Seattle's Medic I program.

Cobb says that a major aim of Medic I is to ensure that persons in cardiac arrest receive emergency treatment within 3 minutes of a call for help. Therapy for cardiac arrest usually begins with cardiopulmonary resuscitation (CPR) to restore the circulation of oxygenated blood to all parts of the body, but especially to the brain. The CPR technique includes mouth-to-mouth resuscitation and external heart massage (exerting firm rhythmic pressure on the chest over the heart). The operation of the Medic I program depends on the fire department, including personnel who have been trained in emergency medical procedures and special paramedical units that can administer more definitive care, and also on the general public.

During the first 4 years of the program, which began in 1970, the Seattle fire department responded to 1106 calls involving persons in cardiac arrest. Overall, 30 percent were resuscitated and 17 percent lived long enough to be discharged from the hospital. But the figures have shown an upward trend as the program has developed. In the first 2 years 34 percent were resuscitated on the scene and 11 percent were able to return home after hospitalization; in the second 2 years, these figures increased to 43 and 23 percent, respectively.

Cobb attributes at least part of the improvement to the involvement of the general public in the program. There has been a massive effort in Seattle to train people of high school age and older to recognize the symptoms of heart attack and cardiac arrest and to administer CPR. Almost 100,000 persons out of a population of 500,000 have completed the training course, which costs about $1.25 per person. Passers-by and others at the scene of the emergency can often begin CPR even before the fire department arrives, an action that can mean the difference between life and death. Passers-by have performed about one-third of the resuscitations. Forty-six percent of these patients eventually recovered sufficiently to be discharged from the hospital, whereas only 18 percent of those resuscitated by firemen did. According to Cobb, the immediacy of action taken by the passers-by makes the difference.

As successful as the Seattle program has been, most cardiologists think that the greatest potential for saving lives lies in identifying those in danger of sudden death from ventricular fibrillation and taking steps, such as drug therapy, to prevent it. The evidence is not extensive, but clinical trials have indicated that treatment with drugs that prevent certain serious forms of ventricular arrhythmias does reduce the risk of dying suddenly. One double-blind study (neither the physicians nor the patients knew who was getting the drug and who received the placebo) was conducted by C. Wilhelmsson and his colleagues at the University of Goteborg in Sweden. All of the participants were individuals who had recently had heart attacks. The investigators found that only 3 of 114 patients treated with the drug alprenolol died suddenly, but that 11 of 116 controls patients did.

A larger double-blind study, including more than 3000 heart attack patients randomized between the control and treated groups, was conducted in 67 hospital centers, most of which were in Great Britain. The results of the study, which was coordinated by K. G. Green of Imperial Chemical Industries, Ltd. in Alderley Park, Great Britain, showed that there were fewer sudden deaths among patients treated with practolol than

among controls (the numbers were 30 and 52, respectively) and fewer of all kinds of cardiac deaths (47 in the treated group and 73 among the controls) during the 12 months the patients were followed. However, the side effects produced by practolol were serious enough that the physicians conducting the trial considered this drug to be unsuitable for long-term use. They recommended that it be replaced by other drugs with similar mechanisms of action.

Practolol and alprenolol are β-blocking agents; they block the transmission of the sympathetic nerve impulses that increase the heart's irritability. Propranolol, the only β-blocker approved by the Food and Drug Administration (FDA) for use in the United States for treating cardiac arrhythmias, is one of three antiarrhythmic drugs most commonly prescribed here. The other two are procaine amide and quinidine. In addition, the drug lidocaine is usually used in hospitals but must be administered intravenously and is not suitable for outpatient therapy.

None of these agents is ideal. All have side effects including weakness, dizziness, nausea, vomiting, diarrhea, or reactions similar to those produced by allergies. And many patients do not respond to any of these drugs. In one study, Bernard Lown and his colleagues at the Harvard School of Public Health found that procaine amide and quinidine controlled the arrhythmias of only about one-quarter of the patients taking them.

One problem is that the doses required to produce therapeutic benefits are only slightly lower than those that produce toxic effects. Many people cannot tolerate doses high enough to do any good. Several investigators expressed concern that so few antiarrhythmic agents are available in this country. They think that the FDA regulations have made it too difficult and expensive for pharmaceutical companies to develop drugs needed by a large number of people.

### New Drugs Are Tested

Nevertheless, three new drugs for controlling arrhythmias, aprindine, disopyramide phosphate, and tocainide, are now undergoing early clinical trials here. All have proven effective in limited numbers of patients chosen because they had a high frequency of life-threatening arrhythmias that were refractory to the more standard agents.

According to Douglas Zipes of the Indiana University School of Medicine, aprindine reduced the number of ventricular premature beats experienced by 20 of the 23 patients receiving the drug, but it did not eliminate the abnormal beats in any of the patients. Ventricular premature beats occur when the ventricles contract earlier in the cardiac cycle than they should. The agent did prevent the recurrence of ventricular tachycardia and fibrillation in 19 of the patients. Here ventricular tachycardia is defined as three or more ventricular premature beats in succession. There are several kinds of tachycardia, which is usually defined as an abnormally fast heart beat; some of them are not dangerous. But ventricular premature beats and ventricular tachycardia are dangerous arrhythmias that may evolve into fibrillation.

Although five of the patients died during the study from heart attacks or heart failure, none died from ventricular arrhythmias not associated with heart attacks. Zipes said that several patients experienced neurological side effects, including tremor, dizziness, hallucinations, and loss of movements, at the higher doses given. Reducing the dosage eliminated the side effects (except the tremor), but not the therapeutic benefits in all the patients except one who had to stop taking the drug.

In a study of 15 patients with intractable arrhythmias, Donald Harrison and his colleagues at Stanford University School of Medicine found that tocainide suppressed the ventricular premature beats of 11 patients. The incidence of the beats was reduced by 90 percent at doses not associated with side effects. The patients served as their own controls, first receiving the placebo and then the drug in a single-blind study.

Harrison says that one of the advantages of tocainide is that the agent is relatively long-lasting and need be taken only two or three times daily. Because the commonly used drugs are rapidly eliminated from the body, patients have to take them every 4 to 6 hours, including during the night, in order to maintain effective therapeutic concentrations in the blood without taking toxic doses.

Disopyramide phosphate is a third experimental antiarrhythmic drug now being studied by a few investigators including Bernard Tabatznik of Sinai Hospital of Baltimore and Leonard Dreifus of the Lankenau Hospital in Lancaster, Pennsylvania. Tabatznik has found that the drug will eliminate or reduce by 90 percent the incidence of a number of different arrhythmias. The duration of the experiment was short, only a few hours for most of the patients, but a few with serious arrhythmias have been maintained on the drug for up to 2 years.

The mechanisms by which the newer agents act are still under investigation and, like those of the older ones, not completely understood. The beating of the heart is normally regulated by an intrinsic pacemaker, a small strip of tissue called the sinoatrial node, located in the right atrium (the atria are the small upper chambers of the heart) near the spot where the blood enters the heart from the veins. The sinoatrial node automatically sends out rhythmic electrical signals that stimulate the atria to contract and that then spread through a specialized conduction pathway to trigger contraction in the ventricles.

The same pathway also participates in the transmission of abnormal signals, which may originate in or around dead or ischemic tissue, that sometimes culminate in ventricular fibrillation. In one way or another, all of the drugs act on the cells in the conduction pathway to make it more difficult for aberrant impulses to enter the path and be transmitted throughout the ventricles. Some of the drugs act directly on the conducting cells; propranolol and the other β-blockers suppress the pathway indirectly by inhibiting the transmission of excitatory signals from sympathetic neurons, but they may, at high concentrations, also have a direct effect.

Many investigators think that the heart tissue becomes electrically unstable as a result of ischemia caused by coronary heart disease and that this predisposes the heart to dangerous arrhythmias and ventricular fibrillation. Lown defines electrical instability as the condition in which a stimulus of threshold intensity (on average, the lowest that will produce a response), which ordinarily produces only a single response, induces repetitive activity in cardiac muscle. A stimulus substantially above threshold is needed to cause repetitive activity in the normal heart. Although the required intensity is lower for the infarcted heart, it is still above threshold.

Lown and his colleagues have developed a technique for assessing the electrical stability of the hearts of laboratory animals, usually dogs in their experiments. With it they showed that 2 minutes after tying off a coronary artery, the threshold for producing ventricular fibrillation dropped markedly; it returned to normal within 5 minutes. Lown says that these changes paralleled the emergence and recession of arrhythmias.

Lown thinks that although the electrical instability predisposes to malignant arrhythmias, the precipitation of ventricular fibrillation probably depends on additional factors, such as stress acting through the sympathetic nervous system. The Harvard investigators showed that stimulating a particular brain center reduced the threshold for electrically induced fibrillation in dogs without occlu-

sions but did not spontaneously elicit arrhythmias. However, stimulation of the brain center produced a tenfold increase in the incidence of spontaneous ventricular fibrillation in dogs with occluded coronary arteries. Experiments with inhibitors of the activity of sympathetic neurons indicated that these changes were mediated by this branch of the autonomic nervous system. Direct stimulation of sympathetic nerve cells also lowered the threshold for ventricular fibrillation.

In order to examine the effects of stress itself on the threshold for ventricular fibrillation, the Harvard investigators suspended the dogs in slings, a situation in which the dogs manifested their stress by a number of physiological symptoms, including increased salivation, restlessness, and an elevated heart rate. According to Lown, the threshold was significantly lower when the dogs were in the slings than when they were left undisturbed in comfortable cages.

As further evidence that stress and the activity of the sympathetic nervous system predispose to dangerous arrhythmias, Lown cites experiments in which the investigators found that the number and severity of ventricular premature beats of 21 of 26 patients with coronary heart disease were reduced during sleep. The five who either had no decrease or an increase (one case) were the only patients in the study who had taken sleeping pills, although the significance of this observation is unclear. Lown thinks that the reduction is due to the decline in sympathetic activity that occurs during sleep.

For some of the patients, sleep was more effective than drugs, including propranolol, in reducing their arrhythmias, even though part of propranolol's action is thought to be the result of its blocking sympathetic activity on the heart. Lown thinks that the results indicate that the neurological trigger for the arrhythmias may be a more appropriate target for drug therapy than the heart itself.

The use of surgery to prevent certain types of arrythmias is also being explored, especially for individuals with a severe form of the Wolff-Parkinson-White syndrome. Persons with this syndrome have one or more abnormal pathways, in addition to the normal one, for conducting contraction impulses from the atria to the ventricles. Many persons with this syndrome have no symptoms and may even be unaware that they have it. A few, however, have frequent and prolonged bouts of very fast heartbeats that may be disabling, life-threatening, and unresponsive to drug therapy. According to John Gallagher and surgeon Will Sealy of the Duke University Medical Center, it is possible to identify the abnormal pathway in these patients and interrupt it surgically. They performed the operation on 78 patients by the end of 1976. Seventy-five of the patients survived and 71 no longer have symptoms.

A development by the Duke group that often facilitates the surgery for Wolff-Parkinson-White syndrome and may permit surgical treatment for other intractable arrhythmias, is the use of a cryogenic probe to destroy the abnormal pathway by freezing it. Gallagher says that when the tissue to be killed is located on the exterior of the heart, the freezing procedure can be carried out without stopping the heart and putting the patient on the heart-lung machine. This makes the operation much simpler and greatly lowers its risks. One 9-year-old boy underwent such surgery and was able to go home 7 days later.

Surgeon Robert Anderson and Gallagher are exploring the possibility that cryogenic surgery can benefit patients with certain other intractable arrhythmias, but Gallagher points out that whereas surgery may be the optimum therapy for some patients with severe Wolff-Parkinson-White syndromes, it will probably be the last resort for most other types of patients.

### Pacemakers May Prevent Arrhythmias

Another strategy for preventing life-threatening arrhythmias involves the use of pacemakers. The devices are often used to accelerate slow heart rates. Several investigators are now attempting to apply the devices to abrogate the electrical signals that give rise to ventricular tachycardia and fibrillation. The devices developed thus far require the patients to turn on their own pacemakers when they feel the heart beating arrhythmically. The next step is to develop a computer-controlled device that can detect the signal and interrupt it automatically.

Because of the side effects of the drugs currently used, cardiologists do not want to prescribe them for all patients with coronary heart disease. Instead, they want to identify those persons at high risk of sudden death from ventricular fibrillation for whom the benefits of therapy should outweigh the risks. Equally important are methods for determining whether therapy with a particular drug is working.

Persons who have already survived one episode of cardiac arrest are known to be at high risk because many suffer additional episodes within a relatively short time. But practically all heart attack victims or individuals with coronary heart disease have occasional ventricular premature beats if their hearts are monitored for long periods of time. Thus, the mere presence or absence of the beats has little prognostic significance. However, most cardiologists think that characteristics of the beats, including their frequency, whether or not they occur in sequences, and their position in the cardiac cycle, determine the severity of the irregularities and can be useful in predicting a patient's prognosis.

The detection methods most commonly used are the stress electrocardiogram (ECG) and 12- or 24-hour monitoring by means of a lightweight recording electrocardiograph worn by the patients. The biggest advantage that stress ECG's have over extended monitoring is that the former can be done quickly and relatively few heartbeats need to be analyzed. During the course of 24 hours the heart beats about 100,000 times. However, investigators, including Jerome Cox at Washington University Medical School and John Fitzgerald at Stanford, are developing techniques for automatically scanning the long records or condensing them by means of computer-assisted devices that only record when the arrhythmias occur.

The idea behind stress testing is that the stress, usually exercise such as walking a treadmill, may cause the heart of a person with coronary artery disease to become deficient in oxygen, with the result that the number of arrhythmic beats is increased. For example, Lown and his colleagues found that exercise increased the number of ventricular premature beats threefold in men with coronary artery disease and increased the frequency of ventricular tachycardia almost eight times in a 3-minute period.

The biggest disadvantage of the stress ECG is that there is a chance that the patient may go into cardiac arrest during the test or shortly thereafter. Despite this danger, numerous investigators have had extensive experience with exercise testing and there have been few fatal complications. Paul Rochmis of Fairfax, Virginia and Henry Blackburn of the University of Minnesota reviewed 170,000 tests conducted at 73 clinical centers and found but 16 deaths within 24 hours after completion of the ECG.

Thus, there are safe techniques for detecting dangerous arrhythmias and predicting which patients are most likely to experience ventricular fibrillation. The most pressing need is the development of therapeutic regimens for controlling the arrhythmias without inflicting unacceptable side effects on the individuals undergoing them. Cardiologists hope that the investigations now under way may help to fill that need.—JEAN L. MARX