Innovative treatments for myocardial infarction; design, purpose and consequences of early studies

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In the 1970s much research was directed to the possibility that myocardial infarct size after total occlusion of a coronary artery could be modified by the use of drugs[1–6]. In retrospect much of the thinking at that time was naïve since the survival of any biological tissue requires oxygen and that would, in the context of a myocardial infarction caused by total occlusion of a coronary artery, only be possible through collateral flow. That sets a discouraging limit to the potential for any substantial benefit. The outcome of much research was the appreciation that infarct size was determined largely by the initial area of myocardium at risk, residual blood flow through the suboccluded vessel, collateral blood flow, and the duration of ischaemia. The timing of any intervention was critical. Species differences existed not only in the sensitivity of individual myocytes to ischaemia but also in other critical variables such as collateral blood flow, so that observations derived from animal experiments could not readily be used to predict a clinical application in man. A further major experimental problem was the method for the determination of infarct size and whether a damaged myocardial cell in the infarct area was inevitably going to progress to oblivion. The ultimate test for the determination of infarct size was close examination of tissue by histological methods at a period of about 3 days when cell destruction is complete but remodelling of the ventricle does not cause misinterpretation of the findings. Histology early in the progression of infarction and enzyme release proved unreliable. The calcium paradox and the reoxygenation paradox had already been described. The concept of reperfusion damage was rife[5–7]. This idea encapsulated the fact that at the moment of reperfusion substantial changes took place in the myocardium in terms of cell swelling, loss of ion homeostasis, mitochondrial dysfunction and the onset of an increase in resting tension (myocardial contracture). A second key observation was that benefit by the use of a drug could only be demonstrated if the drug was given prior to the period of ischaemia[8,9]. There was little evidence of benefit of any drug given at the moment of reperfusion or soon afterwards. The damage caused by reperfusion was attributed to cytosolic calcium overload, the uptake of calcium into mitochondria[8,9], the presence of free radicals modifying the function of biochemical pathways and enzyme function[7,10], and activation of sodium–calcium and sodium–hydrogen exchange[11–13]. In general, the predictions from this knowledge were in accord with the outcomes of clinical trials. The trials of intravenous magnesium in myocardial infarction in man are an example where the outcome seems to have been greatly influenced by the timing of the intervention.

The eventual realisation that the reestablishment of blood flow was the dominant mechanism for the diminution of infarct size led to a therapeutic approach dominated by thrombolysis and more latterly by the use of interventions to open vessels and maintain them open. Even then the opening of a major blood vessel does not necessarily lead to reperfusion of the myocardium because many other factors influence blood flow through capillaries. An open artery is not synonymous with normal tissue perfusion. Nevertheless the greatest benefit in the management of patients with myocardial infarction has unquestionably been the reestablishment of blood flow as early as possible after occlusion.

Several interventions other than the use of older drugs such as beta-blockers and calcium antagonists have now been studied in man in an attempt to limit infarct size. These include inhibitors of oxygen radicals[14,15] and modification of sodium–hydrogen exchange[12]. Some agents have been used because they might increase capillary blood flow (e.g. adenosine). Success has not been achieved despite the majority of results emerging from experiments in animal models being favourable.

A second theme runs through the approach to the treatment of myocardial infarction and that is modification of the pathological consequences of an initial occlusion of a coronary artery[16,17]. These include the invasion of the infarcted site by other cell moieties as part of the inflammatory response, the occurrence of haemorrhage within the myocardium and the modification of repair processes, which would contribute to later alterations in shape of the ventricle (commonly called remodelling). In man, the use of steroids was shown to be harmful[18]. Studies with inhibitors of CD18 in man have not shown benefit; CD18 is expressed as part of an integrin on the surface of neutrophils which interacts with intercellular adhesion molecule-1 (ICAM-1) on the endothelium in infarcted myocardium.
The paper in this issue is a study to determine whether one inhibitor of a part of the complement pathway (C1-inhibitor) could be used to modify the inflammatory response to infarction and lead to clinical benefit. The work is innovative and for that reason is of considerable interest. The paper does have considerable limitations and raises important questions as to how early investigations of novel treatments should be undertaken in man. The study was observational in design on a small number of patients, only 22. The authors argue in favour of the design on the grounds that the inclusion criteria were limiting and recruitment would be difficult. C1-inhibitor can predispose to thrombosis; the substance was administered at least 6 h after the onset of infarction so as to avoid any interaction with thrombolytic treatment. The inhibitor was shown to have the expected biological effects in terms of reducing C4 fragments. The outcome was largely assessed by measurement of enzyme release (TNT and CK-MB) and comparison made with historical controls with adjustments for the use of different assays. The authors show that the substance had a biochemical effect but claim safety and hint at efficacy. That is difficult to accept when the number of patients is tiny, the comparison is with a small historical control group, and the entity measured is enzyme release known to be affected by many variables. The possibility of a misleading hint cools the ardour for dalliance with an attractive concept.

The study raises a critical question, namely what is the correct and most appropriate methodology to test out such novel substances in humans so as to minimize any risk to a patient and to maximize the chances of providing a meaningful answer to the initial question? There have been so many false starts in attempting to reduce infarct size. An alternative approach would have been to include a slightly greater number of patients (accepting the delay inevitable with slow recruitment) and to randomize the patients to treatment with the intervention or with an appropriate placebo. Though the authors might claim there is a learning curve in the use of new drugs, particularly in relation to means of delivery and dose, that argument is countered by the fact that in the evaluation of most treatments the learning curve is a crucial piece of information which must be known if that treatment is ever to be used more widely by other groups or in a larger trial which is aimed at obtaining critical outcome information. There are simple statistical methods by which the impact of a learning curve on overall outcome can be minimized, for example by making a decision prior to the onset of the study that the data will be analysed with and without an initial number of patients first going into the trial.

The issue impacts on many areas of cardiovascular research. At the present time innovative treatments are entering into cardiology not only in the management of myocardial infarction but also in the use of devices for pacing, angina, intervention, heart failure and valve surgery. Patients do have high expectations, are altruistic and perhaps even over-enthusiastic to assist the medical profession in advancing medicine. Doctors need to respect that goodwill. Patients would rarely choose to be the early guinea-pigs in the introduction of a new technique or drug because there will inevitably be unknown risks. In cardiovascular medicine careful thought needs to be given to this problem; it is my view that randomization of patients should be used as a scientific method even in early exploratory studies. Early experiments should be designed in such a way that key questions can be answered by the most efficient method with the least risk to patients.

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Risk stratification of patients with right ventricular infarction: is there a need for a specific risk score?

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This issue features a report by Gumina et al. of 580 consecutive patients hospitalized with acute inferior or lateral wall myocardial infarction, 102 (18%) of whom were retrospectively identified as having had right ventricular infarction. These patients had worse in-hospital outcomes than those without right ventricular infarction, and as their Thrombolysis in Myocardial Infarction (TIMI) ST-elevation risk scores[1] increased, so did their in-hospital and long-term mortality rates. However, unlike the cohort of patients in whom the TIMI risk score was originally devised, there was no further increase in mortality with risk scores beyond 4–5[2] (Fig. 1).

The TIMI risk score[1] is one of several that have been developed to risk-stratify patients with acute ST-elevation infarction[3]. These scores have been devised and validated in cohorts of patients with left ventricular infarction, but have not been separately validated in patients with right ventricular infarction. Given the higher morbidity and mortality[4] and the unique pathophysiology of right ventricular infarction, it is important that these risk scores are also evaluated in these patients. The TIMI risk score is a simple bedside scoring system[1]. Eight variables are dichotomously classified as positive or negative, and a weighted score is assigned to positive variables (Fig. 1). The score was originally devised in 14 114 patients from the Intravenous NPA for the Treatment of Infarcting Myocardium Early (InTIME)-II trial, which compared lanoteplase with alteplase, and was validated in patients from the TIMI-9 trial, which compared hirudin with unfractionated heparin[1]. The 30-day mortality rate was <1% in patients with a score of 0, rising gradually and almost uniformly to a rate of 36% in patients with a score of >8, i.e. more than a 40-fold increase (Fig. 1). The two major predictors of mortality are the presence of left bundle branch block (LBBB) and the time of treatment (Fig. 1).

Figure 1 Associations between TIMI risk scores and 30-day mortality in the InTIME-II trial of 14 114 patients[1] ( ) and in-hospital mortality in the Gumina study[2] of 102 patients with right ventricular infarction[2]. LBBB = left bundle branch block.

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