Cardiac arrest is the cause of up to half of cardiac deaths, and in turn, cardiac death is the most common cause of death in Western society. The initial cardiac rhythm diagnosed is most often ventricular fibrillation (VF) and most patients have coronary artery disease with or without left ventricular dysfunction. However, cardiac arrest is usually an “electrical accident” rather than the consequence of acute myocardial necrosis. Contrary to popular belief, a new myocardial infarct, i.e., new Q-waves or enzymatic evidence of an infarct, is infrequently seen at the time of an out-of-hospital cardiac arrest.

Widespread use of bystander-initiated cardiopulmonary resuscitation (CPR) and early defibrillation have led to a potentially greater survival in such patients than has previously been possible. Many communities, both large and small, have highly trained paramedics who can respond to cardiac arrest within a short time period and perform advanced cardiac life support (ACLS), including endotracheal intubation, intravenous access and drug administration, defibrillation, and sophisticated rhythm diagnosis. Paramedics, as well as physicians in emergency rooms and in-hospital, who treat cardiac arrest victims usually follow the algorithms described in the “recommendations for treatment of cardiac arrest” published by the Emergency Cardiac Care Committee and Subcommittees of the American Heart Association. Although published as “guidelines,” these recommendations have been widely adopted as the standing orders for paramedic services across North America and are usually followed closely by physicians administering ACLS.

How effective is antiarrhythmic therapy during ACLS?

Although lidocaine, bretylium, and procainamide are indicated for the treatment of VF or pulseless ventricular tachycardia in ACLS guidelines, there is in fact no objective evidence that any of these therapies are better than placebo therapy. Early effective CPR and early defibrillation are undoubtedly of benefit, although it has been difficult to demonstrate this in controlled clinical trials. However, some patients cannot be electrically converted to sinus rhythm despite three successive defibrillation shocks as recommended in the guidelines for therapy of VF. These patients generally receive intravenous epinephrine, further attempts...
at defibrillation, and one or more of lidocaine, bretylium, and occasionally procainamide. Not surprisingly, survival in such patients is very poor, due probably in large part to the length of time that elapses between the original cardiac arrest and the time that medications are administered.

So far, there has not been a properly controlled randomized blinded study that has shown that any of these drugs are superior to placebo in assisting restoration of sinus rhythm and improving survival to hospital admission, let alone improving survival to discharge. Small studies have suggested that bretylium and lidocaine may be equivalent;\textsuperscript{2} however, this does not imply that either drug is necessarily effective. Even epinephrine, a standard agent used in cardiac arrest, has not been shown to be effective at restoring or maintaining effective circulation.\textsuperscript{3}

**Antiarrhythmic drugs and ventricular fibrillation**

Against this background, it is useful to examine the theoretical and experimental evidence concerning the use of more traditional antiarrhythmic drugs for ventricular fibrillation.\textsuperscript{4} In two separate meta-analyses, IV lidocaine, used as prophylaxis for primary VF in acute myocardial infarction, appeared to reduce the incidence of VF. However, overall mortality was 62 ± 28\% higher in the IV lidocaine than in the placebo-treated groups in one analysis,\textsuperscript{5} and the odds ratio for mortality during treatment was 1.76 (CI 1.04-2.98) in the other.\textsuperscript{6} This worse survival following lidocaine has been attributed to a higher incidence of asystole or pulseless electrical activity following lidocaine treatment.\textsuperscript{6}

In experimental animals\textsuperscript{7} and in man,\textsuperscript{8} lidocaine increases the amount of electrical energy required to defibrillate from VF. In an experimental animal model of cardiac arrest, lidocaine was ineffective in assisting restoration of sinus rhythm with defibrillation, whereas amiodarone was associated with a high resuscitation rate.\textsuperscript{9} Bretylium has been associated with no change\textsuperscript{10} or a decrease\textsuperscript{11} in defibrillation thresholds in animal models. It is likely effective at preventing VF recurrence in patients with “electrical storm,” although its use is associated with a very high incidence of serious hypotension.\textsuperscript{12} There is extremely sparse data on the use of procainamide for refractory VF, and virtually no experimental or controlled clinical data to support its efficacy in this setting.

Intravenous amiodarone, a drug indicated for the treatment of refractory life-threatening arrhythmias,\textsuperscript{4} is not mentioned in the ACLS guidelines since it was unavailable for commercial use at the time the guidelines were published. Interpreting the experimental and preliminary clinical data on the potential use of IV amiodarone in cardiac arrest is not straightforward. Given its complex pharmacokinetics and very long half-life, it may not be expected that amiodarone should have very rapid onset of effect, which of course is required in the treatment of cardiac arrest. However, amiodarone appeared to be at least as effective as bretylium in the treatment of electrical storm in a large randomized study of amiodarone versus bretylium,\textsuperscript{13} in which 10\% of patients were in VF at the time they were randomized.

**The ARREST trial**

Based on this information, Dr. Peter Kudenchuk, Director of Arrhythmia Services at the University of Washington in Seattle, Washington, and his colleagues conducted a large trial of IV amiodarone versus placebo in patients with out-of-hospital cardiac arrest resistant to electrical defibrillation. The Amiodarone in the out-of-hospital Resuscitation of REfractory Sustained ventricular Tachyarrhythmias (ARREST) trial is the first prospective randomized blinded trial to evaluate antiarrhythmic drug therapy in refractory VF. It was conducted with the collaboration of the King County Pre-Hospital Advanced Cardiac Care Services and its preliminary results were presented at the American Heart Association annual meeting in Orlando in November, 1997.
The ARREST trial was a randomized comparison of 300 mg of IV amiodarone given by intravenous push versus the amiodarone diluent in patients with cardiac arrest who had VF as the initial or ensuing rhythm, and who had failed three successive defibrillation shocks and IV epinephrine. Standard ACLS care was administered to all patients. A total of 504 patients were randomized: 246 received amiodarone and 258 received placebo.

The elapsed times to treatment were rapid compared to many large urban communities, with an average time to the arrival of the first emergency medical technicians of 4.3 minutes, arrival of the ACLS trained paramedics of 8.4 minutes, time to first defibrillation of 7.3 minutes, placement of the IV by 13.3 minutes, and administration of the study drug by 21 minutes after the receipt of the 911 call.

On average, patients received five defibrillation shocks and 22% had a transient return of a perfusing pulse, with subsequent recurrence of VF. Their average age was 66 years and about 65% of the patients had a known prior history of coronary heart disease. Seventy percent of the cardiac arrests were witnessed by bystanders.

As expected, time-to-study drug administration was an independent predictor of survival to hospital admission, which was the primary endpoint of the study. In addition, patients with transient return of pulse during ACLS had better survival than those in VF continuously during the arrest, which was in turn better than those who initially had asystole and later converted to VF.

As Dr. Kudenchuk reported, survival to hospital admission was significantly greater following amiodarone than following placebo. The overall survival to admission after amiodarone was 44% versus 35% in the placebo arm (a 25% relative improvement). In patients with continuous VF, it was 49% after amiodarone versus 39% after placebo (a 25% improvement), and in those with transient return of pulse during the arrest, it was 64% following amiodarone versus 40% after placebo (a 56% relative improvement).

Additional unblinded antiarrhythmic therapy was administered to 82% of patients in the amiodarone group and 85% of patients in the placebo group, respectively.

The study was not powered to show any difference in survival to discharge from hospital, and the absolute survival rates to discharge were very low. Amiodarone showed a 1% absolute advantage, which was not statistically significant and this potential advantage of amiodarone was labelled “inconclusive” by Dr. Kudenchuk. Fifty percent of patients who survived to hospital discharge had no neurological impairment.

This very important study is the first to show a benefit for any antiarrhythmic drug over placebo in the setting of shock-refractory ventricular fibrillation. Although improved survival to hospital discharge was not demonstrated, this study will require a reevaluation of the suggested algorithms in the guidelines for advanced life support as published by the Committee on Emergency Cardiac Care.

The ALIVE study

Based on a similar hypothesis to that of the ARREST study, the Toronto-based Amiodarone versus Lidocaine In Ventricular fibrillation Evaluation (ALIVE) began in November, 1995. The aim is to randomize 350 patients with shock-refractory VF to IV amiodarone versus IV lidocaine in the Metropolitan Toronto Emergency Medical Services System. As in the ARREST trial, patients with VF refractory to three successive shocks and IV epinephrine will be randomized to receive amiodarone 5 mg/kg, followed by a 2.5 mg/kg repeat dose if necessary, versus 1.5 mg/kg of lidocaine followed by a repeat dose of 1.5 mg/kg of lidocaine, if necessary, in a double-blinded manner. This study is expected to finish recruitment in 1999.

Conclusion

The treatment of ventricular fibrillation is difficult and often frustrating. Early defibrillation is undoubtedly the most effective therapy and should be administered with the least possible delay to all patients with VF, whatever other therapies are given. The increasingly widespread application of semi-automatic defibrillators by trained non-medical personnel such as policemen, firemen, security agents, etc. will hopefully increase the number of patients who can be initially resuscitated from out-of-hospital VF.
Many of these patients, however, relapse to ventricular fibrillation in the seconds to minutes after original restoration of sinus rhythm. A similar scenario is often seen during in-hospital resuscitation efforts in emergency rooms and acute care units. The advent of sophisticated cardiac therapies for patients who have been successfully resuscitated, including revascularization and implanted defibrillators, should increase the resolve of the medical community to treat all cardiac arrest victims as aggressively as possible.

Given this context, a better understanding of the efficacy of various antiarrhythmic agents in patients with VF is essential. The preliminary report of the ARREST trial is an important landmark in the evolution of our understanding of how best to treat these patients.

References

Editor’s note: In a previous issue of Cardiology Scientific Update entitled Multifactorial Approach to the Treatment of Cardiovascular Disease by Dr. Paul Dorian, the source for Figure 2: Glucose levels and chronic disease, was not acknowledged. It should have read: Reproduced with permission from Gerstein HC, in: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ. Eds. Evidence-based Cardiology (BMJ Books 1998).