Sudden unexpected cardiac death

Why are we not doing more to prevent sudden unexpected cardiac death? Why is prevention of the principal cause of death occurring during acute myocardial ischaemia and impending myocardial infarction ignored?

The majority are caused by ventricular fibrillation. This is most common within the first hour after the onset of an acute coronary syndrome and occurs with decreasing frequency thereafter. While this has been known and adequately documented for many years[1,2], only two approaches to combat this very early mortality have been made and both are too late to make any large impact on mortality. One has been the use of paramedics and nurses to provide immediate resuscitation[3] with rapid transit of patients to emergency areas. The other is the use of implantable defibrillators[4]. The former has increased the survival rate. The latter has had no effect on early death during the first attack, since the defibrillator is inserted for repetitive ventricular arrhythmias occurring many hours after the initial crisis.

The main reason for the onset of ventricular fibrillation in this early acute phase of ischaemia is a myocardial metabolic crisis due to an excess uptake of free fatty acids resulting from catecholamine stimulation of tissue lipolysis[5]. At the same time, the availability of glucose is reduced as a result of reduction in the myocardial uptake of glucose due to insulin suppression and limited glycaemia, and also inadequate myocardial glycogenolysis[6]. In ischaemia, beta-oxidation of lipids in the mitochondria is inhibited by accumulation of acylcarnitine and acyl-coenzyme A leading to cytosolic calcium overload and potentially to arrhythmias. Detergent CoA derivatives can also favour the onset of arrhythmias. Uncoupling of oxidative metabolism with irreversible electron transfer may occur[7,8].

What is needed is an otherwise harmless solution to protect against the onset of ventricular fibrillation. It should be injected intravenously immediately the patient is first seen by paramedics in the patient’s home, office or in the street, whenever acute ischaemia is suspected. It should be designed to modulate and minimize the metabolic crisis.

There are already some possibilities. One is a solution of omega-3 fatty acids which have a very rapid action in establishing normal rhythm, probably as a result of restoring to normal the calcium/sodium exchange in injured or hypoxic cells[9,10]. How this occurs is unclear but the conversion of relatively hard cytoplasmic and mitochondrial membranes to softer ones is likely to render them more permeable to normal ion exchange. Recently it has been demonstrated that men without evidence of prior heart disease who have high blood concentrations of omega-3 fatty acids have a reduced incidence of sudden death[11]. Another is the potential of nicotinic acid derivatives, some of which have a rapid anti-lipolytic action blocking the release of free fatty acids from adipose tissue and thereby allowing the myocardium to utilize glucose in preference to fatty acids[12]. A third may be the manipulation of fatty acid intermediates so that glucose becomes the preferred substrate[13,14]. This has been achieved by ranolazine, for example.

But none of these — or other approaches towards protection against ventricular fibrillation — has been formally tested with a randomized control trial, although the GISSI trial of n-3 fatty acids has shown encouraging results[15]. It would be legitimate and ethical to compare whatever preparation is favoured with a placebo, since we do nothing at present to protect our patients. Such a trial might not need either to be enormous or lengthy or expensive. The benefit, if any, should be measurable in 2000 patients treated for 12 h or thereabouts. The establishment of such a trial should not be insuperable in communities where rapid retrieval systems already operate. The exact design of a trial needs planning since the possibility of a rebound effect, after withdrawal of the treatment, should be considered. The likelihood of this will decrease as the acuity of the myocardial ischaemia passes and, by then, the patients should be in a facility with a defibrillator. The initiative would have to come from cardiologists dealing with frontline crises. Until now, their interest has been more towards the initiation of thrombolysis and angioplasty.

A fourth therapeutic regime, which has been assessed through randomized control trials, is the use of glucose–insulin–potassium (GIK) infusions. Unfortunately, all the published trials[16] were
conducted after the patient arrived in hospital, often many hours later and at a time when primary ventricular fibrillation is uncommon. Most have been inadequate in numbers and design and some have used solutions of GIK which are insufficiently strong to suppress free fatty acid concentrations in plasma and insufficient to increase the uptake of glucose by ischaemic myocardial cells. However, one\textsuperscript{[17]} has reported encouraging results 1 year after the acute event, although there was no reduction of in-hospital mortality. In diabetics, subcutaneous insulin reduced in-hospital mortality by 58\%\textsuperscript{[18]}, but whether this was a result of preventing ventricular fibrillation is not reported.

Sudden unexpected cardiac death occurs proportionately more often in middle-aged than in older adults. The latter have often developed sufficient myocardial collaterals to afford protection against a suffocating wave of ischaemia or have already survived such an event. It is all the more important to embark on new initiatives to protect individuals suddenly unexpectedly struck with an acute coronary syndrome\textsuperscript{[12,19]}. These people, who have “Hearts too good to die” (Claude Beck) are vital to their families and economically viable. Yet no research group or pharmaceutical company seems to be willing to take the challenge seriously. Why?

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