Metabolic treatment of myocardial ischaemia

The metabolic treatment of myocardial ischaemia is the topic of the Supplement which accompanies this issue.

Alterations of metabolic pathways are recognised as primum movens of myocardial ischaemia. Although there are several possible definitions for myocardial ischaemia, it is common knowledge that myocardial ischaemia is a condition that occurs when blood flow cannot supply the required amount of oxygen needed for mitochondrial oxidation. Once mitochondrial impairment is established, a series of typical metabolic alterations, such as intracellular acidosis, anaerobic metabolism and reduced production of high energy phosphates, occur. These all result in haemodynamic impairment, such as contractile down-regulation and reduction of ventricular compliance.

Even though the above-reported metabolic alterations seem to be intrinsic to the concept of myocardial ischaemia, and, thus, closely linked to the myocardial ischaemia itself, it is also a fact that the maintenance of the metabolic capacities of the cell should be the primary objective of the treatment of myocardial ischaemia. In fact, maintenance of the metabolic capacities of the cell is synonymous with the maintenance of its vitality, as is largely demonstrated by the recent discovery of the hibernating myocardium.

Although all the above seem very easy to bring into practice, no consensus has been reached on the metabolic treatment of myocardial ischaemia, despite the uncontroversial theoretical principles lying behind it. We actually ‘prefer’ to cure myocardial ischaemia with drugs as they have definite haemodynamic effects, which, in turn, result in definite metabolic effects. Thus, the real challenge — the topic of this Supplement — is the possible clinical use of drugs which might bypass the ‘relatively-easy-to-achieve’ haemodynamic effects, exerting ‘primary’ metabolic activity.

The research in this field is still ongoing, but promising substances are already giving results. One of these substances trimetazidine, is one of the so-called ‘metabolic’ agents for the treatment of ischaemia[1]. Trimetazidine inhibits fatty acid oxidation and increases the oxidation of glucose [2]. In addition, it is believed that trimetazidine acts at a cellular level, maintaining a high energy and store and reducing cell acidosis. Experimental studies also show that trimetazidine may reduce oxygen free-radical production and exert a cytoprotective effect on ischaemic myocytes.

Cytoprotection is the capacity of the molecule to exert its action on the cell without affecting the haemodynamic condition of the cell itself[1]. This can occur by maintaining ionic homeostasis, enhancing mitochondrial respiration, or ameliorating membrane function. These characteristics of trimetazidine render its approach, in conventional combination therapy, unique. The clinical efficacy of trimetazidine in stable angina has been demonstrated when administered as a single agent (vs propanolol), or in combination with diltiazem, beta-blockers or isosorbide dinitrate[3-5].

Given its differing mechanism of action, the beneficial effects of trimetazidine may be additive to haemodynamic treatment, and possibly effective in patients resistant to such agents. All this — and much more — is the topic of the enclosed supplement.

R. FERRARI
Editor, European Heart Journal Supplements
Editorials 1145

ACE inhibitor use in heart failure: would that it were so

See page 1182 for the article to which this Editorial refers

The paper by Bart et al.[1] published in this issue addresses a clinically important issue. It is well recognised that despite overwhelming evidence confirming the efficacy of ACE inhibitors on both morbidity and survival in heart failure, these agents are seriously under-used. Most studies indicate that this is due to a false perception, especially among primary care physicians, that the drugs may be difficult to use in practice; the fears usually expressed concern symptomatic hypotension and renal dysfunction.[2] Only a small percentage of this under-usage can be explained by real intolerance to ACE inhibitors, i.e. cough. Bart et al. attempt to quantify the use of ACE inhibitors in contemporary, hospital-based management of patients with heart failure. The authors conclude that use of ACE inhibitors is considerably higher than previously reported (80%) and that the most common reason for not using these agents is perceived intolerance (9%).

This conclusion is a most welcome development and suggests that clinical practice in this field is finally interpreting the evidence appropriately. However, although this analysis of the Study of Patients Intolerant to Converting Enzyme Inhibitors (SPICE) registry is clearly of value, there are some major limitations. The reader must view these results critically in that the impact of the methodological flaws in data collection may be substantial and not easily quantified. The good news is that the database is very large (9580 patients) and the cohort is precisely defined. Patients’ records were reviewed from 105 centres in eight countries evenly distributed between North America and Europe relatively recently (between August 1996 and April 1997). All patients had an estimated ejection fraction <35%, 26% were women and the aetiology was coronary artery disease in 63% of patients. There are some useful observations regarding the use of drugs in relation to clinical features, especially the frequent use of aspirin (62%) and the infrequent use of calcium antagonists (17%) and antiarrhythmics (17%) in patients with ischaemic heart disease. It is also interesting that advanced age, female sex, ischaemic aetiology, higher creatinine and North American origin were independent predictors of not being treated with an ACE inhibitor. Surprisingly, systolic blood pressure and serum sodium had no independent predictive value.

A serious source of bias results from the limitation that the information was collected by hospital physicians who participate in clinical trials. This is clearly not representative of usual practice in the participating countries. A randomly selected group of all eligible hospitals in a prospective trial would have been a far preferable design. Another major limitation concerns the method by which these 100 retrospective and ‘consecutive’ cases were ascertained at individual centres. No specific instructions or strategy were required; patients were identified arbitrarily from hospital records of inpatients, outpatients or from other registries such as cardiac catheterization or nuclear imaging laboratories.

Investigator bias may well have been important in that this registry was established in order to identify patients considered intolerant to ACE inhibitors who would represent potential candidates for participation in an efficacy trial with the angiotensin II antagonist candesartan. Investigators were motivated by an opportunity to participate in a clinical trial. Although the authors argue that this bias would tend

References