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Reviews in Medicine

Recent advances in cardiology

Clive S. Lawson and D. John Coltart[1]

Department of Cardiology, The London Chest Hospital, Bonner Road, London E2 9JX and [1]Department of Cardiology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK

Introduction

There has been substantial progress in recent years in the understanding of cardiovascular pathophysiology and the application of these advances to clinical cardiology. In addition, medical technology continues to advance at a relentless pace and has provided a host of new diagnostic and therapeutic devices. Perhaps most importantly, the newer therapeutic techniques have been subjected to large controlled trials to establish whether or not they are safe and effective. The purpose of this review is to highlight the most significant advances made in the field of cardiology since the previous such review in this journal 2 years ago.[1]

Coronary artery disease

Management of chronic stable angina

Use of aspirin Although previous studies have established substantial benefits from the use of aspirin following acute myocardial infarction[2] or episodes of unstable angina,[3] until recently there has been little hard evidence to support its routine use in chronic stable angina. In the SAPAT (Swedish Angina Pectoris Aspirin Trial) study, 2,035 patients were randomized to receive either aspirin or placebo.[4] With a mean follow-up of 4.2 years the use of aspirin reduced the incidence of non-fatal myocardial infarction to 0.7% from 8% and the incidence of cardiac events to 8% from 12%, although the overall death rate (8% versus 10%) and the incidence of fatal myocardial infarction (1.5% in each group) were similar in the two groups. Thus, the routine use of aspirin can be recommended in patients with chronic stable angina in view of its capacity to reduce cardiac morbidity, although it does not appear to carry the prognostic benefit accrued when used in acute myocardial infarction and unstable angina. This is probably a consequence of the relatively good prognosis of most patients with chronic stable angina.

PTCA versus medical therapy Despite being introduced into clinical practice in 1977, it has only been in recent years that randomized trials have been performed to allow a precise definition of the role of percutaneous transluminal coronary angioplasty (PTCA) in the management of patients with chronic stable angina. The ACME (Angioplasty Compared to Medicine) study was a prospective study in 212 patients with single vessel coronary artery disease randomized to either PTCA or anti-anginal drug therapy.[5] Those patients undergoing PTCA had earlier and more complete relief of their symptoms, with twice as many patients being free of angina at one month compared with those treated medically. This symptomatic improvement was translated into a superior effect on exercise capacity assessed objectively by treadmill testing.

However, the PTCA procedure is not without risk. Seven patients required coronary artery bypass grafting (CABG) in the PTCA group, compared with none in the medically treated group, two of these as an emergency procedure following complications of the initial PTCA. In addition, 16% of patients required a second PTCA, almost all as a consequence of restenosis. The only death occurred in the medically treated group. Thus, PTCA can offer better symptomatic relief than medical therapy in patients with single vessel coronary artery disease, although this is achieved at an increased cost both in financial terms and with respect to complications.

PTCA versus CABG A series of studies have been initiated to compare the results of PTCA and CABG in similar patient populations. The RITA (Randomised Intervention Treatment of Angina) study,[6] which randomized 1,011 patients, recently

Correspondence: C.S. Lawson, M.A. (Camb.), M.R.C.P. (UK).

reported interim results following a mean follow-up period of 2.5 years. The patients involved could have single- or multi-vessel coronary artery disease, but prior to randomization it was agreed between a cardiologist and a cardiac surgeon that equivalent revascularization could be achieved by either PTCA or CABG. Although the convalescent period was longer following surgery, CABG was initially superior in achieving symptomatic relief with 89% of patients free of angina at 6 months compared to 68% in the PTCA group. However, this difference was less marked after 2 years. The risk of death or myocardial infarction was similar in the two groups, but substantially more patients in the PTCA group required an additional revascularization procedure and more required anti-anginal medication.

As both procedures appear to have similar prognostic implications, one interpretation of these results is that patients who can be revascularized by PTCA should undergo that procedure first, with the option of subsequent surgery if symptomatic relief is not satisfactory. However, the selection of patients for revascularization procedures remains a highly controversial topic. The results of several other comparative studies will be published shortly and hopefully will shed further light on this complex issue.

Acute myocardial infarction

Thrombolysis (i) Choice of thrombolytic agent Three thrombolytic agents are generally available in the UK for the treatment of acute myocardial infarction, streptokinase, anistreplase and t-PA (tissue plasminogen activator). All three agents clearly reduce mortality from acute infarction but differ widely in cost, with streptokinase being the cheapest and t-PA the most expensive. Direct comparisons of these agents have recently been performed. In the ISIS-3 (Third International Study of Infarct Survival) study[7] all three agents were found to be equally effective in reducing cardiovascular mortality, and in the GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivena nell'Infarto Miocardico) study[8] streptokinase and t-PA were also found to be equally effective. In both studies, however, there was an increased number of haemorrhagic stroke in those receiving t-PA. The results of these studies suggested that, on grounds of safety and cost, streptokinase should be used as the standard thrombolytic agent.

Proponents of t-PA have criticized the design of these studies as heparin was administered subcutaneously and not until at least 4 hours following the thrombolytic agent. In contrast, in the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator) trial[9] t-PA was given in an accelerated manner with early intravenous heparin administration. This combination was found to be superior both to streptokinase (with either subcutaneous or intravenous heparin) or the combination of 'standard' t-PA and streptokinase with intravenous heparin. The combination of t-PA and streptokinase had an effect intermediate between those of the individual agents.

Thus, the issue of what constitutes the 'ideal' thrombolytic regimen for acute myocardial infarction remains controversial. This should not obscure the more important consideration that patients with suspected acute myocardial infarction should receive a thrombolytic agent unless it is specifically contraindicated. In the UK considerations of cost will ensure that streptokinase remains the standard thrombolytic for the foreseeable future.

Thrombolysis (ii) Use of heparin The circumstances and manner in which heparin should be used as an adjunct to thrombolytic therapy have been formally addressed in the GISSI-2, ISIS-3 and GUSTO studies.[7–9] In contrast to t-PA, streptokinase and anistreplase themselves cause a relatively prolonged period of systemic anticoagulation. Both GISSI-2 and ISIS-3 indicated that the addition of subcutaneous heparin to these agents was not beneficial with regard to mortality and resulted in an increased incidence of haemorrhagic complica-tions.[7,8] In addition, the GUSTO study showed that, with streptokinase, the effects of immediate intravenous heparin were similar to those of subcutaneous heparin given at 4 hours.[9] Thus, heparin therapy does not appear to be a necessary adjunct to treatment with streptokinase or anistreplase and may be harmful.

The situation is less clear with t-PA. The GUSTO trial results suggest that the use of *early intravenous* heparin with t-PA results in a further reduction in mortality over the combination of streptokinase and heparin.[9] As this additional benefit was not apparent with subcutaneous heparin in GISSI-2 and ISIS-3,[7,8] the results taken together might suggest that intravenous heparin is specifically beneficial when given with t-PA. Such an effect might indeed be expected as t-PA does not have a profound effect on systemic anticoagulation. There has never been a direct comparison of intravenous heparin versus no heparin with t-PA and until such a study is performed it would seem to be prudent to give intravenous heparin when t-PA is used.

Thrombolysis (iii) Late administration of thrombolysis Most major trials of thrombolysis in acute infarction have limited patient entry to the first few hours following the onset of chest pain. These studies showed clear prognostic benefit when therapy was administered within 6 hours, with the

beneficial effect waning beyond this time. However, those studies that continued to enrol patients beyond this time, including ISIS-2,[2] have indicated that there may still be benefit to be gained from administration 6–24 hours after the onset of chest pain. Two recent large studies have sought to define more precisely the role of thrombolysis administered relatively late after the onset of chest pain. In the LATE (Late Assessment of Thrombolytic Efficacy) study, 5,711 patients received either recombinant human t-PA (rt-PA) or placebo between 6 and 24 hours after the onset of symptoms.[10] Patients receiving thrombolysis between 6 and 12 hours had a significant reduction in overall mortality at 35 days, from 12.0% in the placebo group to 8.9%. In the patients receiving treatment beyond 12 hours, however, there was no clear survival benefit, with 35 day mortality rates of 8.7% in the rt-PA group and 9.2% in the placebo group. The EMRAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) group studied 4,534 patients, again between 6 and 24 hours after the onset of symptoms, using streptokinase as the thrombolyic agent.[11] Again, there was no prognostic benefit from treatment given beyond 12 hours. These studies have clarified the time window for effective thrombolytic therapy, with prognostic benefit up to 12 hours after the onset of symptoms but no evidence of benefit beyond that time.

Thrombolysis (iv) Role of out of hospital administration As the efficacy of thrombolytic therapy wanes with time, measures which allow early administration may enhance its beneficial effects. Two studies have examined the safety and efficacy of initiating thrombolytic therapy prior to the patient arriving in hospital. Both used anistreplase which has the benefit of being administered by a single bolus injection. In the EMIP (European Myocardial Infarction Project) study 2,750 patients were randomized to receive anistreplase either when first seen by emergency medical personnel or, on average 55 minutes later, following arrival in hospital.[12] The cardiac mortality at 30 days was significantly lower in patients receiving 'out-of-hospital' thrombolysis (8.3% versus 9.8%), with a trend towards a lower overall mortality (9.7% versus 11.1%). These results indicate that prehospital administration of thrombolysis is both feasible and safe, and appears to provide additional benefit in terms of prevention of cardiac mortality.

The GREAT (Grampian Region Early Administration of Thrombolysis) study[13] showed an even more clear prognostic benefit from home administration of anistreplase, despite involving only 311 patients. Patients were again randomized to treatment initiated at home by general practitioners or on arrival in hospital. There was a 49% reduction in total mortality (from 15.5% to 8.0%) at 3 months in the patients in whom treatment was initiated at home. This apparently enormous benefit may be explained by the difference in time between onset of infarction and the initiation of treatment. The home-treatment group received thrombolysis on average 139 minutes earlier, the difference representing the delay in transfer of patients to hospital from the rural community from which the patients involved in this study were drawn. The effect of this delay is apparent from the very high mortality in the hospital-treatment group, which is much higher than in other hospital-based thrombolytic trials. These results suggest that attention needs to be given to ambulance transfer times which can significantly limit the benefits of thrombolysis and, for patients in rural locations where delays might be anticipated, initiation of thrombolysis by properly trained and equipped general practitioners may be appropriate.

ACE inhibitors following myocardial infarction Following myocardial infarction the left ventricle may undergo a slowly progressive period of remodelling, resulting in left ventricular dilation and progression into heart failure. Evidence from laboratory studies suggests that this process can be attenuated by angiotensin converting enzyme inhibitor (ACE-I) therapy. Three clinical studies have been published which address whether ACE-I therapy is beneficial in patients following acute myocardial infarction.

Patients with mild, or transient, heart failure following infarction are currently rarely commenced on ACE-I therapy; however, in the AIRE (Acute Infarction Ramipril Efficacy) study over 2,000 such patients were randomized to receive either ramipril or placebo.[14] Ramipril had a beneficial effect on prognosis which was apparent after as little as 30 days. At 15 months the mortality rate in patients receiving ramipril was 17% compared to 23% in the placebo-treated group.

The SAVE (Survival and Ventricular Enlargement) study[15] went one step further and assessed the effect of ACE-I in *asymptomatic* patients with significantly impaired left ventricular function (defined as an ejection fraction of $<40\%$) following myocardial infarction.[15] In contrast to the AIRE study[14] there was no effect on prognosis during the first year of treatment, however, as follow-up continued, treatment with captopril was associated with significant survival benefit. After a mean follow-up of 3.5 years survival in the patients treated with enalapril was 25% compared with 20% in the placebo-treated group.

In the CONSENSUS-2 (Second Co-operative North Scandinavian Enalapril Survival Study) trial[16] enalapril was given to patients following infarction irrespective of symptoms or extent of left

ventricular dysfunction. The study was stopped early because two patients treated with enalapril fared *worse* than those in the control group. The major difference between this study and the AIRE and SAVE studies[14,15] was the timing of the initial drug administration. In the CONSENSUS-2 study[16] enalapril was given within 24 hours of infarction, whereas it was commenced later in both AIRE and SAVE.[14,15] Very early initial administration may have a number of adverse consequences, including effects on the inflammatory and healing processes, and detrimental haemodynamic effects in the setting of acute infarction.

At a meeting of the American Heart Association in November 1993 as yet unpublished data from the ISIS-4 and GISSI-3 studies were presented. These studies have confirmed the results of the AIRE and SAVE studies[14,15] and indicate that there is indeed a small but significant prognostic benefit from ACE-I therapy initiated in the first few days following infarction. Mortality in the first few weeks following infarction was reduced from 7.3% to 6.9% in ISIS-4 and from 7.1% to 6.3% in GISSI-3. Whether this benefit is limited to certain patient subgroups, such as those with demonstrably abnormal left ventricular function, remains to be determined from further analysis of the data. Thus, patients with significantly impaired left ventricular function following infarction should be commenced on long-term ACE-I treatment irrespective of symptoms, although it would appear prudent not to initiate therapy within the first 24–48 hours. Furthermore, all of these studies used doses of ACE-I at the upper end of their licensed range, and it would appear that these high doses are required if prognostic benefit is to be gained from their use.

The use of nitrates in the peri-infarct period Nitrates possess a number of properties that may, potentially, be beneficial in the peri-infarct period as an adjunct to thrombolytic therapy, including the capacity to increase collateral flow to the region of myocardium at risk. Both ISIS-4 and GISSI-3 have addressed whether nitrates affect mortality when used routinely in the early stages of infarction, but neither study found any beneficial effect on mortality. Nevertheless, nitrates can afford relief of chest pain and may have beneficial haemodynamic effects in the acute phase of myocardial infarction. The results of these studies should not prevent their use when clinically indicated.

Magnesium In animals models of ischaemia- and reperfusion-induced injury magnesium has a variety of protective effects including enhancement of recovery of contractile function and protection against arrhythmias, in part due to limitation of damaging cellular calcium overload. It has been suggested that magnesium might also protect against ischaemia/reperfusion-induced injury in man. Encouraging results were obtained in the LIMIT-2 study (Leicester Intravenous Magnesium Intervention Trial) which suggested that the routine use of magnesium might save lives in acute myocardial infarction.[17] Early administration of magnesium resulted in a 24% reduction in mortality and a 25% reduction in the incidence of heart failure. Furthermore protection occurred irrespective of whether or not patients received thrombolytic therapy. However, when this was subjected to closer scrutiny in a much larger group of patients as part of the ISIS-4 study, magnesium was found to have no prognostic benefit. Thus, currently available data do not support the routine use of magnesium as an adjunct to thrombolytic therapy.

Nothwithstanding these results, magnesium has a number of interesting properties which can be exploited therapeutically. Amongst these are its complex electrophysiological effects and magnesium is being increasingly recognized as a potent anti-arrhythmic agent.[18] Although never subjected to a controlled clinical trial, numerous case reports testify to the efficacy of magnesium in reverting the heart to sinus rhythm from a wide range of rhythm disturbances, particularly ventricular arrhythmias refractory to conventional pharmacological agents.

Role of PTCA in acute infarction One of the major limitations on the efficacy of thrombolysis is the occurrence of reocclusion of the infarct-related vessel. Reocclusion is particularly likely to occur in the presence of a high-grade residual stenosis of the coronary artery and is associated with increased morbidity and mortality. Several studies have shown, however, that the routine use of PTCA following thrombolysis does not result in additional myocardial preservation or reduced rates for mortality or reinfarction.[19,20] However, three recent prospective randomized trials have compared the efficacy of immediate PTCA used as an *alternative* to thrombolysis.[21–23] In all three studies immediate angioplasty resulted in lower mortality rates and a reduced incidence of recurrent ischaemic events. In addition, the use of immediate PTCA led to shorter in-hospital stays, lower follow-up costs and fewer re-admissions.

Thus, where facilities are available, immediate angioplasty should be considered for patients with acute myocardial infarction, at the very least for those in whom thrombolysis is contraindicated and where infarction carries a high mortality, such as for patients in cardiogenic shock. The major limitation to this approach is access to interventional facilities and personnel. Even in the USA only 18% of hospitals have the capability to provide angio-

plasty services and even fewer can provide the service on an emergency basis.

Novel interventional techniques

Currently, the major drawback of PTCA is the occurrence of restenosis of the dilated coronary segment which occurs in up to 40% of cases. In addition, some lesions can prove impossible to treat by conventional balloon techniques and abrupt vessel closure may be impossible to manage satisfactorily without emergency bypass grafting. In an attempt to improve on the present results of balloon angioplasty a host of novel techniques have been introduced with variable degrees of success.

Stents The use of metal endocoronary stents has proved invaluable in the management of abrupt vessel occlusion occurring as a consequence of intimal dissection of the coronary artery during PTCA. Their use can reduce the requirement for emergency CABG,[24,25] which carries relatively high risks of infarction and death. In addition, initial reports have suggested that restenosis may occur rather less commonly where stents are used as part of the initial PTCA procedure, with rates of between 7% and 18% reported.[26] Should these results be confirmed in larger, long-term studies stenting may become established as a primary procedure for certain lesion types. Lesions in saphenous vein bypass grafts can be particular hazardous to treat by PTCA because distal embolization of friable plaque material occurs in 2–3% of cases. Anecdotal evidence suggests that trapping any debris with a stent may reduce the risk of embolization.

The major drawback of the current generation of endocoronary stents is that they are highly thrombogenic, necessitating the use of very aggressive antithrombotic measures. This results in a significant risk of haemorrhagic complications which occurred in almost 10% of patients in one series.[27]

Directional atherectomy During balloon angioplasty, although coronary stenoses are dilated, the causative atheroma is not removed. A number of devices have been developed to allow the removal of atherosclerotic plaques, with the hope of improving the success rate of the initial procedure and reducing the rate of restenosis, the most commonly used being the Simpson Coronary AtheroCath (Baird Ltd). The use of this device has increased rapidly and in 1992 it accounted for 10% of the worldwide sales of angioplasty devices.

Two randomized studies have compared directional atherectomy with balloon angioplasty and both suggest that the two techniques are associated with similar clinical outcomes. In the CAVEAT (Coronary Angioplasty versus Excisional Atherectomy Trial) study directional atherectomy was associated with a significantly better rate of procedural success and a marginally lower restenosis rate, but at the expense of more complications and higher cost.[28] There was no difference in event-free survival between the two techniques. In the CCAT (Canadian Coronary Atherectomy Trial) study[29] the two techniques were compared for lesions in the proximal segment of the left anterior descending coronary artery, the segment where directional atherectomy is most commonly employed in clinical practice. There were no significant differences between the two techniques in procedural success, complications, restenosis or event-free survival. Stenoses within saphenous vein bypass grafts are frequently bulky and the second phase of the CAVEAT study is currently addressing whether directional atherectomy possesses advantages for the treatment of these lesions.

Laser angioplasty Although a number of laser devices have been designed, only xenon chloride Excimer lasers, which produce ultraviolet laser energy at a wavelength of 308 nm, are in common clinical use. In contrast to conventional balloon angioplasty, Excimer lasers act by photochemical ablation of atheromatous tissue, resulting in its removal. One major limitation of this technology is that the final vessel lumen is determined by the size of the fibreoptic catheter passed into the coronary artery; these currently have a diameter no greater than 2.3 mm. Because of this Excimer laser angioplasty frequently requires balloon supplementation to achieve an adequate lumen size. However, these devices appear to be useful for certain lesion morphologies, particularly ostial lesions,[30] long or heavily calcified lesions, and lesions in saphenous vein grafts.[31] Unfortunately, the restenosis rate appears to be rather higher than that reported following conventional balloon angioplasty alone, and ultimately this will limit the more general use of the Excimer laser.

Rotational devices Both low- and high-speed rotational devices have been introduced as potential alternatives to conventional balloon angioplasty. Initial results with low-speed rotational angioplasty were disappointing, however, with a high incidence of vessel trauma. The Rotablater is a high-speed rotating burr which appears to be particularly useful in diffusely diseased or heavily calcified coronary arteries. Provisional data from 1,362 patients treated with this device are encouraging with an overall success rate of 95% and relatively few major complications in a wide variety of lesions.[32]

Intravascular imaging

Direct imaging of coronary arteries has recently become feasible following the introduction of intravascular ultrasound and angioscopy.

Ultrasound Intravascular ultrasound (that is, using a probe advanced into the artery) is capable of providing cross-sectional images of human coronary arteries. The images produced allow the definition of normal arterial layers and the identification of diseased intima (due to atheroma), injured media (due to vessel dissection) or injured adventitia (due to vessel rupture).[33] Successful PTCA is frequently associated with some degree of dissection of the coronary artery, although this is generally limited in extent and heals without adverse consequence. More extensive dissection, however, can result in abrupt closure of the vessel and even localized dissection has been implicated in the mechanism of vessel restenosis following PTCA. Intravascular ultrasound offers the potential for identifying the extent of dissection following PTCA, allowing prospective studies to determine its role in restenosis and to decide when stent implantation is required due to a high risk of abrupt vessel closure.

Angioscopy In contrast to intravascular ultrasound, angioscopy allows direct visualization of the coronary vessel wall and the nature of any occlusive material. This technique appears to be superior to conventional angiography for the detection of intravascular thrombus and dissection following interventional therapy.[34]

Lipid lowering and atheroma regression

In animal models of hyperlipidaemia-induced atherosclerosis, regression of arterial lesions occurs when lipid levels are returned to normal. Although these plaques are anatomically very different from those of advanced human atherosclerotic disease, recent studies have indicated that some regression can occur in patients with coronary artery disease following a reduction of lipid levels. After 4 years follow-up in the Cholesterol Lowering Atherosclerosis Study (CLAS)[35] angiographic regression of coronary lesions was seen in 18% of patients treated with high doses of nicotinic acid and colestipol, but only in 6% of those treated by diet alone. Similarly, whereas 40% of control patients had new coronary lesions, these were apparent in only 14% of patients in the treatment group, and 52% of treated patients had non-progressive disease compared with 15% of control patients. Favourable changes in coronary lesions were also seen in actively treated patients in the Familial Atherosclerosis Treatment Study (FATS)[36] using a variety of lipid-lowering agents and the St Thomas' Atherosclerosis Regression Study (STARS)[37] using diet alone or diet and cholestyramine. Furthermore, in these studies the regression was associated with a reduction in adverse cardiac events, although in none of the studies was there a reduction in overall mortality.

Although cholesterol-lowering drugs can reduce *coronary* mortality, no study of lipid-lowering therapy has yet demonstrated a beneficial effect on the overall death rate. For ill-understood reasons patients on these agents appear to have an increased death rate due to accidents and suicide. Thus, despite the results of these atheroma regression studies it is still not clear precisely which groups of patients with coronary artery disease should receive lipid-lowering drug therapy. Indeed, with the exception of familial hypercholesterolaemia, it has been suggested that there should be a moratorium on the prescription of lipid-lowering drugs, at least for use in primary prevention in view of these risks and their relatively poor cost effectiveness.[38] On current data it would appear prudent to provide firm advice to all patients with coronary artery disease on the benefits of a lipid-lowering diet (as confirmed in the STARS trial)[37] and to restrict drug therapy to those in whom the cholesterol level remains very high despite such advice.

Effect of birth weight on coronary artery disease

Epidemiological studies have been carried out on middle-aged and elderly adults born in Hertfordshire, Preston and Sheffield, where very detailed records were made on all babies when newborn and during their first year of life. These have indicated that low birthweight babies, and those who gain weight at a below average rate during their first year, are at a substantially increased risk of developing coronary artery disease in later life.[39] Maternal undernutrition is thought to be a major determinant of impaired fetal growth and thus may be of crucial importance in the aetiology of coronary artery disease.

This effect has been interpreted as an example of 'programming', whereby influences during a crucial period of early life can permanently affect the structure and function of developing organs. The nature of this programming remains to be precisely determined, but evidence is accumulating to suggest that low birthweight and poor weight gain are associated with known risk factors for coronary artery disease including adult hypertension, glucose intolerance and raised plasma levels of fibrinogen and apolipoprotein B.[40]

Heart failure

Acute myocarditis

Until recently it was customary to take ventricular biopsies from patients with dilated cardiomyopathy, especially if there were clinical features suggestive of an antecedent viral illness, to look for evidence of acute myocarditis with a view to using immunosuppressive therapy. In a recent study over 100 patients with impaired left ventricular function and histological evidence of myocarditis were randomized either to treatment with prednisolone and cyclosporin or to conventional medical therapy alone. Many patients in both groups showed improvement in left ventricular function but the death rates were the same. Thus, the practice of performing ventricular biopsies solely to establish the diagnosis of mycarditis is no longer justified and such patients should be treated along conventional medical lines.[41]

Drug therapy

Vasodilators The role of vasodilators in the management of chronic heart failure has become more clear following the results of a number of multicentre studies, principally involving the use of angiotensin converting enzyme inhibitors (ACE-Is). Following the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial,[42] which had shown a clear improvement in survival for patients with severe heart failure treated with enalapril over those who received placebo, questions remained concerning the use of these drugs in patients with less severe heart failure and those with asymptomatic left ventricular dysfunction. The SOLVD (Studies of Left Ventricular Dysfunction) trials addressed both of these issues. In the 'Treatment' wing of the study[43] patients with mild to moderate heart failure receiving enalapril also had a clear survival advantage over those who received placebo, suggesting that all patients with symptomatic heart failure should receive ACE-Is unless contraindicated. In the 'Prevention' wing[44] no prognostic benefit was accrued by patients with asymptomatic left ventricular dysfunction (defined as a left ventricular ejection fraction of $<35\%$) from ACE-I therapy. These patients were, however, less likely to progress into heart failure and less likely to require hospital admission. It is debatable if these beneficial effects on morbidity are sufficient to justify the routine use of ACE-I therapy in asymptomatic patients.

Even before the CONSENSUS study,[42] the VeHeFT (Veterans Administration Heart Failure Trial) study[45] had shown that the combination of hydralazine and isosorbide dinitrate afforded prognostic benefit to patients with heart failure. In the VeHeFT-II study[46] this combination was compared directly with enalapril. Although enalapril was superior with regard to prognosis, the combination therapy had some advantages in terms of exercise capacity. The results of these studies indicate the ACE-Is should be first-line vasodilator therapy used in chronic heart failure, but that the hydralazine-isosorbide dinitrate combination can be used as an alternative if ACE-Is are contraindicated or not tolerated. As with studies of vasodilators following infarction, these trials all involved the use of high drug doses. Thus, if these agents are to be used on prognostic grounds, even when patients have relatively mild symptoms, it is essential that they should be used in the highest dose that is tolerated by the patient and within recommended dosage guidelines.

Inodilators A number of inotropic agents have been used in the treatment of chronic heart failure. Although these have beneficial haemodynamic effects acutely and are associated with symptomatic benefit, long-term results have been disappointing. Of the agents marketed to date, all have been found to increase mortality, possibly due to the precipitation of arrhythmias. The latest drug to fall at this hurdle is flosequinan. In contrast to previous inodilators, most of which have been more or less selective phosphodiesterase inhibitors, it had been suggested that this agent had a novel mode of action, possibly involving elevation of intracellular inosine triphosphate levels.[47] Unfortunately, flosequinan is also associated with an increased mortality in treated patients and has now been withdrawn from the market.

Initial reports of a novel agent, vesnarinone, which combines the inodilator activity of the phosphodiesterase inhibitors with potentially antiarrhythmic actions on ion channels, including prolongation of the action potential and slowing of the heart rate, have suggested that this agent may actually improve prognosis.[48] This effect appears to be dose dependent, however, and higher doses are associated with worsening of prognosis. In light of previous experience with inodilator agents, longer terms studies of this agent are required before its introduction into routine clinical practice.

Digoxin Although digoxin is undoubtedly useful in the management of patients with both heart failure and atrial fibrillation, its role in the management of heart failure in patients in sinus rhythm is controversial and its use varies markedly with geography. In many European countries it is unusual for such patients to be given digoxin, whereas in the USA the converse is true and it is unusual for them not to be taking digoxin. In the

1980s a number of studies were performed to try to determine whether digoxin had any beneficial effect in patients with chronic heart failure who remained in sinus rhythm, however, most of these were methodologically flawed. Two recently reported studies have attempted to overcome these design limitations. In the PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin) study patients with mild to moderate heart failure on diuretic and digoxin therapy either had their digoxin withdrawn or continued.[49] Withdrawal of digoxin resulted in a worsening of exercise capacity, more rapid and more frequent failure of medical therapy, and a fall in left ventricular ejection fraction.

The findings were similar in a parallel study, RADIANCE (Randomized Assessment of [the effect of] Digoxin on Inhibitors of the Angiotensin-Converting Enzyme), of the effect of digoxin withdrawal in patients on an ACE-I in addition to digoxin and diuretics.[50] Again withdrawal of digoxin resulted in a worsening of exercise capacity, more rapid and more frequent failure of medical therapy.

Two important issues remain to be resolved. Firstly, although digoxin withdrawal appears to have adverse effects in patients with mild to moderate heart failure, this cannot necessarily be extrapolated to benefit when therapy with digoxin is initiated. Secondly, although digoxin has been used for many years, a number of more recently introduced agents have been shown to have beneficial actions on haemodynamics and symptoms, but later demonstrated to increase mortality. Digoxin has never been exposed to this scrutiny, although a study is currently under way to address this issue.

Cardiac transplantation

Cardiac transplantation remains the most effective symptomatic and prognostic therapy for patients with severe heart failure, although its use is strictly limited by the availability of donor organs. Survival has improved to 69% at 5 years,[51] but the patients require sophisticated medical care. Despite improvements in immunosuppressive therapy, most patients experience an episode of rejection in the first year and 1 in 4 have multiple episodes.[52] Although the threat of rejection reduces with time, patients then become at risk of accelerated coronary artery disease with up to 50% of patients having significant coronary lesions at 3 years.[53] The management of coronary artery disease in these patients is difficult, not least because it is generally asymptomatic and, currently, its accurate detection requires regular coronary arteriography.

Valvular heart disease – aortic balloon valvoplasty

In the 1980s balloon dilation of stenotic aortic valves was introduced to clinical practice. Although the precise indications for the procedure were incompletely defined at that time, it was adopted by some as the procedure of choice for 'sick' patients over the age of 80. Recently, however, Bernard *et al.*[54] have challenged this view as a consequence of their study comparing balloon dilation with conventional surgical valve replacement in well-matched patients with aortic stenosis. Although the in-hospital mortality rates were similar, there were many more deaths in the subsequent follow-up period amongst those patients treated by valvoplasty (52% versus 13%) suggesting that long-term relief of left ventricular outflow tract obstruction was inadequate. The results of this study suggest that the use of aortic balloon valvoplasty should be limited to moribund patients requiring emergency intervention or those with a very poor life expectancy due to other pathology.

Arrhythmias

Adenosine

Adenosine is an endogenous nucleoside that blocks atrioventricular (AV) nodal conduction and has recently been licensed in the UK for use in the treatment of acute arrhythmias. It has a dual diagnostic and therapeutic role, terminating re-entrant supraventricular arrhythmias involving the AV node, slowing the ventricular rate of arrhythmias due to enhanced atrial automaticity, such as atrial flutter, thereby allowing the diagnosis to become more readily apparent and having no effect on ventricular arrhythmias.[55] These properties make it particularly useful for clarifying the diagnosis in patients with a broad complex tachycardia of uncertain nature, that is, ventricular tachycardia or supraventricular tachycardia with aberrant conduction. In contrast to verapamil, which is frequently used inappropriately in such cases and can lead to haemodynamic collapse, the actions of adenosine are very short-lived owing to its very short half-life in the circulation of approximately 1 second, and thus may be used safely under these circumstances. More recently adenosine has been used to reveal accessory atrio-ventricular pathways that are not apparent on the surface electrocardiogram (ECG).

Management of ventricular arrhythmias

Class 1c agents Although drug therapy remains the mainstay of anti-arrhythmic treatment and can

provide excellent symptomatic relief, there is very little evidence to indicate that their use has a beneficial effect on patients' prognosis. Unfortunately, all effective anti-arrhythmic drugs have the potential to promote arrhythmias ('proarrhythmic effect') which affects approximately 15% of treated patients. The importance of this potential has been highlighted by the results of the CAST (Cardiac Arrhythmia Suppression Trial) study.[56] In this trial three class 1c agents, flecainide, encainide and morizicine, were used prophylactically in patients with six or more ventricular premature beats/hour following myocardial infarction. Such patients are at increased risk of sudden death; however, the study was terminated prematurely due to increased cardiac and arrhythmic mortality in the patients receiving flecainide or encainide. The study was continued as CAST II with morizicine but with further recruitment this drug also resulted in excess mortality and this was also stopped.[57]

The implications of this study for clinical practice in this country are not entirely clear, as it is most unusual to treat patients whose only demonstrated rhythm disturbance is ventricular premature beats and who remain asymptomatic. Furthermore, the results of this trial may not be directly relevant to patients with symptomatic sustained ventricular arrhythmias in whom the risk of arrhythmic death is substantially greater. It would appear to be prudent, however, to avoid class 1c agents in patients with established ischaemic heart disease if alternatives are available. Neverthless, it would be wrong to extrapolate these data to other groups of patients in whom class 1c agents can be particularly beneficial, such as those with accessory atrioventricular pathways.

Electrophysiological testing versus Holter monitoring

The results of the CAST study[56] have been interpreted as indicating the importance of demonstrating that drugs used to treat ventricular arrhythmias are effective in individual cases. However, objective testing of the efficacy of anti-arrhythmic drug therapy in patients with sustained ventricular tachycardia and survivors of cardiac arrest is fraught with difficulty. Both invasive electrophysiological studies and non-invasive Holter monitoring have been used to predict whether a drug will prevent the recurrence of an arrhythmia, and both are capable of identifying patients at low risk of arrhythmic mortality. Recently, the ESVEM (Electrophysiological Study Versus Electrocardiographic Monitoring) study reported results from 486 patients prospectively randomized to undergo serial drug testing by electrophysiological study or Holter monitoring.[58] Holter monitoring proved to be the more effective in predicting the efficacy of anti-arrhythmic drug therapy. Of the drugs studied, sotalol was found to be more effective than several other agents (propafenone, procainamide, quinidine, mexilitine, imipramine and pirmenol) in preventing both arrhythmic and non-arrhythmic cardiac mortality.[58]

On the basis of these data the authors suggest that patients with severe ventricular arrhythmias should be treated initially with Sotalol and treatment evaluated by ambulatory Holter monitoring. Whether the data from this study can be extrapolated to the general management of patients with ventricular arrhythmias is, however, open to question. Of the patients enrolled into the study, less than a quarter were eventually randomized, due largely to a requirement that assessment would be possible by both invasive and non-invasive methods. Thus, those actually studied represent a highly selected group that may not be representative of the majority of patients with severe ventricular arrhythmias.

Further studies are required to establish the best way of managing such patients. Of all the currently available antiarrhythmic agents amiodarone is generally considered to be the most effective in suppressing ventricular arrhythmias. Preliminary data are now available from the CASCADE (Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation) study which has shown that empirical treatment with amiodarone results in similar rates of rehospitalization as drug therapy chosen by serial testing.[59]

Radiofrequency ablation for supraventricular tachycardia

Patients with recurrent supraventricular arrhythmias associated with accessory atrio-ventricular pathways (Wolff–Parkinson–White syndrome) may be cured by ablating the aberrant conduction tissue. Previously catheter ablation techniques utilizing high-energy DC shocks have had several limiting adverse effects, including barotrauma and skeletal muscle activation resulting in a requirement for the procedure to be performed under general anaesthetic. Radiofrequency energy has a number of advantages for use in transcatheter ablation. It acts by desiccating cardiac tissue, can produce well-localized lesions, is associated with fewer side effects and procedures can be performed under local anaesthetic. Several centres have reported very encouraging results with this technique.[60–62] Lesch *et al.*[60] have reported an 89% success rate in a series of 109 accessory pathways with less than 10% recurrence of aberrant conduction. Jackman *et al.*[62] have reported a 99% success rate in 177 accessory pathways. The accurate localization of lesions produced by radiofrequency

energy has allowed its use to be extended to ablating re-entrant circuits which lie exclusively within the AV node itself.

Management of atrial fibrillation

Surgical treatment In only a small minority of patients with atrial fibrillation is there a readily reversible cause, and thus in the majority of patients management is directed towards either: (i) reversion to (and maintenance of) sinus rhythm, or (ii) control of the ventricular rate and prevention of thromboembolism. However, it has been suggested that pharmacological therapy to maintain sinus rhythm may result in an increased mortality and the strategy of rate control with anticoagulation is associated with loss of atrio-ventricular synchrony and exposure to a chronic risk of both thromboembolism and bleeding. A novel surgical treatment, the Maze procedure,[63] has recently been described in which multiple incisions are made in the atria to interrupt re-entrant loops. This procedure is highly effective in preventing atrial fibrillation, with only one patient out of 65 undergoing the procedure suffering clinical recurrence of the arrhythmia 3 or more months post-procedure. The technique requires further analysis of its risks and benefits before it can be recommended for more general introduction into clinical practice, but it offers a new therapeutic strategy for patients whose atrial fibrillation cannot be controlled adequately by drug therapy or for those with recurrent thromboembolism.

Prevention of stroke and systemic thromboembolism It is generally accepted that anticoagulation is effective therapy for the prevention of emboli in patients with atrial fibrillation and mitral valve disease. Rheumatic heart disease has become less prevalent in the West in recent decades and alternative aetiologies of atrial fibrillation, particularly ischaemic heart disease, have become relatively more common. Patients with atrial fibrillation associated with structural heart disease are still at significant risk of stroke, even in the absence of valvular disease and 80% of strokes in such patients are embolic. A number of recent trials have examined whether anticoagulation, antiplatelet therapy or both are beneficial in the prevention of stroke and systemic thromboembolic events in patients with what has become termed 'non-rheumatic' atrial fibrillation.

The AFASAK (Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation) study[64] compared the effects of warfarin (with an international normalized ratio (INR) of 2.8–4.2), aspirin and placebo. Warfarin was associated with the lowest rate of major thromboembolic events. The BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation) study[65] showed that even with lower INRs of 1.5–2.7 the use of warfarin reduced the incidence of ischaemic stroke. Similarly, the CAFA (Canadian Atrial Fibrillation Anticoagulation) study[66] showed that warfarin, with an INR of 2–3, reduced the incidence of systemic thromboembolism. Even less aggressive anticoagulation was used in the VASP (Veterans Affairs Stroke Prevention) study.[67] With a target INR of 1.2–1.5 a similar reduction in the risk of stroke was achieved with little in the way of excess bleeding. The SPAF (Stroke Prevention in Atrial Fibrillation) study,[68] the largest of these trials, showed that both aspirin and warfarin were superior to placebo in preventing ischaemic strokes and systemic thromboembolism. The study also identified a number of risk factors for thromboembolism including previous thromboembolism, hypertension, systolic left ventricular dysfunction and left atrial enlargement.[69,70]

A subgroup analysis from these studies has indicated that patients with 'lone' atrial fibrillation (that is, occurring in the absence of structural heart disease), and with no previous neurological event or history of hypertension or diabetes, have a very low annual risk of stroke (1%).[71] With the exception of this subgroup, patients with non-rheumatic atrial fibrillation should be anticoagulated with warfarin unless it is contraindicated, although the target INR may be relatively low (for example, 1.5) unless the patient is deemed to be at a particularly high risk of thromboembolism. Patients with a previous transient ischaemic attack or minor stroke are at particular risk and the EAFT (European Atrial Fibrillation Trial) study has shown that in this group the benefits of anticoagulation are even greater.[72] If warfarin cannot be tolerated 300 mg of aspirin/day provides a rather less effective alternative. The BAATAF study reported that patients with intermittent atrial fibrillation were at similar risk of stroke as those with sustained atrial fibrillation and such patients should also be considered for anticoagulation.

Pacing

Pacing in neurocardiogenic syncope The hypotension responsible for neurocardiogenic ('vasovagal') syncope has two components, peripheral vasodilatation and bradycardia, either of which may predominate in an individual patient. A few patients have frequent, severe attacks which can be extremely disabling. Many such patients have undergone permanent pacemaker implantation and there has been anecdotal evidence of symptomatic benefit. Pacemaker implantation would appear to be rational therapy for those patients in whom hypotension is predominantly due to bradycardia. However, this approach has been

called into question following a study by Sra *et al.*[73] in 48 patients suffering from neurocardiogenic syncope with a profound bradycardic component. Pacemaker implantation was found to be ineffective in preventing symptoms, presumably because almost all patients with neurocardiogenic syncope have a substantial vasodilator component to their hypotension, even where bradycardia is a prominent feature. Unfortunately pharmacological therapy, with vasoconstrictor drugs or mineralocorticoids, is equally unreliable in achieving relief of symptoms and neurocardiogenic syncope remains difficult to treat satisfactorily.

Pacing in hypertrophic cardiomyopathy Patients with left ventricular outflow tract obstruction due to hypertrophic cardiomyopathy can gain symptomatic relief if left ventricular diastolic filling is improved. This can be achieved by slowing the heart rate using beta blockers or calcium antagonists. Patients refractory to medical therapy may require surgical intervention with septal myectomy and/or mitral valve replacement. An alternative approach is the use of sequential AV pacing which can significantly reduce the left ventricular outflow tract gradient.[74,75] The mechanism of this effect is not entirely clear but may be due to altered septal motion as a consequence of abnormal ventricular activation. Sequential AV pacing is required as patients with hypertrophic cardiomyopathy are critically dependent on atrial transport for satisfactory diastolic ventricular filling. However, the reduction in gradient achieved by pacing is less dramatic than following myectomy. Although pacing is less invasive and cheaper than surgery, greater clinical experience will be required with the technique before it can be universally recommended in preference to a myectomy performed by an experienced surgeon.

Use of complex pacemaker systems Permanent pacemaker implantation is a common and, in terms of symptomatic relief, highly effective treatment of bradycardia. In the UK it is usual for the right ventricle only to be paced, on demand, at a constant rate. Advances in pacemaker technology have made pacing of the right atrium a straightforward and reliable procedure. Thus, atrial pacing can now be used in addition to, or instead of, ventricular pacing, and in addition, many pacemakers now have the facility to vary their rate according to the patient's requirements. Beneficial effects of more 'physiological' pacing modes include a reduction in the occurrence of 'pacemaker syndrome', a symptom complex in patients with ventricular pacemakers which may include lethargy, palpitation, dyspnoea, oedema, dizziness and syncope which occurs most commonly due to the loss of atrio-ventricular synchrony.[76] Numerous studies have indicated that complex pacemakers can have beneficial effects on exercise capacity, and subgroup analysis has indicated that dual chamber pacing may also be superior with regard to prognosis in patients with congestive heart failure.[77]

These considerations have led some authorities to suggest that fixed rate ventricular pacing may be outmoded[78] and the British Pacing and Electrophysiology Group have recently published detailed guidelines on optimal pacing modes, dependent of the electrophysiological indication for pacemaker implantation.[79] The universal adoption of these guidelines would have very significant cost implications,[80] however, and the additional benefits of a complex pacing system may not be required by elderly or immobile patients. Thus, the final choice of pacemaker modality should take into account not only electrophysiological considerations, but also the amount of use to which the pacemaker will be put and the general condition of the patient.[81]

Implantable cardioverter-defibrillators No large, well-designed study has yet provided conclusive evidence that any of the current generation of anti-arrhythmic drugs is capable of reducing mortality from ventricular arrhythmias. The development of safe and effective implantable devices which can recognize such arrhythmias, particularly ventricular fibrillation, and deliver DC shocks to revert the heart to sinus rhythm provides the potential for a life-saving intervention in patients at risk of sudden arrhythmic death. The original implantable cardioverter-defibrillators (ICDs) were very bulky, required a thoracotomy for implantation and used large plate electrodes which covered a large proportion of the surface of the heart. Technological advances have resulted in the production of much smaller devices which can be used with endocardial electrodes. These sytems can now be implanted in a manner similar to that for permanent pacemakers, without the requirement for major surgery. The precise indications for ICDs remain to be fully defined, however, certain groups of patients are at high risk of sudden arrhythmic death, including survivors of cardiac arrest and patients with ventricular arrhythmias resistant to drug therapy. In these patients a number of retrospective studies have indicated that implantable cardioverter defibrillators are remarkably effective in preventing sudden cardiac death.[82–84]. Several prospective studies are currently under way to define specifically the groups of patients who will benefit from ICDs. Currently the major limiting factor preventing the more widespread use of these devices is their cost, which is of the order of £10,000 per unit in this country.

Imaging

Transoesophageal echocardiography

Although first described in 1976, it has only been in the 1990s that, with improvements in transducer technology, transoesophageal echocardiography (TOE) has become widely used. The close anatomical relationship between the oesophagus and the heart and great vessels allows high-quality images to be obtained in almost all cases, and a transoesophageal study has rapidly become an integral part of many echocardiographic examinations. Unlike TOE, transthoracic echocardiography frequently produces inadequate views of the left atrium (especially in the presence of a prosthetic mitral valve) and it is rare to obtain satisfactory visualization of the left atrial appendage. As a consequence of this, TOE is a superior technique for detecting cardiac sources of emboli and it has been used to select patients for cardioversion from atrial fibrillation without prolonged preceding anticoagulation where atrial thrombus was not detected.[85] TOE also produces superior images of the inter-atrial septum and, with suitable use of colour-flow Doppler mapping and ultrasonic contrast, has been suggested as the method of choice for the detection of inter-atrial shunts.[86] Because of the high resolution achieved with most TOE examinations the technique is highly sensitive and specific for the diagnosis of vegetations in patients with bacterial endocarditis,[87] and also allows early detection of septal and aortic root abscesses.[88] TOE is also highly sensitive for the detection of malfunctioning mitral valve prostheses. The role of TOE in the diagnosis of aortic dissection is well established and comparative data indicates that it is as good, or better, than the other commonly employed imaging technologies.[89]

MRI

Magnetic resonance imaging (MRI) is capable of providing high definition cross-sectional images of the heart and giving functional information on blood flow through the cardiac chambers. However, much of this information can be acquired using less expensive and less time-consuming noninvasive methods (for example, echocardiography). Coronary arteriography remains the gold standard for assessing the severity of coronary artery disease, but the procedure is invasive and carries a small, but finite risk. MRI has brought noninvasive imaging of the coronary arteries one step closer. In a recent study Manning *et al.*[90] were able to produce interpretable images for 98% of coronary arteries studied, and thereby to infer the presence or absence of significant coronary disease with relatively high degrees of sensitivity and specificity (0.9 and 0.92, respectively). Nevertheless, substantial improvement in resolution will be required before this technique can be adopted into routine clinical practice. Clinically significant stenoses can occur in the smaller, more distal coronary artery branches and this information is required in deciding whether interventional therapy is feasible, and if so which technique is most appropriate. One possible clinical use of MRI coronary angiography might be in screening for the presence or absence of coronary artery disease. In order to be used in this context MRI will need to prove itself in direct comparisons with other non-interventional techniques, such as radionucleotide imaging.

Ultrafast CT scanning

The resolution of conventional computed tomographic (CT) scanning for cardiac structures is limited because the time taken to acquire images with a rotating X-ray source results in motion artefact. The need for a moving source has been obviated, however, by a novel scanner design that produces a rapidly rotating beam of X-rays, allowing a cross-sectional image to be acquired in as little as 50 milliseconds. Scanners of this design have been applied to the measurement of myocardial blood flow and may be able to assess both absolute perfusion rates and differences in subendocardial and subepicardial perfusion.[91]

Congenital heart disease

Fetal echocardiography

Congenital heart disease is the most common congenital anomaly causing death in children. Certain pregnancies are at increased risk of congenital heart disease, particularly if there has been a previous child with congenital heart disease, if the fetus has an extracardiac abnormality on routine ultrasound scanning or if the mother has diabetes or has been exposed to teratogenic drugs. Improvements in echocardiographic equipment now mean that satisfactory views of the cardiac chambers and their major connections can be obtained in most cases from 18 weeks of gestation. The prognosis where defects are detected is poor, with approximately 25% spontaneous fetal loss and of the continuing pregnancies only 30% survival, frequently with severe handicap, to one year.[92] Antenatal diagnosis allows parents the option of terminating the pregnancy at a relatively early stage.

Interventional therapy

Although congenital heart anomalies are generally treated surgically, in recent years catheter-based interventional techniques have been introduced which allow certain lesions to be treated without resort to major surgery. Whilst several of these techniques have become generally accepted, others remain rather controversial. One of the best established techniques is balloon dilatation of pulmonary valvular stenosis, now the treatment of choice for the lesion. In a series of 100 patients balloon dilatation resulted in a significant reduction in the trans-valvular gradient which was maintained at 12 month follow-up.[93] Balloon dilatation for congenital aortic stenosis is more controversial, but can provide an alternative palliative procedure to surgical valvotomy where time is required to allow growth prior to definitive therapy by valve replacement. In the largest series reported to date the mean gradient was reduced from 77 to 30 mmHg, comparable with the results of surgical valvotomy, although there is a small (< 5%) risk of producing severe aortic regurgitation.[94] Coarctation of the aorta is also amenable to balloon dilatation, the major complication being local aneurysm formation. Although surgery remains the preferred initial treatment, recoarctation can occur under which circumstance balloon dilatation has become the treatment of choice.[95]

The other major interventional technique is the transcatheter closure of intra-cardiac defects. In many centres in Europe the procedure of first choice for closure of a patent ductus arteriosus has become the implantation of a double umbrella device (Rashkind occluder). Licensing had been more cautious in the USA where the device is still considered to be investigational by the Food and Drug Administration. In a recent retrospective study from the USA, Gray *et al.*[96] reported that use of the Rashkind occluder is associated with a lower success rate than surgical closure (77.3% compared with 99.8%), a higher rate of major complications (2.7% versus 0.2%) and a significantly higher cost per case. Taken at face value these results might suggest a limited future role for the Rashkind occluder, but complication rates decrease with operator experience and appear to be rather lower in European centres. In addition, the follow-up period in the study by Gray *et al.*[96] was very short and complete occlusion of the ductus following implantation of the occluder may take several months.

Basic science

Most major advances in clinical cardiology follow, although often some years behind, those occurring in basic science laboratories. Currently three areas of research in cardiovascular science offer the prospect of a significant impact on the future practice of clinical cardiology; molecular genetics, the functioning of the vascular endothelium and ischaemic preconditioning.

Molecular genetics

Hypertrophic cardiomyopathy Although hypertrophic cardiomyopathy is a relatively uncommon condition, it is an important cause of sudden death in young people. Familial hypertrophic cardiomyopathy is inherited in an autosomal dominant manner with a high degree of penetrance. The original family studied,[97] and most of these examined subsequently,[98] have been found to have mutations of the genes on chromosome 14 which code for myosin heavy chains, the major structural component of heart muscle. The precise mutations involved differ, but in 40 unrelated families these have been found to involve single DNA base pair substitutions (as opposed to major rearrangements or deletions). This finding has led to the possibility of using genetic techniques for disease screening and antenatal diagnosis. It must be borne in mind, however, that not all familial hypertrophic cardiomyopathy can be attributed to myosin heavy chain gene mutations.[99] Equally importantly, the use of family studies has established that there is considerable variability between families in the severity of the disease, with some families showing far greater morbidity and mortality than others. As more specific mutations are identified it may be possible to predict the prognosis of an individual patient on the basis of their genetic defect.

Dilated cardiomyopathy It is likely that dilated cardiomyopathy has many causes and may represent the end stage of a number of heart muscle diseases. Recently, however, familial screening has revealed that approximately 20% of patients have an affected close relative.[100] This finding lends weight to the common assertion that there may be a significant genetic component predisposing to the development of dilated cardiomyopathy. Indeed, it has recently been demonstrated that one familial form of the disease is linked to a defect on the X-chromosome coding for the protein dystrophin,[101] which forms part of the cytoskeleton of myofibres.

Inherited prolonged QT syndromes The Romano–Ward and Jervelle–Lange–Neilson syndromes are inherited conditions in which prolongation of the QT interval on the ECG is associated with sudden death due to ventricular tachyarrhythmias. Recently linkage has been made between a gene that causes the long QT syndrome

and a segment of chromosome 11 in families with the autosomal dominant form of the disease.[102] It is possible, however, that, as with hypertrophic cardiomyopathy, mutations at several different loci may cause the long QT phenotype. Analysis of other pedigrees will be required before this work may be used to provide a screening test for these syndromes.

Vascular function

Nitric oxide The tone of vascular smooth muscle in resistance vessels is controlled principally by local mechanisms. The importance of the endothelium in local control has been emphasized by the discovery of an endothelial-derived relaxing factor which has now been characterized as nitric oxide.[103] Although this discovery provides a molecular mechanism for the pharmacological actions of nitrates used in the treatment of angina and heart failure, the precise physiological and pathophysiological roles of this novel chemical transmitter have not been precisely defined.

Endothelium-dependent relaxation of human coronary arteries (for example, in response to acetylcholine or serotonin) is impaired by the presence of atheroma and the response may even be converted to vasoconstriction.[104] Similar responses can occur in macroscopically normal segments of coronary arteries in patients with angina.[105] These paradoxical vasoconstrictor responses may explain the propensity of atheromatous vessels to occlude following intimal injury as this results in the release of a number of vasoactive mediators.

One further pathological situation in which nitric oxide release may be of pathophysiological significance is the inappropriate vasodilatation that occurs during septicaemia and which can result in irreversible hypotension. Data from animal models of endotoxic shock strongly suggest that the vasodilatation and hypotension are due, in part, to increased synthesis of nitric oxide.[106] In these animal models inhibitors of the L-arginine nitric oxide synthesis pathway, such as L-NMMA, can restore blood pressure and vascular responsiveness, and recent data indicate that the same occurs in patients with septic shock.[107] Clinical trials are now required to determine whether the use of L-NMMA improves outcome in such patients.

Endothelins Until recently angiotensin II was the most potent vasoconstrictor substance known. However, the identification of a family of peptides derived from endothelial cells, the endothelins, with even more potent vasoconstrictor properties has altered our understanding of the local control of vascular tone.[108] Whilst the precise physiological role of these peptides remains to be completely elucidated, levels of endothelin-1 are greatly increased in patients with congestive heart failure. The levels of endothelin-1 appear to correlate with the degree of haemodynamic disturbance, suggesting that the endothelins may contribute to the excessive vasoconstriction occurring in patients with heart failure.[109]

Ischaemic preconditioning

Perhaps the most exciting advance in our understanding of the pathophysiology of acute myocardial ischaemia in recent years has been the discovery of ischaemic preconditioning,[110] the capacity of the heart to adapt very rapidly to sublethal episodes of ischaemia such that its resistance to the damaging effects of a second ischaemic challenge is substantially increased. Classically this protection is manifest as a reduction in infarct size,[110] although it can also be demonstrated as a limitation in the severity of post-ischaemic contractile dysfunction[111] and ischaemia- and reperfusion-induced arrhythmias.[112] In contrast to pharmacological agents which have proven to be unreliable in reducing infarct size under strict experimental conditions, there have been no reports of failure by ischaemic preconditioning to delay the development of irreversible myocardial injury. Evidence is now accumulating that this phenomenon may occur in man and may be amenable to exploitation in clinical situations in which the heart is exposed to repeated ischaemic insults, such as cardiac surgery[113] and PTCA.[114]

Concluding comments

A number of significant advances have been made over the last few years in the practice of clinical cardiology and it is gratifying that many of these have now been subjected to formal evaluation in controlled clinical trials. In the forthcoming years the many exciting new medical devices, techniques and therapeutic agents outlined above will be subjected to similar rigorous assessment which, hopefully, will define for them specific roles in the management of patients with cardiovascular disease.

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