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Commentary

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Sudden cardiac death: the lost fatty acid hypothesis

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Summary

Evidence that an excess of plasma free fatty acids (FFA) might lead to primary ventricular fibrillation and sudden cardiac death has hardened over the 36 years since the hypothesis was proposed. When the sympathetic nervous system is stimulated during the onset of an acute coronary syndrome, catecholamine-induced tissue lipolysis occurs, with a surge of plasma FFA. This may overload the acutely ischaemic myocardium and impair glucose utilization. Myocardial oxygen consumption can increase in regional areas of ischaemia, and could lead to abnormal electrophysiological conduction and refractoriness, with irreversible ventricular arrhythmias. Efforts to combat the adverse effects of excess FFA include beta-blockade, increasing glucose availability and extraction, or inhibition of lipolysis. This last approach appears promising, but no method has yet been clearly shown to prevent primary ventricular fibrillation or sudden cardiac death. The hypothesis remains viable. More research is needed to derive treatment that can be applied as soon as the onset of acute myocardial ischaemia is suspected.

Introduction

Some ideas are lost because they never really see the light of day. But 36 years ago, the free fatty acid (FFA/NEFA) hypothesis[1] did, although subsequently it has been largely lost. Yet it remains viable. Renewal of the idea is appropriate today, since knowledge about the causes and prevention of ventricular fibrillation has advanced greatly. Ventricular fibrillation is the commonest cause of sudden unexpected death in most apparently healthy people, as well as in those with declared coronary heart disease.

Two potentially irreversible events occur in the myocardium during an 'acute heart attack'. One is that there is massive and sudden impedance of blood flow, whether from coronary thrombosis or spasm, reducing available oxygen for normal oxidative metabolism. The other is that profound changes in systemic metabolism occur, and these may result in the myocardium no longer receiving the optimum balance of energy substrates allowing it to contract and function normally. The combination may lead to lethal ventricular fibrillation.

Catecholamine activity

The catecholamine surge which occurs with the acute stress, fear (the *angor animi*) and pain of a developing coronary syndrome might, in certain circumstances, have deleterious effects on myocardial metabolism, making the ischaemic myocardium vulnerable to the local development of electrophysiological changes leading to primary ventricular fibrillation.[1]

Norepinephrine, released from postganglionic sympathetic nerves, binds to adrenergic receptors in myocardial cells and in the media of coronary arterioles. A moderate increase in catecholamine activity will augment inotropy and help to maintain

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contractility in the face of impaired myocardial oxygenation. But excess catcholamine activity may also lead to profound systemic metabolic responses that increase myocardial energy demands, with deleterious effects on myocardial function.

Normally, at rest, efficient aerobic myocardial metabolism depends on the relative proportions of free fatty acids that account at rest for 60–70% of ATP (glucose accounting for 20–25% of ATP), and lactate and ketones. Fatty acid oxidation uses more oxygen per mole than glucose. This is easily met in aerobic conditions, but less so or not at all when oxygen supply is reduced. The cell's requirements for ATP are set by the external workload performed by the heart. The rate of ATP breakdown is balanced by ATP synthesis. This cycle depends on the efficiency of myocardial oxygen consumption, and may be imperilled during haemodynamic or catcholamine-induced stress. Reduced coronary flow results in an abnormal metabolic response, aerobic ATP formation is impaired and regional myocardial ischaemia occurs. During ischaemia, catcholamine stimulation of tissue lipolysis leads to more FFA and less glucose being presented to the myocardium. Lactate and pyruvate are not utilized.

Plasma norepinephrine concentrations increase within minutes of the onset of an acute coronary syndrome[2–4] and remain elevated for up to 20 h, depending on the severity of the response to stress. This increases circulating FFA concentrations.[5,6] In the liver, it increases glycogenolysis but decreases pancreatic insulin secretion.[7] During the first hours of acute myocardial infarction, plasma FFA rise very rapidly and can be double or treble resting values.[6] The turnover rates for glucose and free fatty acids are independently increased.[8] Plasma cortisol and cyclic AMP concentrations also rise rapidly.[2] While these changes lead to some increase in plasma glucose concentrations, transport of glucose into myocardial cells is critically dependant on insulin availability, and the surge in catecholamines decreases pancreatic beta-cell production of insulin.[9] A relative glucose debt can occur locally, although this may be compensated for temporarily by local release of adenosine, stimulating myocardial glucose utilization.

Free fatty acids and primary ventricular fibrillation

In 1963, when studying electrophoretic analyses of lipoproteins, we observed that a fast moving fat-staining band, which we identified as albumin-bound free fatty acids, was intense in patients with acute myocardial infarction. Subsequently, we reported that an increase in plasma FFA also occurred in shock, renal colic, non-myocardial causes of pain and in cerebral infarction.[6] We regarded the rise in plasma FFA as a universal non-specific response to stress, or a catecholamine-induced response.

Patients with acute myocardial ischaemia who had particularly high plasma concentrations of FFA also had an increased incidence of ventricular arrhythmias and ventricular fibrillation.[10] Our proposal that these were related[1] was later confirmed by others.[11] More recent, indirect confirmation has come from the Paris Prospective Study of 5250 men.[12] After 22 years of follow-up, an increase in circulating FFA at baseline examination was significantly related to subsequent sudden death, defined as natural death that occurred within 1 h after onset of acute symptoms. The authors regard this correlation as a manifestation of increased adrenergic tone. Furthermore (as we showed for ventricular fibrillation) the risk of sudden death increased with increasing values of FFA. There was no correlation in the Paris Study between plasma FFA concentrations and other causes of fatal myocardial infarction.

The precise mechanism through which profound local metabolic gradients in ischaemic myocardial cells lead to arrhythmias is still unclear. Study of anaesthetized dogs following coronary occlusion, using three-dimensional maps of regional metabolism, blood flow and epicardial activation at the time of early ventricular arrhythmias, suggested that inhomogenieties of glycolytic activity within a central ischaemic area might be of critical importance in determining pathways of re-entrant excitation, conduction and hence arrhythmogenesis.[13]

The possibility that, in the presence of myocardial ischaemia, an increase in plasma catecholamines alone might induce ventricular fibrillation needs consideration. There is compelling evidence, however, to suggest that the concurrent rise in FFA is a primary intermediate cause. The intravenous injection of long-chain saturated fatty acids into anaesthetized healthy dogs induces ventricular arrhythmias.[14] Inhibition of adipose tissue lipolysis by a nicotinic acid analogue, which reduces the incidence of ventricular arrhythmias,[15] is not associated with reduction of cyclic AMP or catecholamine concentrations.[16] Heparin-induced plasma lipolysis can also lead to ventricular fibrillation in dogs[17] and heparin-induced ventricular arrhythmias are both prevented and reversed by protamine sulphate. Heparin activates plasma

chylomicron and triglyceride lipolysis and, in the presence of postprandial hyperlipaemia, leads to high plasma FFA concentrations. Parenthetically, the use of heparin in the management of an acute coronary syndrome might, if there is concurrent postprandial lipaemia, favour the development of ventricular fibrillation. Also, perfusion of isolated rat hearts with high-molar ratios of albumin-bound fatty acids has a direct arrhythmogenic effect.[18,19] Lastly, there is the positive relationship between baseline FFA levels and subsequent sudden cardiac death in the Paris Prospective Study[12] referred to above.

Free fatty acids and ischaemic myocardial metabolism

Myocardial ischaemia occurs regionally according to the extent of coronary arteriole underperfusion and local reperfusion. The areas affected may be quite small, and probably change rapidly, since myocardial energy kinetics are in continuous flux.[20] The availability and utilization of substrates locally is unpredictable. The fatty acid uptake of the myocardium can determine myocardial oxygen requirements.[21] An excess of FFA in some underperfused areas could be temporarily deleterious and increase local myocardial oxygen consumption patchily, leading to the development of gradients in substrate utilization and electrolyte transfer, with temporary interruption of the distribution of action potential as well as impairment of contractility.[22,23] Increased FFA suppress glucose oxidation through inhibition of pyruvate dehydrogenase.[24] In severely hypoxic localized areas of the myocardium, impaired glucose utilization and uptake, due to insulin suppression, may worsen the oxygen-wasting effects of increases in myocardial FFA concentrations.[21,25,26] Energy wastage due to futile cycling of unproductive reactions, such as repeated lipogenesis and lipolysis,[27] may also contribute and will vary regionally. When beta-oxidation is already impaired, all these metabolic changes may increase myocardial oxygen consumption critically.

Circulating FFA are bound with various degrees of affinity to albumin. Saturation of the two main binding sites occurs at about 1.2 µmol/l, corresponding to a free fatty acid/albumin molar ratio of >2.0. There is an exponential tissue uptake of FFA above this level,[28] and it is probable that when higher molar ratios are reached, the uptake by ischaemic areas of the myocardium is increased, with a greater risk of ventricular fibrillation. In isolated rat hearts, FFA are directly arrhythmogenic even in the absence of ischaemia, if the molar ratio to albumin is high.[18] The importance of the molar relationship between FFA and albumin is well illustrated by the demonstration that lipid-free albumin infusions that reduce the free fatty acid/albumin ratio simultaneously decrease the extent of ST elevation in dogs with coronary occlusion.[29]

Fatty acid toxicity

The mechanisms of fatty acid toxicity are complex.[7,24,30,31] A membrane detergent effect has been postulated.[1] A regional excess of fatty acids may lead locally to peroxidation of membranes with dispersion of membrane potentials, and activation of cytokines. Plasma FFA enter cardiomyocytes and thence into the mitochondria where they may uncouple mitochondrial respiration.[31] Uncoupling proteins lower the proton gradients by allowing protons to re-enter the mitochondrial matrix with the production of heat rather than ATP.[32] During ischaemia, beta-oxidation of lipids in mitochondria may also be inhibited, with accumulation of acylcarnitine and acyl-CoA. This could lead to cytosolic Ca^{2+} overload, with the occurrence of electrical re-entry and arrhythmias.[33] The accumulation of detergent CoA derivatives and lysophospholipids resulting from instability of membrane lipids also favours the development of arrhythmias. FFA may inhibit the Na^+, K^+, ATPase pump, leading to high intracellular sodium and calcium.[34] Excess FFA may lead to accumulation of extracellular K^+,[35] and shortening of action-potential. Additionally, the activity of the insulin-responsive glucose transporter (GLUT4) falls in the presence of excess FFA.[32,36] Thus, elevated FFA and intracellular lipid reduce insulin-stimulated glucose transport, mediated by a decrease in GLUT-4 translocation. High FFA levels also impair capillary recruitment and acetylcholine-mediated vasodilatation.[37]

Not all fatty acids behave similarly, and not all are pro-arrhythmic. Some polyunsaturated fatty acids have an anti-arrhythmic action. There have been consistent observations that n-3 polyunsaturated fatty acids from fish oils (particularly eicosapentaenoic, EPA, and docosahexaenoic, DHA, acids) decrease the tendency of experimentally-induced myocardial ischaemia to develop ventricular fibrillation[38,39] and that they reduce the incidence of sudden cardiac death.[40–43] Three large clinical trials have supported the evidence that n-3 fatty acids prevent sudden cardiac death,[44–46] although, recently, a contradictory report from the authors of one of these was negative. In DART-2, the risk

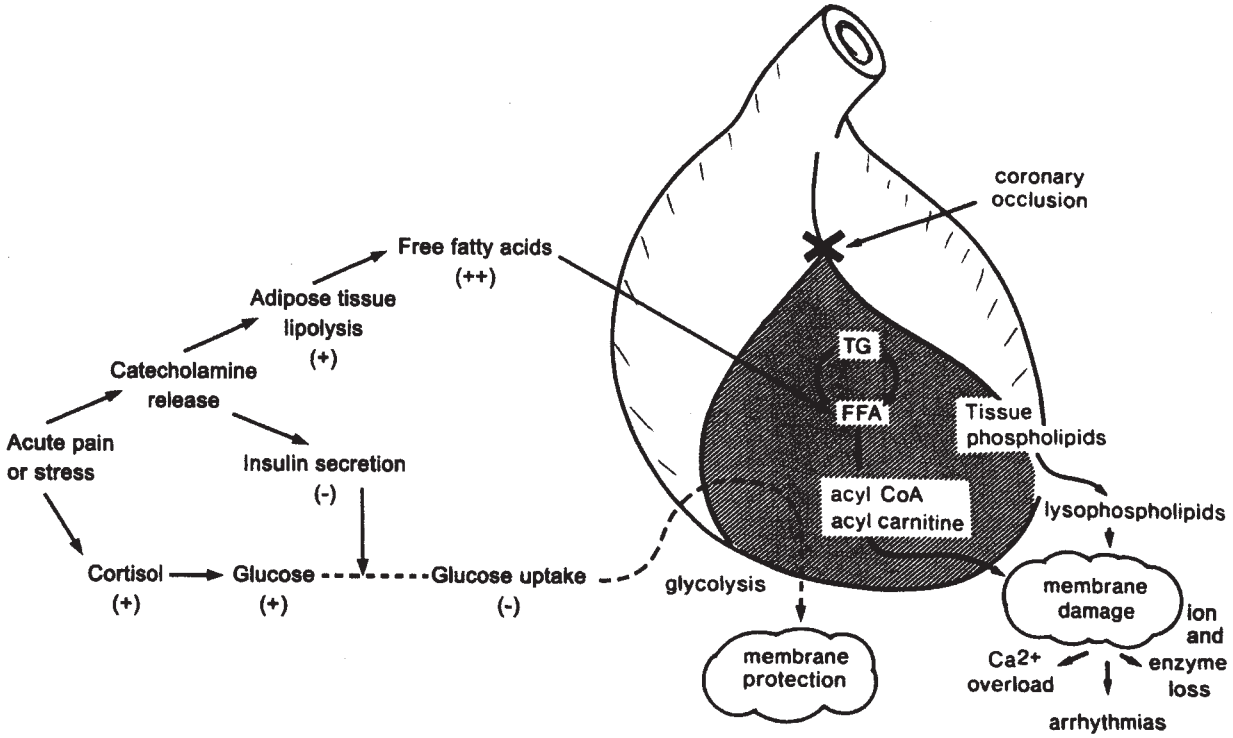

Figure 1. The main changes that occur in peripheral and myocardial metabolism during the development of acute myocardial ischaemia. CoA, coenzyme A; FFA, free fatty acids; TG, triglycerides. Reprinted from Oliver MF, Metabolic Causes and Prevention of Ventricular Fibrillation during Acute Coronary Syndromes, *Am J Med* 2002; **112**:305–11, Copyright 2002, with permission from Excerpta Medica, Inc.

of cardiac death was higher among subjects advised to take oily fish than among those not so advised; and was even greater for sudden cardiac death.[47] This contradictory report may relate to the use of EPA capsules, leading to excess fatty acid storage in adipocytes, with very high plasma FFA when catecholamine stimulation occurs.

The blood levels of n-3 fatty acids taken at baseline were found in a 17-year follow-up of the Physicians Health Study to be inversely related to subsequent sudden cardiac death.[43] It might therefore be argued that populations with an adipose polyunsaturated/saturated (P/S) ratio of <1.0, such as the Scots,[48] would be more liable to sudden cardiac death than Mediterranean races, where the P/S ratio is much higher. Additionally, in patients who had been taking EPA- and DHA-rich oils, there were fewer carotid artery plaques with thin fibrous plaques and signs of inflammation, compared with patients who had been taking n-6 fatty acids, suggesting that n-3 fatty acids also stabilize atherosclerotic plaques.[49]

The anti-arrhythmic effects of n-3 fatty acids may be explained by their effect on several basic electrophysiological mechanisms. They can lead to Na^+ channel inhibition and prolongation of refractory periods in cardiomyocytes. This might interfere with re-entry circuits. Polyunsaturated fatty acids, not exclusively n-3, appear to act through stabilizing cardiac myocytes by modulating conductance of ion channels in the sarcolemma, particularly the fast, voltage-dependent sodium current and the L-type calcium currents, though other ion currents are also affected. The primary site of action may be on the phospholipid bilayer of the heart cells in the microdomains through which the ion channels penetrate the membrane bilayer, rather than directly on the channel protein itself. These polyunsaturated fatty acids then alter allosterically the conformation and conductance of the channels.

All prostaglandins and thromboxanes produced from arachidonic acid (n-6) were found to be potent arrhythmic agents, whereas none of the comparable 3-series cyclooxygenase products of eicosapentaenoic acid were arrhythmogenic.[50] Also, in contrast to mono-unsaturated and n-6 fatty acids, saturated fatty acids such as palmitate and stearate may induce apoptosis in myocardial mitochondria.[51]

Therapeutic options for the prevention of sudden cardiac death

There would appear to be four possible ways of minimizing the adverse effects of high plasma FFA on myocardial ischaemic tissue during an acute coronary syndrome. One is to reduce adrenergic tone. Another is to reduce or inhibit adipose lipolysis. The other two are to act through the 'glucose hypothesis',[6] either by augmenting myocardial glycolysis, or by increasing myocardial uptake of glucose by infusing high concentrations of glucose with insulin and potassium (GIK).

β-adrenergic blockers

The obvious way to reduce hyperadrenergic tone is to use β-adrenergic-blocking drugs and these have been shown to reduce the incidence of ventricular fibrillation.[52,53] A recent comprehensive review confirms the cardioprotective and anti-arrhythmic effects of long-term treatment with β-blockers, and β-blocking drugs with a high degree of lipophilicity may be the most effective.[54] However, in the *earliest* stages of an acute coronary syndrome, hypotension and reduction of the inotropic activity of catecholamines might be harmful. The latter is essential for maintaining myocardial contractility, and it is no surprise that a recent very large meta-analysis (COMMIT) has demonstrated that, even in low risk patients, β-adrenergic blockade was associated with an increased incidence in early cardiogenic shock.[55] Also, when adrenergic activity is severely antagonized, insulin secretion is reduced: a potential metabolic disadvantage to the ischaemic myocardium.

Anti-lipolytic agents

If we wish to redress the imbalance of substrates reaching the ischaemic myocardium during the acute phase, inhibition of the release of FFA from adipose tissue is an approach needing more serious study. Nicotinic acid has been known for many years to have such an effect,[56] and has now been shown to bind to a specific protein receptor in adipocyte membranes.[57] Interest in the nicotinic acid receptor might allow the development of powerful rapidly-acting anti-lipolytic drugs, and needs more research.[58] Such a drug might be given immediately by intravenous or intramuscular injection when the patient with a developing acute coronary syndrome is first seen, and repeated hourly for 6–10 h. It would have to have no other effects, and no rebound elevation of FFA when stopped.

Nicotinic acid should not be used at the onset of an acute coronary syndrome, since it could lead to profound hypotension, but its analogues deserve study. β-pyridyl-carbinol both inhibits lipolysis and reduces the severity and extent of myocardial ischaemic injury during experimental coronary occlusion.[59] Most derivatives are however either too weak or too slow in action to lower raised FFA rapidly and sufficiently. A small clinical trial of an analogue of nicotinic acid reduced elevated plasma FFA rapidly and was associated with fewer episodes of ventricular arrhythmias,[15] but also led to gastric histamine release and tachyphylaxis. More encouragingly, nicorandil, a nicotinamide ester, has been studied because of its putative preconditioning effect against myocardial ischaemia. It reduces FFA concentrations and opens ATP K^+ channels. A recent large randomized trial (IONA), demonstrated a significant reduction (−21%) in acute coronary syndromes and fewer cardiac deaths over 1.6 years of follow-up in 5126 patients with known coronary heart disease.[60] Data concerning sudden cardiac deaths are not reported. There were more gastrointestinal symptoms in the treated group.

Another possibility is the development of A_1 adenosine receptor agonists that antagonize catecholamine-induced lipolysis without producing adverse haemodynamic effects.[61]

Augmentation of myocardial utilization of glucose

Another therapeutic option is to adopt the 'glucose hypothesis'[62] by stimulating the myocardium to increase glucose utilization preferentially. This can be done by direct stimulation of pyruvate dehydrogenase, the rate-limiting enzyme for glucose oxidation.

One way to approach this is to try to inhibit FFA oxidation.[63–65] Recently, several drugs have been developed and they have the advantage of being devoid of haemodynamic effects. Piperazine derivatives, such as trimetazidine[66] and ranolazine,[67] partially inhibit fatty acid β-oxidation. Trimetazidine has cardioprotective effects in *in vitro* models of ischaemia, and improves exercise tolerance in patients with chronic angina.[68] Ranolazine was effective in chronic stable angina in preliminary clinical trials,[69,70] and also has anti-arrhythmic properties.[71]

L-carnitine and proprionyl L-carnitine also stimulate glucose oxidation secondary to an increase in pyruvate dehydrogenase activity. Drugs which stimulate their action might theoretically to be of use.[72] Dichloroactate has such an effect. Compounds which decrease the transport of

acylcarnitines across the inner mitochondrial membrane need more study. None of these drugs has yet been clearly shown to benefit myocardial ischaemia.

Glucose and insulin

An alternative approach to the 'glucose hypothesis' is the administration of glucose/insulin/potassium (GIK). Insulin increases myocardial glucose uptake, and promotes glycogen storage. This can serve as a source of glycolysis, thereby increasing adenosine triphosphate availability. Since insulin also reduces the mobilization of FFA from adipocytes, a further benefit of GIK is to reduce the concentration of circulating FFA. This will occur soon after initiation of the infusion and, if is started early (say, within 6 h of the onset of myocardial ischaemia) the incidence of ventricular fibrillation should be reduced.

Overall, the results of GIK trials have not been impressive. The focus has been on long-term survival from 1 month to 3 years, and not on the incidence of primary ventricular fibrillation or early sudden death. In most, the time of starting the infusion has been too late to benefit acutely ischaemic myocardial metabolism. The results been inconsistent, possibly because the concentrations of GIK used did not reduce FFA levels sufficiently.

There have been many GIK trials, and five require mention. The ECLA (Estudios Cardiologicos Latinoamerica)[73] reported a better 1-year prognosis for patients receiving a high-dose regimen. Unlike most earlier trials, the dose used was at a level that would be expected to suppress plasma FFA concentrations, although these data were not reported. But there was no difference in the ECLA trial regarding in-hospital mortality between high-dose and low-dose infusions. The much larger CREATE-ECLA controlled trial of GIK in 20 201 patients with ST-segment elevation acute myocardial infarction (STEMI) had no impact on mortality, cardiac arrest or cardiogenic shock.[74]

In the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) trial,[75] after 3.5 years the absolute mortality in those receiving intensive insulin at the time of the myocardial infarct was reduced by 11%. The main benefit in those who received intensive subcutaneous insulin was evident within the first month. In those who had not required insulin before hospital admission, in-hospital mortality was reduced with insulin by 58% ($p<0.05$). Whether or not this benefit was also present within the first few hours or days is not reported. The effect was most apparent in patients who had not previously received insulin treatment and who were at a low cardiovascular risk. A second larger trial (DIGAMI-2) in type-2 diabetic patients failed to produce adequate control of HbA1c, and concluded that acutely-introduced long-term insulin infusions did not improve survival in patients with acute myocardial infarction.[76]

The results of the GIK trials are contradictory and not encouraging. Interpretation of these various trial results is often difficult. How adequate was the regimen used? For example, none report FFA concentrations. The key for the success of GIK is likely, from the metabolic point-of-view, to start a high-dose regimen in high-risk patients early, e.g. while in the ambulance transporting patients to hospital. It is encouraging, therefore, that a recent Dutch study with early administration (2.5 h after the onset of symptoms) of GIK infusions, mostly in conjunction with angioplasty, reduced mortality in those without heart failure.[77]

An editorial[78] reviewing this particular metabolic approach to myocardial conservation concluded: 'the present data are not firm nor extensive enough to support the routine use of GIK in patients with acute myocardial infarction'. This is still true.

Reasons for the fatty acid hypothesis being lost

There are several reasons why the proposal that excess elevation of plasma FFA accompanying acute myocardial ischaemia may lead to primary ventricular fibrillation has largely been forgotten. The main one has been the lack of interest in and understanding of the vital role of sustaining myocardial energy sources during acute ischaemia.[20,25,31,79] Ischaemic myocardial metabolism has recently been described as 'the lost child of cardiology'.[79] Cardiologists and interventionists have rightly focussed their skills on the imperative of using thrombolysis and angioplasty to restore myocardial blood supply. This is their immediate therapeutic manoeuvre, and it has been very successful.

Little enthusiasm has been shown for the potential use of metabolic control during an acute coronary syndrome to prevent ventricular fibrillation and cardiac death. While theoretically beneficial, modulation of the hyperadrenergic state by β-adrenergic blockers can have serious haemodynamic complications during the *acute* phases, and is not an approach to be recommended. The contradictory and mostly negative results of the GIK trials has reduced the interest of many in the effectiveness

and need to support aerobic metabolism during acute ischaemia.

Drugs that will have a rapid inhibitory effect on tissue lipolysis are my preferred choice,[80] but both intellectual and actual investment in their development has been disappointing. The case for their development is strong; as shown, hopefully, by this commentary.

Whatever the future developments, there is always the difficulty of providing appropriate treatment at the earliest stages of a developing coronary syndrome. Primary ventricular fibrillation is most common in the first hour after the onset of an acute coronary syndrome, and at a time when it is all but impossible to treat the patient. Many who die unexpectedly and suddenly are not previously identifiable as being specifically at risk for primary ventricular fibrillation: only 10% of such victims have a high-risk profile.[81] Most do not declare themselves early enough. These deaths often occur where there are no available emergency facilities. But the risk of primary ventricular fibrillation is increased for at least 6 h after the onset of an acute coronary syndrome and there is thus a window of opportunity if the right treatment were available.

So far, little of practical value has been derived from the original concept that a metabolic cause may lead to fatal ventricular fibrillation during acute myocardial ischaemia. The paradox is that the fatty acid hypothesis is still sound. Lacking appropriate drugs, it has not been formally tested. Like patients with ventricular fibrillation, it needs resuscitation. And let us not forget that sudden unexpected death accounts for one-fifth of all deaths.

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