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Recent advances in cardiology

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Introduction

The rapid advances in cardiology in the latter half of the 1980s were promoted by the success of percutaneous transluminal coronary angioplasty (PTCA) and the significant mortality reduction in myocardial infarction achieved by thrombolytic therapy. As with all new techniques and modes of treatment, subsequent clinical trials and comparisons have better defined the indications of these techniques and their application. Thus in the last few years the advances in cardiology have been more orientated to consolidating our experience with new techniques and better defining their use. Ischaemic heart disease is still a major cause of mortality in the western world and that cardiac intervention may reduce the mortality continues to provide impetus for research in that field. The major issues in clinical cardiology still remain the optimal management of acute myocardial ischaemia and chronic stable angina.

Thrombolysis

Thrombolysis has a well-established role in the management of patients with an acute myocardial infarction. The observation of a reduction in mortality in excess of 20% in placebo controlled trials of streptokinase (SK), tissue plasminogen activator (t-PA) and acylated plasminogen streptokinase activator complex (APSAC) led to further trials comparing the efficacy and safety of the various agents. Efficacy of an agent can be assessed in terms of the re-canalization rate, subsequent left ventricular function and mortality. It is likely that early re-canalization within the time frame of salvaging ischaemic myocardium would result in preserving myocardium hence ventricular function and a reduction in mortality. Indeed, there is evidence that early treatment (within 6 h) has a greater reduction in mortality.¹ However, one of the findings of the Second International Study of

Infarct Study (ISIS-2 1988) was the benefit of late reperfusion up to 24 h. In fact, despite the higher early re-canalization rates achieved with t-PA when compared with SK², this does not result in a difference in preservation of myocardium or final outcome.^{3,4}

The apparent lack of correlation between initial efficacy and final outcome is interesting, and the mechanism for this has not been defined by the recent trials. There are several possible explanations for the lack of correlation. Firstly, the initial efficacy of t-PA may be offset by subsequent re-occlusion. Secondly, delayed re-canalization or other factors may be more important for clinical benefit. Thirdly, the studies to date are inadequate to assess clinical outcome accurately.

Effect of thrombolysis on mortality

There have been two recent megatrials that have compared the efficacy of SK and t-PA. The first is ISIS-3 which although not complete, has released a preliminary report.⁵ This trial compared the efficacy of SK, t-PA and APSAC and determined that early mortality was no different with all three agents. In addition the report indicated a lower incidence of intracerebral haemorrhage with SK. However, there has been some criticism that the dose of t-PA was inadequate.⁶ The second trial is the International t-PA/SK Mortality Trial which also found that the primary end-point of in-hospital death was no different with SK or t-PA.^{6a} Thus it would appear that there is no clinical advantage of t-PA over SK to date, but the controversy is far from over. A new comparative mortality trial called Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) has been launched to compare SK, t-PA and a combination of both agents. The study aims to correlate early and late efficacy with clinical outcome, and hopefully resolve the issue of the correlation between patency and clinical outcome.

A more recent study as part of the larger Thrombolysis and Angioplasty in Myocardial

Infarction (TAMI)-5 trial has also examined the effects of combination thrombolysis with t-PA and urokinase.⁷ Combined therapy was associated with a less complicated clinical course with a lower rate of re-occlusion (2%), lower rate of recurrent ischaemia (25%) and greater freedom of adverse event rate (68%) than either t-PA or urokinase monotherapy. Early patency rates were also lower in the combination group, but late patency was no different. Thus, the early patency rates seem higher with combination therapy but the benefits may not be sustained. Some studies are now focusing on determining factors detrimental to reperfusion. More recently, a study has measured the levels of plasminogen activator inhibitor (PAI) and confirmed elevation during acute myocardial infarction.⁸ The study concluded that high baseline levels of PAI may be detrimental to reperfusion, but the results are not wholly convincing. This is an area where current studies are trying to identify factors likely to cause re-occlusion and prevent them.

ISIS-2 demonstrated the value of adjunctive aspirin medication with streptokinase. Subsequently other studies have examined the role of adjunctive heparin. Nearly all the t-PA trials had involved the concomitant use of heparin. One large TAMI trial⁹ concluded that bolus heparin did not enhance the fibrinolytic effects of t-PA at 90 min. More recent studies, however, have demonstrated higher patency rates at 7–24 h,¹⁰ 48–72 h,¹¹ 48–120 h¹² if heparin is used as an adjunct to t-PA. The data would indicate that it is beneficial to use intravenous heparin with t-PA. The ISIS-3⁵ trial specifically examined the effects of subcutaneous heparin and concluded that concomitant use with a thrombolytic resulted in 25 extra total bleeds per 1,000 patients. This is partially offset by a reduction in mortality of 5 per 1,000 in the first week, although this is not sustained at 35 days. In addition, there is also a modest fall in the re-infarction rate. One of the criticisms of the ISIS 3 trial was the fact that the heparin was administered late and subcutaneously. This is contrary to the practice of most American clinicians who favour the use of early intravenous administration of heparin after t-PA. Thus it is a valid criticism that the reason t-PA failed to show a clinical benefit over SK was the mode and timing of the heparin. However, in the open trial a combination of t-PA and early heparin had a much higher stroke rate. Therefore it could be argued that the higher stroke rate in the ISIS-3 with t-PA would have been even higher with the more aggressive heparin regime.

Other parameters of clinical benefit of thrombolysis

The fact that mortality reduction can occur without improvement in left ventricular function and

also by the late treatment of thrombolytic therapy (6–24 h), it would appear that factors other than early re-canalization are important in determining clinical outcome. This was highlighted by the Tissue Plasminogen Activator: Toronto (TPAT) placebo controlled trial.¹³ The initial study revealed that treatment with t-PA resulted in improved left ventricular function (assessed with radionuclide ventriculography). A subsequent evaluation from the same study tried to establish a relationship between early patency, infarct size (using quantitative thallium scintigraphy) and left ventricular function.¹⁴ Early patency (17 h) resulted in reduced infarct size and improved left ventricular function. However, continued patency at 10 days was not associated with similar salutary effects. This suggests that mortality benefits in such patients are not mediated by myocardial salvage. Other possible mechanisms that could contribute to a reduction in mortality include: limitation of infarct expansion, modification of ventricular re-modelling, increased electrical stability (reducing chances for malignant ventricular arrhythmias) and collaterals supplying ischaemic but viable myocardium.¹⁵ Verification that even late treatment with thrombolysis reduces mortality is being sought by three trials. The EMERA trial is examining the late administration of streptokinase in South America, the LATE study in Europe, North America and Australia with t-PA, and TAMI-6 with t-PA versus placebo at 6–24 h.

Acute angioplasty

The controversy that had existed regarding whether the correct management of acute myocardial infarction should involve thrombolysis or PTCA re-canalization has been largely resolved. Previous large-scale randomized trials failed to demonstrate any additional benefit of PTCA with thrombolysis.^{16–18} This has been supported more recently by The Thrombolysis in Myocardial Infarction II-A study.¹⁹ After 586 patients with acute myocardial infarction were treated with t-PA, they were randomly assigned to either of three treatment groups. The first group was immediate angiography with angioplasty if indicated even if the vessel was occluded, the second group was delayed angiography and angioplasty (but not for occluded vessels) at 18 to 48 h, and the third group was pre-discharge angiography with angioplasty if clinically indicated. The results showed that vessel patency was similar on discharge in all three groups, as was subsequent left ventricular function, re-infarction and mortality rates at 6 weeks. Recently it has become apparent that the morphology of coronary lesions after infarction and thrombolysis changes over the subsequent week,²⁰

such that lesions that appeared 'sinister' gradually resolved.

PTCA in acute myocardial infarction may have a specific role in certain patients with contraindications to thrombolysis. A recent non-randomized study examined 250 consecutive cases of direct angioplasty without thrombolysis.²¹ The success in re-opening the left anterior descending artery (LAD) was 96%, and the right coronary artery (RCA) was 98%. Sustained patency was demonstrated in 95% of LAD lesions and 90% of RCA lesions. Hospital survival was reported as 93% for LAD infarctions and 96% for RCA infarctions. The European Cooperative Study Group in 1988 concluded from a randomized study of t-PA plus aspirin and heparin, with and without angioplasty, that the invasive strategy did not result in a small infarct size, better left ventricular function or lower mortality rate.¹⁸ The study has been re-analysed because it was alleged that the patients randomized to the invasive group had a higher baseline risk.²² The analysis revealed that re-infarction and re-occlusion occurred more frequently in the invasive group. However, in the patients who did not have these outcomes, there was a trend towards improved regional ventricular wall motion in the invasive group. This would suggest that in patients with contraindications to thrombolysis, acute angioplasty is a realistic alternative, especially if the complications of angioplasty can be minimized. Another potential use for acute angioplasty is in cardiogenic shock complicating myocardial infarction, a condition at present with a 90% mortality. A recent non-controlled trial²³ examined the effects of thrombolysis and angioplasty in patients with cardiogenic shock. Thrombolysis with SK only achieved a patency rate of 34%. This is supported by the previous Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio (GISSI)²⁴ which demonstrated a high mortality in patients with cardiogenic shock treated with SK. If angioplasty was successful, the seven day survival was 69%, and if unsuccessful survival was only 20%. At a mean follow-up time of 32 months the successful angioplasty group had a survival rate of 55%, and the unsuccessful group only 20%.

Secondary prevention after myocardial infarction

Beta-blockers and aspirin remain foremost as secondary preventative measures aimed at prolonging life after myocardial infarction. There have been 15 major beta-blocker trials since 1974. Combined results of all trials have demonstrated a reduction of mortality by 22%, sudden death by 33%, non-sudden death by 20% and non-fatal re-infarction by 20% compared to placebo. Most recently, the large Acebutolol et Prevention Secon-

daire de l'Infarctus (APSI) study examined the effects of the partial agonist beta-blocker in the late prevention of late death in high risk post-infarction patients. There was a 48% decrease in overall mortality compared to placebo.²⁵ Vascular mortality was reduced by 58%, the greatest benefit achieved by any beta-blocker. This would suggest that partial agonist activity may be useful and effective in such patients. The use of beta-blockers in the early phase of myocardial infarction has been examined further. The TIMI study¹⁷ demonstrated that the acute addition of metoprolol may improve clinical outcome to a greater extent when combined with t-PA than if t-PA or metoprolol is used alone.

The mechanisms of clinical benefit of beta-blockers in reducing mortality are still being examined. In addition to antiarrhythmic activity and reducing myocardial oxygen requirements, it has been proposed that beta-blockers may reduce the incidence of plaque rupture induced by sudden surges in adrenergic activity.²⁶

Ventricular re-modelling

Recent attention has focused on changes in shape and geometry after myocardial infarction, so called ventricular re-modelling. Detailed echocardiographic studies have demonstrated that early after the acute transmural event there is a phase of infarct extension, where there is acute dilatation and thinning of the area of infarction without further myocardial necrosis. This is characterized by echocardiographic elongation of the non-contractile segment within 2 weeks. In addition, there is a physiological adaption to infarction, with expansion and hypertrophy of the healthy contractile segments. The pathological and physiological dilatation of the ventricle results in maintaining stroke volume despite the infarct-induced fall in ejection fraction. As a result of increased ventricular dilatation, there is an increase in ventricular wall stress that induces further ventricular enlargement.²⁷ Thus the initial ventricular enlargement after infarction to compensate for the loss of contractile tissue culminates in an increasing chamber volume.

Left ventricular volume is a strong predictor of survival after myocardial infarction. Experimental evidence in rats followed by clinical evidence showed that treatment with an angiotensin converting enzyme inhibitor (ACE) can modify ventricular modification after myocardial infarction.²⁸ There is now substantial evidence from three trials (see Heart Failure) that treatment of patients with mild to severe heart failure with enalapril improves survival. It remains to be seen whether ACE inhibitors are indicated in patients with left ventricular dysfunction after infarction without heart failure. Two trials: the Survival and Ventricular Enlargement (SAVE) with captopril given between

days 3 and 16 and the prevention arm of SOLVD trial are currently underway to examine this. In addition, the ISIS-4 trial is set to examine the safety of giving ACE inhibitors in the acute stages of a myocardial infarction. If the results indicate that it is safe and that ventricular enlargement can be curtailed, then ACE inhibitors may find their way on to the growing list of treatment drugs in acute myocardial infarction.

Elective angioplasty

Since the advent of PTCA in 1977, an increasing number of patients with stable angina are being treated with this technique when symptoms are refractory to medical therapy. At Emory University, a recent survey²⁹ indicated that approximately 60% of patients being investigated for coronary artery disease were subsequently re-vascularized, and half of those were with PTCA. The role of angioplasty was traditionally reserved for single vessel disease; however lately there is a significant trend towards multi-vessel angioplasty. Procedural success for angioplasty in such patients was reported as up to 95% despite multi-vessel disease being a factor predisposing to complications. A recent study however has demonstrated that in selected patients, a high procedural success and fewer complications could be anticipated if patients with chronic occlusions and angulated or tortuous lesions were excluded.³⁰ Two features have however limited the success of the procedure: abrupt closure and restenosis, and much research is now focused on the mechanisms and management of such complications.

Abrupt closure

Abrupt closure within the first 24 h of the procedure can be due to either vascular spasm, acute thrombus formation or coronary dissection. The latter is the most common cause and traditionally has been managed by immediate coronary artery bypass surgery (CABG). Over the last few years, improved selection of patients and better expertise have resulted in a decrease in the acute closure rate. The National Heart, Lung and Blood Institute's (NHLBI) PTCA Registry recently reported an acute closure rate of 6.8%³¹ which marks an improvement from the early days of angioplasty where it approached 34%. There is also a trend for an increasing proportion of patients with dissection to be managed without surgery. The NHLBI registry reports an emergency CABG rate of 3.4%³² and Emory and colleagues report a 4.8% rate.³³ The decline in emergency CABG reflects technological advances in dealing with intimal flap

tears using perfusion balloon catheters, intraluminal stents and laser balloon angioplasty (see later).

Restenosis

After endothelial injury induced by coronary balloon angioplasty, a well-described sequence of events ensues which ultimately results in a proliferative intimal lesion and intraluminal narrowing. The reaction is a normal response to vascular injury, and will depend on the extent of injury. Restenosis can be characterized by one of three processes. Firstly, the deposition of platelet thrombi can occur. Secondly, the phenomenon of elastic recoil can occur whereby the initial dilatation is reversed by the elastic elements in the vessel wall. Finally and most importantly, restenosis can occur due to the unrestricted proliferation of smooth muscle cells in the media, and subsequent invasion of the intima. A range of mechanical devices was developed with the aim of reducing restenosis, however to date there is no direct evidence that any of them does.

Mechanical devices

Laser angioplasty

Since the advent of balloon angioplasty and its subsequent limitation of restenosis, much attention has focused on other mechanical devices. Unfortunately, for the most part, these new devices have not demonstrated any reduction in restenosis. There is increasing evidence that excimer laser can be used to treat lesions successfully and with few complications.^{34,35} Laser technology has improved considerably in the last two years with improved flexibility of the fibres (decreased from 200 μm to 100 μm), increased energy fluence (energy applied by the laser) from 30 mJ/mm^2 to 60 mJ/mm^2 , less dead-space and modified catheter tip geometry.³⁶ Several studies have highlighted the concurrent use of balloon angioplasty during laser procedures: Karsch reported 53%, and Webb-Peploe³⁷ 50%. Although increasing success has been reported with the procedure, the restenosis rate does not appear any lower than balloon angioplasty. This could reflect case selection, as the procedure is less tried and tested than balloon. It is being tried on relatively more severe cases.^{36,37} The addition of balloon angioplasty to ensure a better reduction in stenosis increases the restenosis rate.³⁵ Despite the current limitations, excimer laser angioplasty is probably preferable in long diffuse lesions and near coronary bifurcations where it now has a clearly defined role. Most recently, a study compared excimer laser success rates in different types of coronary narrowings.³⁸ The initial success rate was

much higher in more complicated lesions (so-called type B and type C lesions) than the anticipated success rates for PTCA. Laser technology is still being refined, with particular efforts being made to increase the diameter of laser catheters. This would improve the ablative power, reduce the residual stenosis, and hopefully reduce restenosis. Although there has been no randomized study of excimer with PTCA, it would appear that the restenosis rate is similar. In theory, excimer should have a lower rate of restenosis rate as its action is photo-ablative and does not cause thermal injury. This has been shown in a recent *in vitro* study in rabbit iliac arteries where less histological destruction occurred compared to thermal laser, however the degree of platelet deposition was similar and this may be important.³⁹

Laser balloon angioplasty has been used successfully in the management of abrupt closure after conventional angioplasty, with good luminal results. It is thought that the simultaneous application of heat using a neodymium yttrium-aluminium-garnet (YAG) laser with balloon inflation pressure remodels the arterial lumen more effectively than by balloon alone.⁴⁰ *In vivo* studies have demonstrated that various bioprotective compounds such as heparin could be delivered encapsulated in albumin microsphere preparations to the luminal wall and attached to the lumen with laser heat.⁴⁰

Intracoronary stents

One thousand have been inserted. They have been applied in abrupt closure, coronary graft stenosis and post-angioplasty restenosis. The Palmar—Schatz stent is a balloon expandable device that has been evaluated recently.⁴¹ In a series of 247 patients, a 99% delivery success was reported. There were no cases of thrombotic acute closure, a 2.8% subacute thrombosis rate and 1.2% mortality. Restenosis defined as greater than a 50% narrowing was reported as 20%. If however, restenosis is defined as a greater than 0.72 mm intimal hyperplasia, the rate is 50%. The Wallstent is a self-expandable device that has been recently evaluated in 117 patients.⁴² Complete occlusion occurred in 24% of stents (the majority within 2 weeks) and the overall one year mortality was 7.6%. The restenosis rate was 13% (using 50% narrowing criterion) or 32% (using 0.72 mm criterion).

The lower apparent restenosis rate using a stent compared to other devices is probably related to the fact that there is less endothelial injury and better post-procedure patency. This has to be balanced against the increased thrombogenicity of the metal which may initiate smooth muscle proliferation. Stenting has gained a more defined role

in coronary vein graft stenosis where the restenosis rates after stenting are less than that after PTCA. In a recent study of 192 patients with coronary vein grafts, the Palmar—Schatz stent was shown to have a subacute closure rate of 1.6% and a restenosis rate of 19% when implanted into a *de novo* graft and 33% when stenting was performed after prior PTCA.⁴³

Atherectomy

Directional atherectomy (DA) has been in clinical use for 3 years. The technique has demonstrated a high procedural success rate and low complication rate. Acute dissections and flaps are infrequent. More recently it demonstrated a high success rate in the treatment of eccentric lesions.⁴⁴ In the presence of calcified lesions, DA has been shown to be less effective than PTCA.⁴⁵

Rotational atherectomy has been in use for about two years. With this device atherosclerotic material is ground up by a rotating abrasive tip (up to 150,000 r.p.m.). It is thought to be effective in debulking eccentric lesions. More recently a study using the Rotablator™ device reported a high procedural success superior to PTCA for calcified lesions.⁴⁶

Restenosis pharmacotherapy

It is hard to imagine that any mechanical device could reduce endothelial injury, the prime instigator of the proliferative process. Thus, increasing attention is being paid to the mechanism of the proliferative response and its possible modulation. A recent histological study of post-mortem angioplasty specimens clarified the chronological sequence of the process.⁴⁷ Within a few days of endothelial denudation, smooth muscle cells begin to change their phenotypic expression from a contractile apparatus to a secretory one. Over the next few months restenosis is characterized by exudation around the proliferative cells. The unrestricted growth pattern of smooth muscle cells bears some resemblance to neoplasia, which has led investigators to observe the effects of anti-neoplastic drugs in animal models. Angiopectin is a somatostatin analogue which has been observed to inhibit myointimal and lymphocyte proliferation in rabbit carotid vessels, and increase leucocyte migration inhibitory factor.⁴⁸ Colchicine is an agent that binds to the microtubular protein tubulin and prevents its function, causing a reduction in chemotactic activity. In addition it arrests cell division in the metaphase.⁴⁹ Colchicine was assessed recently in a randomized study examining restenosis in man, but unfortunately was shown to be ineffective.⁵⁰ Other animal studies have exam-

ined the effects of other anti-neoplastic drugs in animals: methotrexate having no effect on smooth proliferation, and a combination of vincristine and actinomycin D demonstrating a reduction in subintimal cells. Other non-antineoplastic drugs have also been shown to reduce intimal proliferation. Low molecular weight heparin and normal heparin have been shown to have inhibitory effects on smooth muscle proliferation.⁵¹ Recently attention has focused on ACE inhibitors, and cilazapril in particular. A recent animal study demonstrated that cilazapril suppressed balloon induced proliferative responses, and a combination of cilazapril and heparin reduced neointimal deposition by 90%.⁵² In addition to having anti-thrombotic and anti-proliferative properties, it has also been noted that heparin increases the extracellular matrix deposition in restenotic lesions. Other agents such as nifedipine, diltiazem, warfarin, aspirin and steroids⁵³ have not been shown to have any effect on restenosis.

If an anti-neoplastic agent is subsequently shown to have a beneficial role in preventing restenosis, the problem will reside of the potential side effects of the drugs particularly as it will only arise in a third of patients. One potential solution is to apply some of the newer mechanical devices to ensure only local delivery of a drug, taking advantage of the relative permeability of the arterial wall.⁵⁴ A newer generation of stenting devices with polymer coatings or of biodegradable composition are being developed which could act as 'local drug delivery systems'. Recently, Wolinsky⁵⁴ demonstrated the perfusion of a perforated balloon catheter with marker substances which were taken up by the arterial wall.

Genetic modification of endothelium

Recent advances in recombinant deoxyribonucleic acid (DNA) technology and comprehension of gene regulation have enabled investigators to apply gene therapy in a variety of diseases. Research is now focusing on experimental models of gene modulation of abnormal endothelial and smooth muscle cells. Genes can be modified either by removing a gene sequence, altering the defective sequence or augmenting it.⁵⁵ In order to transfer genes into cells several techniques have been applied: using viral vectors to 'infect' cells, micro-injection of plasmid DNA, electrical manipulation of cell membranes or by incorporating DNA into liposomes. Endothelial cells which have become dysfunctional could become modified with calcitonin gene related peptide to enhance its vasodilator potential. Abnormal smooth muscle cells may become modified to reduce the rate of proliferation. Myocardial cells may become modified to enhance angiogenesis potential in areas of

ischaemic myocardium. Although no experiments have been carried out in man, *in vitro* and *in vivo* animal studies have been encouraging. Gene transfer to the endothelium has been accomplished *in vitro*, with preservation of endothelial phenotype, function and morphology when 'infected' with murine sarcoma viruses.⁵⁶ *In vivo* studies have also demonstrated that gene modified endothelial cells harvested from the Yucatan minipig could be re-inserted in the pigs ileo-femoral artery using a balloon catheter, and subsequent re-examination demonstrated persistent gene expression.⁵⁷ Further studies by Nabel and others^{58,59} demonstrated that endothelial cells could be 'infected' directly *in vivo* to result in altered gene expression, and the result to be maintained. The above experiments used retroviral transfer which would cause worries about true infection if applied to man, thus the technique of liposome transfer of DNA (which has been demonstrated successfully by Nabel *et al.*) would be more acceptable.

Intracoronary imaging

Although coronary angiography is used as the gold standard in the assessment of coronary artery disease, it provides little information about vascular wall architecture and the morphology of composition of coronary lesions. Plaque morphology may play a more important role in predicting clinical outcome of a coronary lesion than conventional angiographic narrowing. Thin fibrous capped lesions with a high concentration of extracellular lipid are more likely to rupture than fibrotic lesions with a low lipid content.²⁰ The fact that the success of angioplasty and potential restenosis is probably also related to plaque morphology has led to a major investigative thrust into coronary imaging with angioscopy and intravascular ultrasound. Coronary angioscopy has been shown to be highly sensitive in detecting intimal flaps, tears and intraluminal thrombi.⁶⁰ Its major limitation is that injection of saline is required to obtain a bloodless field for endothelial visualization. In addition, although it appears more sensitive than angiography in detecting thrombus, it is less sensitive in determining whether it is occlusive⁶¹ and cannot determine vessel run-off or patency after the initial narrowing. The technology is still quite primitive, and advances are sought in reducing the calibre and increasing flexibility. However, its major role in the near future is likely to be in the assessment of the effects of mechanical devices on the endothelium, and restenosis.

Intravascular ultrasound has been developed and provides more detailed information about subintimal structures of the coronary vessels and function effectively in opaque media such as blood.

In vitro validation of catheter mounted transducers in atherosclerotic lesions have had good results. Recently a system was evaluated in the coronary arteries of 30 patients⁶² which had a 5.5 F diameter, was mounted on a 0.014 in guide wire. The transducer was mounted at the tip and operated at 20 MHz. The coronary dimensions and the extent of disease correlated well with angiography. Further development is aimed at reducing the diameter to 3.5 F and further increasing the signal strength of the crystals to further improve imaging.

Valvular heart disease

Transoesophageal echocardiography (TOE) was first developed 14 years ago, and has gradually been refined from an M-mode facility to having colour flow Doppler. The proximity of the probe to the cardiac chambers removed the problem of chest wall interference and intrathoracic attenuation that limits transthoracic echocardiography in up to 30% of cases.⁶³ TOE has become especially useful in the visualization of the aortic root, aortic aneurysms (intimal flaps can be defined), atrial appendages, cardiac thrombi, mitral prosthetic dysfunction and endocarditic vegetations. More recently, the development of biplane probes has overcome the major limitation of TOE, namely single plane imaging. The biplane probe consists of two transducers mounted on the gastroscope shaft such that longitudinal and transverse imaging is possible. Recently a study examined the application of TOE to diagnose left coronary artery mainstem disease, and claimed a sensitivity and specificity of 94% and 90% respectively using colour flow Doppler, which was far better than the transthoracic technique.⁶⁴ In another study the probe was used to grade the severity of mitral regurgitation using maximal regurgitant jet areas, with the sensitivity and specificity approaching 88% and 94% respectively when compared to angiography.⁶⁵ One of the major advantages of the new probe is the better realization of anatomical structure and flow haemodynamics, because of the three-dimensional nature of the recording. The only limitations of the probe are that the two transducers are 1.5 mm apart and thus scan from different points, and currently can only record sequentially. Future refinements of TOE are underway which include a multi-plane head, development of a smaller probe, a more durable dedicated endoscope, and a higher frequency transducer for tissue characterization.

Aortic and mitral valvuloplasty

Aortic balloon valvuloplasty was initially developed as a treatment for aortic stenosis. The initial

results suggested that there was a significant improvement in valve area and gradient. The procedure has subsequently been shown to have a high mortality and complication rate and in addition, a high restenosis rate. Recently the largest series of aortic valvuloplasty was published from the Mansfield Scientific Aortic Valvuloplasty Registry. In a group of 492 patients a mean complication rate of 20% was observed.⁶⁶ This included a mortality of 4.9% and embolic rate of 2.2% in the first 24 h. Although there was an initial modest improvement in valve area from 0.56 cm² to 0.87 cm², this was not sustained at 6 months (mean of 0.63 cm²).⁶⁷ When the majority of patients were re-studied, 59% had recurrence of symptoms within 6 months.

Recurrence of symptoms was more directly related to a fall in ventricular performance than restenosis of the valve. Follow-up of patients revealed an in-hospital mortality of 11.9%, a 6 month mortality of up to 42% and a restenosis rate of 50% within one year.⁶⁸ The in-hospital mortality was no worse for patients with a low cardiac output. It has been argued that the poor outcome of the procedure could be related to the selection bias of the patients, namely the elderly, frail and critically ill. Younger patients (i.e. < 70 years) however were not shown to have a better outcome.⁶⁹

Mitral valvuloplasty in high-risk patients who were considered unsuitable for surgery has recently been assessed in a series of 126 patients.⁷⁰ In patients that with adverse prognostic factors such as: aged ≥ 70 years, poor ejection fraction and pulmonary hypertension, the mortality of mitral valvuloplasty was 9%. Although this is higher than for low-risk patients, it is substantially lower than the 16–26% mortality for surgery on similar high-risk patients.

Heart failure

The first Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I)⁷¹ showed an improvement in survival of patients with severe heart failure treated with enalapril. More recently two clinical trials have been concluded that have examined the effects of enalapril on survival in patients with mild to moderately severe cardiac failure. The first, the Studies of Left Ventricular Dysfunction (SOLVD)⁷² compared survival in an enalapril and placebo-treated groups. There was a moderate reduction in mortality in the enalapril-treated group, particularly at 6 months. The second trial is the second Vasodilator-Heart Failure Trial (V-HeFT-II).⁷³ This study compared the effects of enalapril and a combination of hydralazine and isosorbide dinitrate in patients with a similar severity as those in the SOLVD study. Enalapril

resulted in enhanced survival when compared to the combination therapy, and the improved survival was most prominent in the first year.

Antiarrhythmia therapy

Catheter ablation

Drug treatment is still the mainstay in the treatment of most arrhythmias although the high incidence of side effects and lack of efficacy has led to developments in catheter ablation, arrhythmia surgery and mechanical devices. Catheter ablation was first developed about 10 years ago as an alternative to surgery in the treatment of drug refractory supraventricular tachycardias (SVT). Initially the technique employed high energy that disrupted the atrioventricular (AV) node. The shock was painful which necessitated general anaesthesia, and the patient then required a permanent pacemaker system. In the last two years catheter ablation has also been applied to treat AV junction re-entry and other accessory pathways.⁷⁴ More recently, radio-frequency energy and short duration non-arcing DC pulses have also been evaluated. Scheinman reported successful ablation with radio-frequency ablation with and without DC shock on 97% of cases of AV ablation. Radio-frequency ablation delivers a more localized energy that is less disruptive to adjacent thin-walled tissues and less painful, thus it has less complications and does not require general anaesthesia. More recently, radio-frequency ablation has been used to modify AV node function with AV node re-entry.⁷⁵ Follow-up of 39 patients for a mean of 8 months demonstrated a success in 82% of cases of AV node re-entry. Radio-frequency ablation has also been shown to have a success rate in treating accessory pathways. Jackman⁷⁶ reported accessory pathway elimination in 99% of patients with Wolff-Parkinson-White syndrome by a median of three applications, with a low morbidity and no mortality. Catheter ablation is now replacing surgery as the first line treatment for drug refrac-

tory SVT.

Although the results of catheter ablation in the treatment of ventricular tachycardia (VT), are less impressive, certain subtypes have been shown to be responsive. Recently, Morady⁷⁷ reported a successful DC ablation in nine out of ten patients with idiopathic sustained monomorphic ventricular tachycardia, and recurrent free follow-up in eight in the subsequent 15–68 months. Despite this, ablation for VT in most cases is reserved for patients in whom antitachycardia devices and surgery are contraindicated.

Antitachycardia devices

Antitachycardia pacing with arrhythmia detection has been used to try to prevent, detect and terminate ventricular arrhythmias. More recently increasing attention has been focused on implantable cardioverter-defibrillators (ICD) in the treatment of ventricular tachycardia and fibrillation. About 7,000 non-programmable devices have been implanted world-wide. The rate of sudden cardiac death has an average 2% per year.⁷⁸ Most recently a study claimed a 62.5% survival at 6 years in 955 patients.⁷⁹ The perioperative mortality associated with implantation has been reported at 2–3%, and the most significant complication was infection, occurring in 5% of cases. The currently available ICDs are limited by the fact that they require surgical implantation, spurious discharges and lack of programmability, which results in high-energy shocks that cause patient discomfort and limited battery life. More recently, newer devices are under trial with potential important advantages. These include: programmability, more sophisticated detection, low- and high-energy cardioversion, antitachycardia and bradycardia pacing, and electrophysiological study capability. ICDs implanted by a non-thoracotomy trans-venous route are currently being evaluated. A recent study reported implantation of a device using endocardial and submuscular patch systems non-thoracically without complications in ten patients.⁸⁰

References

Thrombolysis

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