Active management of myocardial infarction

Acute myocardial infarction is a gradual process. In animals ligation of a coronary artery causes cardiac ischaemia with immediate functional and biochemical effects—but so long as the ischaemia is limited to 15 minutes or so recovery is complete and there are no sequelae. Longer, or repeated, periods of ischaemia cause some permanent damage, but useful function can return in time, perhaps implying that the myocardium has been “stunned.” Several hours of ischaemia are necessary to produce transmural infarction and irreversible loss of function.

In man the process is more complex because the underlying cause, coronary atheroma, is generally widespread; collateral blood vessels may be present; the occlusive thrombus is dynamic and may propagate; and both spasm of the coronary arteries and increased cardiac work induced by sympathetic overactivity may temporarily exacerbate the ischaemia. Not surprisingly patients with myocardial infarction present in an untidy fashion with a stuttering history of cardiac pain and variable electrocardiographic and enzymatic changes of infarction. After the initial infarct some patients, especially those with non-transmural infarcts, suffer a recurrence.

Patients with coronary artery disease may develop myocardial infarction as a discrete event evolving over several hours, usually associated with coronary thrombosis, or through repetitive minor episodes of ischaemia, which may be detected before and after the recognised infarct. Any loss of myocardium, overt or covert, alarms cardiologists because the greater the loss the poorer the prognosis. Once 40% of the myocardium is lost cardiogenic shock supervenes, and the mortality exceeds 85%. The evidence from studies on animals suggests that early reperfusion of the ischaemic myocardium can minimise the extent of permanent loss. Should the same approach be applied to man?

Emergency surgery to the coronary arteries is certainly feasible in patients with evolving myocardial infarction. The work of Phillips and his colleagues over the years has also shown that it is safe. They now report commendable results from a combination of coronary artery thrombectomy with bypass grafting in 156 patients. The average time from the onset of chest pain to complete revascularisation in their recent study was six hours, a tribute to the emergency medical services in Des Moines, Iowa. There were only six deaths in hospital (3-8%). At elective reinvestigation two weeks later ventricular function was improved overall, but 107 patients had residual electrocardiographic Q waves. No injuries due to reperfusion had been observed—a remarkable finding, since reperfusion of ischaemic myocardium in animals may cause haemorrhagic infarction, a complication which has also been reported in man after surgical revascularisation and administration of intracoronary streptokinase. Phillips’s use of hypothermia to preserve the myocardium in his patients is one possible explanation for this good fortune.

Reperfusion of the myocardium during acute infarction may also be achieved by catheter techniques. The lysis of coronary thrombi using intracoronary streptokinase is provoking great interest. The early results have been confirmed; four out of every five vessels occluded by thrombus can be recanalised, with improvement in the usual markers of cardiac ischaemia, including ventricular function. Treatment must be started within four hours of the onset of symptoms. Randomised trials are under way and the procedure has been combined with balloon dilatation of the underlying atheroma. Phillips and his colleagues now use this last approach for patients with acute myocardial infarction and single vessel disease, reserving surgery for the medical failures and those with multiple vessel disease (S J Phillips, personal communication).

This is exciting stuff and the intellectual appeal is obvious, but the question posed in an editorial in 1979 remains: “You can . . . but should you?” In Britain we have to take a detached view because our resources do not permit an assessment of such expensive treatment—but we must watch with care. Intravenous streptokinase has been reported to reopen coronary arteries blocked by thrombus in acute myocardial infarction; this may be the way forward.

Hitherto our management of patients with myocardial infarction has been conservative and directed towards alleviating the complications—pain, arrhythmia, and failure. This passive approach is easy and, at the moment, respectable. We must not allow the Nottingham nihilism to stifle our curiosity. We should contemplate acute coronary arteriography in some patients with suspected infarction. The young man with the left main stem lesion and limited myocardial damage stands to gain a great deal from the information, and the earlier the better since there is nothing to suggest that acute arteriography is dangerous. Every patient with cardiac ischaemia, especially those with unprovoked pain, is inviting us to think about what is going on in his coronary arteries, and where, and how much myocardium is at risk. Some will benefit from active management directed towards reopening or bypassing the diseased vessels.

M C Petch

Consultant Cardiologist, Regional Cardiac Unit, Papworth Hospital, Cambridge CB3 8RE
Size of clinical trials

Almost all clinical trials are simple comparisons between two randomized groups, and the number of patients entered into the trial is usually determined in advance. Plainly, however, in most trials the clinical objectives are not taken into account when the size of the sample is chosen. Instead the numbers are usually determined by the length of time or amount of money available, or even some arbitrarily chosen “round” number. Recent reviews of general medical publications1 and of clinical trials in particular2-3 have shown that many studies are too small to have a reasonable chance of detecting a clinically important benefit of the treatment being investigated.

Statistical methods for determining an appropriate sample size have been available for at least as long as clinical trials have been around, but these methods are rarely found in the simpler textbooks on medical statistics. This may explain why calculations of power are still rarely used in the planning of clinical trials—as indicated by three further reviews of publications. The 12% of papers reporting such calculations of power in the most recent review4 is, however, a vast improvement over earlier figures of 0%5 and 1-5%.6

The usual method (although not the only one) by which the size of the sample is determined is closely related to significance testing. The objective of the procedure is to reduce to an acceptable level the risk of obtaining a misleading result by making statistical significance and clinical importance coincide as nearly as possible. The primary requirement is for the physician(s) to specify either the smallest benefit of the new treatment that would be considered to be of clinical importance or the smallest benefit that it would be important not to miss. This may not be easy, for in one sense any improvement might be worth having, but a minimum important difference can usually be specified.

For trials where the outcome measure is qualitative (or categorical)—improved or not improved, survived or died—an estimate is needed of the proportion with that outcome (such as the death rate) that may be expected in one group, usually the controls. When the measured outcome is a continuous variable such as blood pressure or lung function an estimate is needed of the standard deviation of the outcome measure. Such estimates have to be sought from previous studies or from a pilot study. Allowance should be made for the fact that participants in a trial are often a highly selected group.

The researchers must then decide with what probability (known as power) they would wish to obtain a statistically significant result if the true treatment benefit was exactly equal to the minimum important difference. They must also specify the significance level. As would be expected, the greater the power required the greater the size of the sample needed. Customarily a power of at least 80% is specified, though 90% is often preferable. The significance level is usually set at 5%; if a smaller level is set, such as 1%, the sample size must again be increased.

An example of this approach was reported by Hansteen et al.7 “The number of patients to be included in the study was calculated in advance to be 700. This assumption was based on an expected sudden death rate in patients taking placebo at one year of 10-12% and a calculated 50%, reduction in mortality in the actively treated group. This would give an 80% chance of detecting a difference between the two groups significant at the 5% level (two tailed test).”

Several authors have provided graphs for the calculation of sample size for clinical trials with categorical outcome measures,8-10 and a simple nomogram is available for continuous variables.11 The calculated size of the sample refers to patients completing the trial rather than to those entering it, so that due allowance should be made for the likely drop outs. Furthermore, the sample size is calculated to allow a high probability of detecting an important therapeutic effect, if it exists, in the trial as a whole. Its ability to detect different treatment effects between subgroups will be considerably less.

Trials carried out with too few patients may easily fail to detect important therapeutic benefits. There is also the danger of false positive findings, a possibility enhanced by the likely publication bias in favour of “significant” results. There have been several instances where conflicting results from a large number of small trials have led to great uncertainty about the benefit of particular treatments. Though the results from several small trials may sometimes be reasonably combined, statistically, each clinical trial should be designed to be