Proceedings of the British Cardiac Society

The 69th Annual General Meeting of the British Cardiac Society was held at the English Riviera Centre, Torquay on 22 to 25 May 1990.

D Dymond was elected Honorary Assistant Secretary and S Cobbe and K A A Fox were elected to Council on the retirement of M Joy and T Treasure.


New Members 1990: P Adams (Newcastle); V Anderson (Lancaster); K Beatt (London); R Best (Cambridge); C Burrell (London); M Chopra (Cheshire); B Clarke (Southampton); I Cooper (London); M Coupe (Manchester); J Cowan (Leeds); B Craig (Belfast); D Gibbons (Penzance); J Gibbs (London); T Greenwood (London); C Handler (London); N Ineson (London); M James (Bristol); B Keogh (Harefield); R Lamb (Southampton); M Lewis (Cardiff); S Lewis (London); A Newby (Cardiff); S Pringle (Edinburgh); R Riemersma (Edinburgh); U Sigwart (London); I Simpson (London); G Thompson (London); R West (Cardiff); D Yellon (London).

New Corresponding Members: M Ballester (Spain); R Bugiardini (Italy); P Cohn (USA); M Henderson (Canada); S Weinberg (USA).

The following are abstracts of the papers that were presented.

The technique used for balloon dilatation of the mitral valve determines the size of the residual atrial septal defect: a transoesophageal echocardiography study

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The incidence and severity of atrial septal defects after balloon dilatation of the mitral valve have been evaluated with transoesophageal echocardiography (TOE) in 17 patients at a mean interval of 15 (range 3–30) months after the procedure. TOE in combination with colour flow mapping and during Valsalva manoeuvre was compared with similar transthoracic studies designed to detect residual atrial septal defects and transatrial flow resulting from different techniques used for balloon catheter transit and valve dilatation. In seven patients (group 1) the atrial septum was dilated with an 8 mm diameter Olbert balloon, and either a single or double balloon (Mansfield) or bifoil (Schneider) balloon was used to dilate the mitral valve. In 10 patients (group 2) the Inoue balloon, with a slimmer deflated profile, was used after dilatation of the atrial septum with a 14 French vessel dilator. In group 1 a surgically significant atrial septal defect was detected by transthoracic echo studies in one patient and transatrial flow detected by colour flow studies in five. TOE colour flow and contrast studies during the Valsalva manoeuvre detected residual transatrial flow easily in all seven patients. In group 2 patients, when the Inoue system was used, no evidence of surgically significant defects or colour flow detected defects were observed with transthoracic echo. With TOE a small defect was detected in one patient and colour flow in two. A contrast study during the Valsalva manoeuvre showed transatrial septal transit of microbubbles in all 10 patients. This TOE and conventional echo study, therefore, shows that some degree of transatrial defect persists in all patients after balloon dilatation of the mitral valve. After the use of the Inoue balloon system this is minimal, but when atrial dilatation is used significant defects are seen in all patients. TOE with colour flow mapping and Valsalva contrast studies provide a sensitive technique for detecting residual atrial septal defects after balloon dilatation of the mitral valve.

Changing indications for transoesophageal echocardiography: clinical experience in 1000 patients

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Transoesophageal echocardiography (TEE) is a new semi-invasive technique that should be applied only in appropriate clinical situations. We have therefore reviewed our first 1000 TEE studies carried out over 5 years to document the changing indications for TEE and to define its current role. From our first study in July 1985 (with colour flow mapping (CFM) added in the last 686 studies) the proportion of TEE studies to total annual echo studies rose progressively from 1% to 14% (p < 0.001). Five diagnostic areas of maximum benefit were identified. (1) Aortic pathology (19% of all TEE studies); TEE confirmed dissection morphology in 58/60 patients but missed type II dissections in two (confirmed at operation or necropsy). (2) Adolescent and adult congenital heart disease (13%); in this group TEE provided unique information on atrial situs; systemic and pulmonary venous drainage; atrial baffle function; and lesions of the ativoventricular junction, left ventricular outflow tract, and ascending aorta. (3) Mitral prosthetic valve dysfunction (10%); TEE dis-
tistinguished inherent physiological regurgitation from pathological paravalvar regurgitation and showed the number and sites of pathological leakage. (4) Endocarditis (13%); TEE is of unique value in recognising retroaortic abscess cavities and fistulas. Endocarditis was diagnosed in 59% of patients studied. TEE, however, missed vegetations in six patients with prosthetic valves (proved at surgery or necropsy in four patients). (5) Intraoperative studies (15% of all TEE studies in the past three years). Though the proportion of TEE studies in patients in groups 1–4 has not changed, a relatively new indication has been the intraoperative monitoring of ventricular function and assessing mitral valve repair. Analysis of pulmonary venous flow patterns by TEE has been particularly useful in assessing valve repair procedures.

In our experience the major indications for TEE are suspected aortic dissection, endocarditis and prosthetic mitral valve dysfunction (patients with these lesions are now referred for surgery based on TEE alone), and for assessment of congenital heart disease after surgery in older patients. Its role has also expanded into intraoperative and immediate postoperative assessment of ventricular function and surgical repair and into studies in paediatric patients (53 patients).

Cerebral incidents and atrial thrombus in patients with mitral prostheses: a comparison of precordial and transoesophageal echocardiography

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Thirty eight patients with prosthetic mitral valves were studied by precordial and transoesophageal echocardiography. Ten of them were examined within five days of either a stroke (n = 5) or transient ischaemic attack (n = 5). In this subgroup (age range 43 to 76 years) four patients had metallic valves and were fully anticoagulated with warfarin (international normalised ratio 2.9-4.2); six had bioprosthetic valves and only two were anticoagulated (2.7 and 3.8). The results of both echocardiographic approaches were compared. None of the patients had clinical suggestions of endocarditis, and blood cultures were sterile. Precordial echocardiography did not detect the presence of atrial or valvarul clot in any of the 38 patients. In contrast, transoesophageal echocardiography showed atrial clot in four of the 10 patients presenting with a cerebral incident and clot on the valve stent in one. Additionally, atrial appendage clot was detected in one of the remaining 28 patients who were studied for other reasons. Clot was more commonly seen in patients with bioprosthetic valves than in those with metallic valves (four out of seven v one out of four), and extensive atrial clot was detected in two patients with bioprosthetic valves who were not receiving anticoagulant treatment.

The results show that the presence of even extensive atrial thrombus or valvarul clot cannot be excluded by precordial echocardiography in patients with prosthetic mitral valves. Study by the oesophageal route is recommended for such patients who present with either a stroke or transient ischaemic attack.

Comparative values of exercise echocardiography and 99mTc-methoxyisobutylisonitrile single proton emission computed tomography in the diagnosis of myocardial ischaemia

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The relative clinical values of exercise cross sectional echocardiography (EE) integrated with a digital cine loop acquisition system versus 99mTc-methoxyisobutylisonitrile single proton emission computed tomography need to be defined. To determine this, 80 consecutive patients with suspected myocardial ischaemia who were referred for single proton emission computed tomography were also submitted to EE during the same symptom limited bicycle exercise testing. Both EE and single proton emission computed tomography were also visually analysed. For each technique three different responses to exercise were defined: (a) normal (absence of rest and exercise induced abnormalities); (b) ischaemic (reversible perfusion defect and reversible wall motion asynergy); and (c) fixed abnormalities (non-reversible perfusion defect and non-reversible wall asynergy). For analysis the left ventricle, as imaged by both techniques, was divided into six corresponding regions. Seven patients were excluded from the study because of unsatisfactory examinations: four had non-interpretable

Prognostic implications of vegetations and abscess formation in infective endocarditis

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We examined the prognostic implications of the presence of echocardiographic evidence of vegetations and abscess formation in infective endocarditis. A consecutive series of 72 patients was retrospectively identified (44 men and 28 women, age range 21-88 years). All had pre-existing valvar disease including aortic (59%), and mitral (29%) valve disease. Blood cultures were positive in 86%; the organism isolated was a Streptococcus sp in 47%; a Staphylococcus sp in 29%; and diphtheroids, Haemophilus sp, and Klebsiella sp each in two patients. Of the 72 patients, 31 had evidence of valvar vegetations (16 aortic and 15 mitral). Three patients with vegetations died; 13 required valve replacement, and 13 were successfully treated medically. A further seven (10%) patients had evidence of aortic root abscess formation (two had aortic and mitral valve vegetations also). In one an aortic Björk-Shiley valve was in situ. Despite the site of infection only one patient developed conduction disease with new right bundle branch block. One patient died and three required aortic valve surgery. The remaining 36 patients without echocardiographic evidence of vegetations and abscess formation were all successfully treated medically without complication or the need for surgery.

Echocardiography showed vegetations or abscess formation in 50% of patients with infective endocarditis and identified a subgroup with an increased risk of illness and death.
EE and four non-interpretable single proton emission computed tomography. The presence of ischaemia was determined by EE in 31 patients and by single proton emission computed tomography in 35. In all, the response to exercise was concordantly classified in 86% (k = 0.78) of patients. Of a total of 438 ventricular regions analysed by EE and single proton emission computed tomography, 405 gave concordant results (k = 0.80). EE showed a non-ischaemic response in seven patients with positive response on single proton emission computed tomography (four patients with small posteroinferior defects and three with partial redistribution within an infarction). In three patients with an ischaemic response on EE a non-ischaemic result was obtained on single proton emission computed tomography.

EE and single proton emission computed tomography provide remarkably similar information on the presence and localisation of myocardial ischaemia. This has major implications for centres where single proton emission computed tomography is unavailable and for cost effectiveness.

Transoesophageal echocardiographic imaging in the longitudinal axis
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Transoesophageal echocardiography (TE) is an established investigative technique, but its evaluation of the heart and great vessels is restricted to single transverse scan planes. A new probe has been developed that has a second transducer mounted at its tip to produce images in the longitudinal axis, orthogonal to standard transoesophageal images. The anatomical correlates of the images thus produced have not been described, and the advantages and limitations of the probe are unclear. We have therefore evaluated the biplane probe initially in 16 patients, and we have performed correlative echocardiographic and anatomical studies in three postmortem hearts. Clinical experience showed that longitudinal imaging from the stomach better demonstrates the inferior caval vein as it enters the right atrium, the left ventricular apex, and the anterior and inferior walls of the left ventricle. The left ventricular outflow tract and the proximal aorta are also visualised and are better aligned for Doppler examination. From a transducer position in the oesophagus opposite the left atrium unique longitudinal images are available of the superior caval vein, the atrial septum, the right ventricular outflow tract, the mitral valve, and the left atrial appendage and upper pulmonary vein. Ultrasonography of the mitral valve along the whole zone of coaptation is greatly facilitated by a biplane probe; the anterolateral commissure is well seen in a transverse plane, but the posteromedial commissure can be visualised only with the longitudinal plane transducer. The ascending aorta is shown by the longitudinal transducer along on average 7 cm of its length. The biplane probe cannot, however, image the whole intrathoracic aorta as the upper ascending aorta and proximal aortic arch are inaccessible to both transducers. A minor disadvantage is that image resolution is affected by the number of crystals incorporated into the two transducers. Anatomical studies suggested, confirmed, and refined the clinical interpretation of images.

Longitudinal axis TE significantly expands the diagnostic potential of TE, especially in adults with mitral valve disease or acute aortic dissection and in older patients with congenital heart disease.

Variability of serum cholesterol measurements: implications for screening and monitoring
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The reliability of screening for high serum total cholesterol concentration is adversely affected by the variability of serum cholesterol concentrations over time. This problem was investigated using data on repeated serum cholesterol measurements for 14 600 men and women in the MRC Mild Hypertension Trial. For measurements one year apart, the within person coefficient of variation (CV) was 7%, which is substantial compared with the between person CV of 15%. In a screening programme within this person variability may lead to the misclassification of subjects and to inappropriate intervention. For example, 28% of middle aged British men with a single serum cholesterol measurement above 6·9 mmol/l have a long term average cholesterol concentration below that value even without intervention. Using averages of several cholesterol measurements reduces, but does not eliminate, these problems. Furthermore, monitoring the effect of interventions in subjects by sequential cholesterol measurements may be unhelpful or even misleading.

These problems cast serious doubt on the value of screening the general population for high serum cholesterol concentrations.

Who gets coronary angiography in Scotland?
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Scotland has one of the highest incidences of coronary heart disease (CHD) in the world. Its health service is made up of 15 area health boards, which differ greatly in the provision of cardiological services. Facilities for coronary angiography are centred in four area health boards: Greater Glasgow, Lothian, Tayside, and Grampian. We examined whether or not the rate of coronary angiography was commensurate with its need, as judged by the standardised mortality rate for CHD. Data were supplied by the information and statistics division of the Common Services Agency of the Scottish Health Service on patients aged 45–64 having coronary angiography during 1985–7, amalgamated by sex and health board of residence, and com-
pared with the standardised mortality rate for CHD in 1985. The rate for coronary angiography varied from 63-4/100 000 (Dumfries and Galloway) to 174-4/100 000 (Lothian), with comparable rates of CHD. Major differences in the rates of coronary angiography were noted in neighbouring health boards with comparable rates of CHD—for example, Greater Glasgow (169/100 000) v Argyll and Clyde (108-5/100 000). The correlation between rates for angiography and CHD was only r = 0.38. The rates for coronary angiography were highest in those four health boards with angiographic facilities, with the exception of Borders. The rates of coronary angiography in women correlated with that in men (r = 0.89) but ranged from 25% to 50% of that in men and tended to be lower in the outlying health boards despite similar rates of CHD.

These data suggest, as in many areas of health care, that ready access to services rather than need may be the major determinant of uptake and support the need for greater provision of cardiological skill.

**Should prevention of coronary heart disease start at school?**

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Children may have risk factors associated with coronary disease in adults, but data from the United Kingdom is sparse. After ethical approval we enrolled 707 11–15 year old children. Their smoking habits we obtained from a confidential questionnaire; anthropometric data, maturity, and blood pressure were measured with standard methods, and blood lipid concentrations were measured enzymatically. Physical activity was assessed by monitoring heart rate for 12 hour periods. In all, 25% had smoked, but only 11% did so regularly; 11% were overweight. Serum total cholesterol concentration was 4-59 (0-75) mmol/l, HDL-cholesterol concentration 1-39 (0-32) mmol/l, and in fasting children triglyceride concentration was 0-76 (0-43) mmol/l and LDL-cholesterol concentration 2-83 (0-65) mmol/l. Mean systolic pressure was 103 (12) mm Hg and diastolic pressure 69 (10) mm Hg. Over three days one in two girls and one in three boys failed to attain a level of physical activity conducive to cardiovascular health.

In terms of smoking, lipids, blood pressure, and low physical activity a third of the children would be defined as potentially at high risk if they were adults. Other work suggests that children retain their approximate rank order into adult life; thus emphasis in schools about the importance of adopting a healthy lifestyle might be a more effective strategy than trying to alter adult behaviour.

**Excess mortality independent of age in women with acute myocardial infarction**

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We compared the effects of acute myocardial infarction on mortality in men and women, in a review of 1158 patients admitted with acute myocardial infarction to our coronary care unit. Women were slightly older than men (mean age 6-7 v 57-1). The sites of acute myocardial infarction and incidence of previous infarction and other recorded risk factors were similar. Mean mortality was higher in women (n = 287) than men (n = 871) (23-3% v 26%, respectively) at all ages (21-3% v 7-1%, p < 0-0002; 23-9% v 13-6%, p < 0-005; and 42-4% v 15-9%, p < 0-02 in those aged 50–59, 60–69 and > 69, respectively). Heart failure developed in 213/1154 patients: the mortality in patients with heart failure was 41-8%, v 6-6%, for the remainder. Heart failure occurred significantly more often in women (72/214 v 141/727, p < 0-005) and was associated with twice the mortality in men (60% v 32%, p < 0-005).

These data show a greater risk of death from acute myocardial infarction and, in particular, an excess incidence of and death from heart failure in women compared with men after acute myocardial infarction, which is independent of age.

**Ambulatory intra-arterial blood pressure monitoring in healthy individuals: differences between men and women**

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It has been suggested that ambulatory blood pressure monitoring is better than casual cuff methods in predicting cardiovascular events, but lack of reference data on a normal population seriously limits its clinical applicability. We therefore performed 24 hour intra-arterial ambulatory blood pressure monitoring in 50 normal volunteers (cuff blood pressure < 140/90 mm Hg) aged 18 to 74. There were 30 men and 20 women, but there were no significant differences between the sexes with regard to age, cuff blood pressure, or body mass index. A diurnal variation in blood pressure was observed, which was qualitatively similar to that in hypertensive individuals and included a prewaking blood pressure rise. Mean daytime intra-arterial pressures differed little between the sexes (124/74 mm Hg in women v 127/76 mm Hg in men, NS) but was lower at night in women than men (96/52 v 102/59 mm Hg respectively, p < 0-02 for diastolic pressure). Based on this group of subjects we defined the upper limit of normal daytime blood pressure in men and women as 150/90 mm Hg and that of mean night time blood pressure as 130/80 mm Hg in men and 115/65 mm Hg in women.

The lower night time blood pressures in women compared with men with similar daytime pressures may explain why women seem to tolerate similar levels of blood pressure better than men.

**Follow up of glucose tolerance and insulin response in apparently healthy men in relation to coronary heart disease**

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Glucose intolerance or insulin insensitivity may predispose to coronary heart disease. The Edinburgh–Stockholm
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study showed that men in Edinburgh had a higher peak insulin during an oral glucose tolerance test than men in Stockholm. The Scottish men (n = 107) were followed for 12 years, and 11 new cases of coronary heart disease were treated; five men had moved away, and the rest were invited to attend a clinic; 83 attended. All clinical and laboratory investigations were repeated. Fasting glucose, but not insulin, increased over the 12 years from 5·15 (0·06) to 6·05 (0·09) mmol/l (p < 0·001). The area under the glucose curve (0–120 minutes) increased from 220 (12) to 270 (18) mmol/l x minutes/l (p < 0·01). Body weight, subcapsular and abdominal skinfold thicknesses, but not triceps skinfold thicknesses, increased (p < 0·001). The increase in fasting and the area under the glucose curve over the 12 years was related to the increase in body weight (r = 0·22, p < 0·05). Changes in insulin area (0–120 minutes) were related to changes in body mass or skinfold thickness (r = 0·30, p < 0·01).

None of the glucose tolerance test variables predicted new coronary heart disease events over the 12 year follow up, in contrast to classic risk factors.

Transcatheter embolisation of coronary fistulas: an alternative to surgery?

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Percutaneous transcatheter embolisation was attempted in six patients with coronary artery fistulas. The age range was 2 to 67 (median 16) years. In five patients the fistulas were congenital and in one the fistula was a complication of aortic valve replacement. The fistulas originated from branches of left (four patients) and right (two) coronary arteries and drained into the right ventricle (two), right atrium (two), coronary sinus (one), and a bronchial artery (one). Two patients (both adults) had symptoms, one dyspnoea and the other angina. Embolisation was performed with detachable balloons (three patients), multiple coils (two), and a combination of a balloon and coils (one). Angiography immediately after embolisation disclosed good position of the devices in all cases. In one patient spontaneous deflation of the balloon occurred after it had been placed in a satisfactory position, and it embolised into the pulmonary vascular bed without secondary effects. This patient was referred for elective surgery. There were no other complications associated with the procedure. Follow up ranged from 4 months to 4 years (mean 10 months). Three patients underwent Doppler evaluation and two repeat cardiac catheterisation. No residual flow was found.

Transcatheter embolisation is a safe and effective approach to treating coronary artery fistulas and should be considered as the best treatment for coronary artery fistulas.

Advantages of percutaneous balloon dilatation of the mitral valve with the Inoue system

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Percutaneous balloon dilatation of the mitral valve was performed in 51 patients by a single operator. In the first 26 patients (group A) after dilatation of the atrial septum with an 8–10 mm Olbert balloon a guide wire was passed through the left heart and stabilised in the descending aorta. A single balloon (25 mm) was used in four patients, a bifoil balloon (19 mm x 2) in six, and two balloons (15 mm x 2 or 25 + 10 mm) in 15. In the last 25 patients (group B) a 14 French dilator was used to facilitate passage through the atrial septum and the Inoue balloon system was used with incremental inflations to between 25 and 29 mm diameter. Cross sectional echocardiography and Doppler colour flow were used after each inflation to assess the immediate result in group B. Mean left atrial pressure fell from 23·2 (6·1) to 13·9 (7·0) mm Hg in group A and from 25·2 (7·0) to 14·0 (1·0) mm Hg in group B; both results were highly significant (p < 0·001). Mitral valve area echocardiographically estimated three to seven days after the procedure increased from 1·1 to 1·73 cm² in group A and from 1·05 to 1·95 cm² in group B (both p < 0·01).

Improvement in symptoms in both groups was comparable at three to 27 months. Mean screening time (20–2 minutes) and procedure time (42 minutes) were dramatically shorter in group B compared with group A, in which the corresponding mean screening time was 61 minutes and the procedure time 105 minutes. In group A three patients developed cardiac tamponade and three transient cerebrovascular accidents with two surgically significant atrial septal defects whereas none occurred in group B patients. Two patients in each group developed important mitral regurgitation requiring subsequent mitral valve replacement.

The Inoue balloon technique has clear advantages, being more easily and quickly performed and associated with fewer serious acute complications. It should become a standard interventional technique in patients with mitral stenosis and a clear alternative to open or closed surgical mitral valvotomy.

Comparison of the results of balloon dilatation and surgical valvotomy in treating pulmonary valve stenosis

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Balloon pulmonary dilatation has superseded surgical valvotomy in treating pulmonary valve stenosis. Results have shown satisfactory relief of obstruction, but before completely accepting the technique it is prudent to compare the results with those achieved by surgery.

We assessed the residual gradient and severity of regurgitation by ultrasonography in 30 patients who had had balloon dilatation for isolated pulmonary valve stenosis and in 28 who had had surgical valvotomy in the preceding period; thus follow up in the balloon dilatation group was shorter than in the surgical. The valve gradient was obtained by Doppler ultrasonography, and the severity of regurgitation was assessed from the right ventricular size and colour Doppler demonstration of backflow towards the valve not through it.

The valve gradient distribution before intervention was statistically comparable in the two groups. In the surgical group it was reduced from 62 (25) to 13 (6) mm Hg after a follow up of 5·3 years and in the balloon dilatation group from 65 (25) to 25 (15) mm Hg after a follow up of 1·9 years. The difference was statistically significant but not clinically important. The degree of regurgitation from both right ventricular size and Doppler backflow was significantly
greater in the surgical group than in the balloon dilatation group.

Surgical valvotomy produces greater reduction of gradient, but this is not clinically important and is achieved at the expense of a greater degree of pulmonary regurgitation. Long term implications of this are not yet known, but the study supports the continued use of balloon dilatation.

Advantages of immediate surgical standby for coronary angioplasty

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The level of surgical cover for percutaneous transluminal coronary angioplasty (PTCA) is widely debated and ranges from full standby to a team at a remote site. Our practice has been to have a team on standby with a vacant operating theatre adjacent to the cardiac catheter laboratory. From 1984 to 1989, 1262 vessels were dilated in 1032 patients (mean age 53) with a primary success rate of 90% and restenosis rate of 21%. Of these patients, 38 (3.7%), five women (mean age 55-8) and 33 men (mean age 53 0), were referred for urgent surgical revascularisation after a complication of PTCA, 36 direct to operation, and two within 24 hours. All survived surgery; 5/38 had a previous PTCA to the same vessel, and one had previous coronary artery grafts; 4/38 had PTCA for unstable angina; 18 had single, 13 double, and 7 triple vessel coronary artery disease. The vessel damaged at PTCA was the left anterior descending (LAD) artery (n = 23, 15 dissection and eight occlusion); right coronary artery (n = 9, six dissection and three occlusion); circumflex (CX) artery (n = 3, one probeble air embolus and two occlusion); and LAD and CX arteries (one occlusion). Five patients required external cardiac massage into the operating theatre, two of whom had a left main stem occlusion. Four patients received internal mammary grafts and 60 reversed saphenous grafts (1-6/patient). Complete revascularisation was achieved in 94.7% of patients. The operation was performed on the fibrillating heart in nine patients, and cardioplegia was used in 29. Mean aortic cross clamp time was 33 minutes. Inotropic support was necessary for weaning from cardiopulmonary bypass in 9/38 (23.6%), and no patient required an intra-aortic balloon. Q wave myocardial infarction occurred in 6/38 (15.8%). One orthotopic transplant was performed in a patient whose LAD artery became occluded 72 hours after PTCA and who developed cardiogenic shock. The final outcome was: none dead; three patients with angina; one late death, one cerebrovascular accident, one late operation for a new LAD artery lesion; and two patients receiving diuretics or an inhibitor of angiotensin converting enzyme, or both. A further five patients died without referral for surgery (0.48%); three had salvage PTCA for inoperable disease, one had a cerebrovascular accident three hours after the PTCA, and one died suddenly 24 hours after PTCA owing to acute occlusion.

We believe that the immediate availability of surgery for most patients has been largely responsible for the zero surgical mortality and low morbidity.

Coronary angioplasty in recipients of orthotopic cardiac transplants

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The long term survival of heart transplant recipients is limited by the development of coronary occlusive disease (COD). COD is the main cause of graft failure after the first year of transplantation. It is unclear whether percutaneous transluminal coronary angioplasty (PTCA) of epicardial coronary lesions in these patients will produce prolonged arterial patency or improved graft function. Eight patients from our orthotopic cardiac transplant programme had PTCA attempted on 13 lesions up to December 1989. All had significant (70%) stenoses; five stenoses affected the left anterior descending artery; three the right; two the left circumflex; and there were three branch lesions. Primary angiographic success was achieved in 10 of the 13 lesions (71%) with a mean reduction in severity from 81.8 (SE 2.9)% to 12.5 (2.5)%. The guide wire could not be advanced across three lesions in two patients. No acute complications occurred. The mean angiographic follow up consequently is 12.6 (range 4–25) months, and the recurrence rate per lesion is 30%, at present. There has been a subjective reduction in breathlessness in 57% of the successfully treated patients.

PTCA is technically possible in patients with COD after cardiac transplantation. In the short term PTCA offers improvement in arterial patency in cardiac transplant recipients comparable to that in ordinary atherosclerotic coronary disease. Long term improvement in arterial patency, reduction of symptoms, or graft survival remains unclear.

Isolated stenosis of proximal left anterior descending coronary artery: Is angioplasty the treatment of choice?

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Patients with isolated, proximal left anterior descending coronary stenoses have a less favourable prognosis than patients with other forms of single vessel disease. We report the short term and long term results of coronary angioplasty in 295 patients with single vessel disease involving the proximal third of the left anterior descending artery. Before angioplasty 76.6% had severe angina, and myocardial infarction had occurred in 27.5%. During the early part of this series non-steerable catheters were used and the angiographic success rate was 83.4% for all patients, but 90.5% for non-occluded vessels treated since 1985. Major complications included myocardial infarction (4.7%) and emergency surgery (3.4%), and clinical success up to hospital discharge occurred in 79.7%. Follow up for up to 8 (median 2-9) years was 99.7% complete at census. Five years after successful angioplasty cumulative cardiac survival was 96.2%, and freedom from cardiac death and non-fatal myocardial infarction was 93.5% (95.6% and 89.4%, respectively on analysis by intention to treat).

Within five years after successful procedures 11.4% had coronary bypass surgery and 17%, required repeat
fistulation. Freedom from all cardiac events at five years was 73-8%, after successful angioplasty but 63-0%, on analysis by intention to treat. At census 73-6%, were free of angina, 42-8% were not receiving regular treatment for angina, and 56-2% were employed.

These results suggest that coronary angioplasty is an effective treatment option for patients with symptomatic, isolated, proximal left anterior descending coronary disease.

Abnormal circulatory reflexes in hypertrophic cardiomyopathy

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In hypertrophic cardiomyopathy (HCM) exercise hypotension is found in a third of patients despite an increasing cardiac index. Abnormal peripheral vasodilation during supine exercise is associated with exercise hypotension (r = 0.95), suggesting a disturbance of vascular control mechanisms. To evaluate autonomic cardiovascular reflexes we measured changes in blood pressure (BP) and heart rate (HR) in response to Valsalva manoeuvre, posture, and respiration in 30 patients with HCM who had stopped treatment. Patients were aged 14–71 (mean 40). Blood pressure was measured intra-arterially with simultaneous electrocardiographic recording. Patients performed the Valsalva manoeuvre by supporting 35 mm Hg for 15 seconds. During the Valsalva manoeuvre 14 patients had <15%, increase in diastolic BP, suggesting impairment of baroreflex. Nine patients had <20%, increase in HR in response to a fall in pulse pressure >20 mm Hg, six of whom also had impaired rise in diastolic BP. Five patients had a Valsalva ratio of longest to shortest RR interval <1.41, implying impaired response. Nine had a reduced HR response to standing with a ratio of change in HR <1.04. Twelve had a mean HR change from inspiration to expiration over six respiratory cycles <15 breaths/minute of whom nine also had impaired Valsalva responses. Impaired autonomic reflexes were associated with non-sustained ventricular tachycardia but not with other clinical, echocardiographic, or 48 hour electrocardiographic variables; increase in HR and the ratio of percentage increase in diastolic BP to that in HR with Valsalva manoeuvre were less in patients with ventricular tachycardia (16 (11) v 33 (17), p < 0.03, 0.9 (0.7) v 0.3 (0.2), p < 0.01 respectively). Similarly, respiratory reflex and postural change in heart rate reflex were less (10 (5) v 17 (6); 1.2 (0.2) v 1.0 (0.06), p < 0.04) in those with ventricular tachycardia. These data suggest that impaired autonomic function is common in HCM and is strongly associated with a recognised marker of increased risk of sudden death.

Abnormal baroreceptor sensitivity in hypertrophic cardiomyopathy

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Exercise hypotension has been shown in about a third of patients with hypertrophic cardiomyopathy (HCM) and is due to a fall in systemic vascular resistance despite an increasing cardiac output. Abnormal peripheral vascular responses correlate with exercise hypotension (r = 0.95) and are strongly associated with young age and a family history of sudden death. To examine the relation between inappropriate peripheral vasodilatation and baroreceptor sensitivity 27 consecutive patients aged 14–71 (mean 41) with HCM were evaluated. Peripheral vascular responses were assessed by forearm plethysmography with a mercury in silastic strain gauge. A mean of five recordings was made at rest and at peak of symptom limited supine bicycle exercise. Results are expressed as percentage change in forearm blood flow (FBF). Baroreflex sensitivity (BS) was assessed by incremental intravenous doses of phenylephrine (100–800 µg). The slope of the regression line relating rise in systolic blood pressure to the succeeding RR intervals (mscconds/mm Hg) was used to express baroreflex sensitivity. FBF decreased by 67 (44%) (range 174 to 230) in 15 (75%) and increased by 23 (17%) (range –4 to 62%) in 12 (45%) (p < 0.001). Baroreflex sensitivity was 12.01 (6.3) msconds/mm Hg (range 2–23) msconds/mm Hg in the 27 patients. In the 12 with a normal decrease in exercise FBF the baroreflex sensitivity was 9.89 (6.0) msconds/mm Hg compared with 14.6 (5.8) msconds/mm Hg in those with an abnormal vascular response (p = 0.05). Univariate analysis showed that of 10 clinical, cross sectional and Doppler echocardiography, and ambulatory electrocardiographic variables only young age (30 (12) v 48 (15) years, p = 0.002) was more common in patients with reduced baroreflex sensitivity. Analysis of covariance to take account of age on baroreflex sensitivity showed that the increased sensitivity in those with abnormal vasodilatation was independent of age (p = 0.007).

The association of increased baroreflex sensitivity with abnormal peripheral vascular responses in young patients with HCM provides strong evidence for altered haemodynamic control as a potential mechanism for sudden death.

Clinical and prognostic significance of enterovirus infection and its persistence in myocarditis and dilated cardiomyopathy

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To investigate the role of enterovirus infection and its persistence patients with suspected heart muscle disease were prospectively evaluated clinically and with endomyocardial biopsy. Virus was detected in biopsy tissue with an enterovirus group specific hybridisation probe. One hundred and twenty three patients (mean age 44, range 6–70) were assessed. Forty one patients (34%) were positive for the presence of the virus and 79 (65%) were negative, of whom 3 had specific heart muscle disease on biopsy and were excluded from subsequent analysis. The two groups did not differ significantly in age, clinical presentation, or haemodynamic characteristics. At follow up (mean 24 months, minimum 12 months), however, patients who were positive had a decreased likelihood of survival (75%, v 93%, p < 0.001). Follow up biopsy was performed in 16 patients (six positive and 10 negative). Of the patients who were initially positive, two remained positive whereas four had become negative. This change was
associated with a clinical improvement in three patients. None of the patients initially negative had become positive at repeat biopsy. These data show that patients who have enterovirus detected on endomyocardial biopsy with a hybridisation probe have an adverse prognosis. Of the patients who survive, a proportion are negative for virus at follow up biopsy. This may reflect virus clearance in this group.

These observations further implicate enterovirus in the pathogenesis and prognosis of myocarditis and dilated cardiomyopathy.

Idiopathic dilated cardiomyopathy: HLA association and relation to clinical and immunological features

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To identify genetic markers in dilated cardiomyopathy (DCM) and to relate them to clinical and immunological features we studied the frequency of HLA antigens and the presence of cardiac antibodies in a patient population from northern Italy and in controls from the same region. Eighty patients with DCM (65 men, 15 women; mean age 43 (10); mean duration of symptoms 33 (34) months) and 400 healthy blood donors (322 men, 78 women; mean age 38 (10)) were studied. Five patients were in New York Heart Association class I, 25 in class II, 48 in class III, and 2 in class IV. HLA typing (class A, B, C, and DR) was performed on peripheral lymphocytes with the microlymphotocytosis assay. The significance of the deviation of HLA antigen frequencies and the strength of associations was measured using Woolf’s formulae; p values were corrected for multiple comparisons (p_C). Cardiac antibodies were detected by indirect immunofluorescence on normal human heart muscle and skeletal muscle. The prevalence of cardiac antibodies in DCM was: organ specific 33%, partially organ-specific 23%, and cross reactive with skeletal muscle 7%. Frequencies of HLA-A,B,-C were similar in patients with DCM and in controls. There was a positive association with HLA-DR4 (17/80, 21%, in DCM v 43/400, 10.7%, in controls, p = 0.03; relative risk (RR) 2.30) and with HLA-DR5 (37/80, 46%, in DCM v 126/400, 31.5%, in controls, p = 0.03; RR 1.87) and a negative association with HLA-DR3 (10/80, 12.5% in DCM v 118/400, 29.4% in controls, p_c = 0.001; RR 0.36). Age, sex, symptom duration and severity, and prevalence of cardiac antibodies were similar in patients with and without HLA-DR3, DR4, and/or DR5.

Thus HLA-DR4 and HLA-DR5 are markers of susceptibility to DCM but, unlike in other autoimmune diseases, do not seem to influence antibody production or progression or severity of the disease.

Upright tilt in investigation of syncope in hypertrophic cardiomyopathy

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Syncope is a common symptom in hypertrophic cardio-

Myopathy (HCM) and is associated with an increased risk of sudden death, but the mechanisms of syncope remain unclear. Upright tilt, alone or combined with intravenous isoprenaline, has been used to reproduce symptoms in cases of unexplained syncope, but the potential of this investigation has not been assessed in HCM. Twenty four patients with HCM, 15 with a history of syncope and nine without, were submitted to upright tilt at 60° for 45 minutes and, if tolerated, further 10 minute tilts during infusions of isoprenaline at 1, 2, and 4 µg/mg/minute. Electrocardiography, heart rate, blood pressure and cross sectional and Doppler echocardiography were monitored throughout. During tilt alone three patients with a history of syncope and one without showed syncope with profound hypotension, variable bradycardia (prolonged asystole in one patient) and reduced ventricular diameter and contractility on echocardiography. With isoprenaline three of nine patients with a history of syncope and none of eight patients without developed presyncope associated with the development of high outflow tract gradients. In addition to these episodes mildly symptomatic or asymptomatic transient falls in blood pressure (systolic <100 mm Hg) were noted, particularly in syncopal patients with a history of syncope. Overall, patients with a history had a higher incidence of total hypotensive episodes than patients without (p < 0.01).

Upright tilt in hypertrophic cardiomyopathy may reproduce syncope in some patients. The addition of isoprenaline may induce syncope in more patients but through a different mechanism. Patients with a history of syncope are more likely to develop hypotension during tilt than patients without.

Borrelia burgdorferi infection: an aetiological factor in dilated cardiomyopathy?

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The aetiology of dilated cardiomyopathy remains obscure in many cases. Borrelia burgdorferi, a tickborne spirochaete, and the causative organism of Lyme disease, is known to produce both cardiac arrhythmias and myocarditis. Serum samples from 150 patients with suspected heart muscle disease who had cardiac catheterisation with a view to endomyocardial biopsy were examined for evidence of borrelial infection. Positive results for Lyme disease were obtained in 26 samples from 18 patients (12%) when tested by standard serological techniques for B burgdorferi with enzyme linked immunosorbent assay (ELISA), indirect immunofluorescence, and immunoblotting for IgG antibody. In 14 of the 18 patients (78%) there was a clinical picture of either dilated cardiomyopathy (seven) or myocarditis (seven). Myocardial histology was consistent with acute or past myocarditis in nine patients and with dilated cardiomyopathy alone in six. Of the remaining four patients, two had significant coronary artery disease and two hypertrophic cardiomyopathy. Sixteen per cent of patients with either dilated cardiomyopathy or myocarditis were positive for B burgdorferi compared with 6% of patients with other diagnoses (p < 0.05). These data show a much higher prevalence of antibody to B burgdorferi among patients with heart muscle disease than in the control population.

Though a direct causal relation has not been established,
these findings suggest that *B. burgdorferi* may be a possible aetiological agent in dilated cardiomyopathy or in patients with suspected heart muscle disease.

**Mapping of gene for familial hypertrophic cardiomyopathy and analysis of genetic heterogeneity**

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We have recently reported the mapping of a gene for familial hypertrophic cardiomyopathy (FHC). Linkage analysis was performed with 41 DNA probes, selected from a panel of 120 probes that identify polymorphic loci spaced throughout the genome, to identify a locus that was co-inherited with disease. A DNA probe identifying a restriction fragment length polymorphism (RFLP) previously mapped to chromosome 14 disclosed two alleles which were co-inherited with the phenotypic presence or absence of FHC in a family with 20 surviving affected members, 24 deceased affected members and 57 unaffected members. There were no recombaiinations (crossovers between the loci in meiosis). Multipoint analysis using the LINKAGE program yielded a logarithm of the odds (LOD) score of +9.37 at a recombination distance of zero. This is equivalent to odds of greater than 2 000 000 000:1 in favour of the FHC locus in this family being on chromosome 14 (band q1). To investigate whether the same chromosomal locus was responsible for disease in other families with FHC members from three additional families were studied by electrocardiography, cross sectional or Doppler echocardiography, and linkage analysis. Twenty two family members had evidence of FHC with unexplained left or right ventricular hypertrophy, or both. Blood samples were obtained from each family member and continuous cell lines established as a source of DNA. Linkage analysis was performed using three probes, CRI-L436, CRI-L329, and pSCI14, which identify polymorphisms at chromosome 14q1, to determine whether these loci are co-inherited with disease states. Of the three new families, one was found to exhibit tight linkage to the pSCI14 locus, with no recombinants in 13 informative meioses. The two other families, however, did not show linkage to these probes; multipoint analysis using the LINKAGE program yielded significant negative LOD scores in both families, excluding linkage to the chromosome 14q1 locus.

These data show that there is genetic heterogeneity in families with similar phenotypic expression of FHC.

**Effects of acute ischaemia on calcium release channel of the sarcoplasmic reticulum: possible role in myocardial stunning**

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The calcium release channel (CRC) of the sarcoplasmic reticulum (SR) is central to the control of the cytosolic calcium concentration and hence the contractile state of the heart. In this study we have investigated the effects of normothermic ischaemia on the CRC from sheep heart. Tritium labelled ryanodine is a specific marker for the CRC, and its binding to a mixed microsomal membrane fraction isolated from sheep myocardium after 0-120 minutes of ischaemia has been used to assess CRC density. Yield of the microsomal membrane fraction was unaffected by ischaemia, but a time dependent reduction in binding sites (57% (SE 5 1) after 60 minutes) indicated CRC degradation. The yield of junctional SR membranes, obtained by fractionation of the microsomal membrane fraction on sucrose density gradients, was greatly reduced by ischaemia, but single CRCs incorporated into artificial planar phospholipid bilayers from tissue subjected to up to two hours of ischaemia seemed normal and were able to bind ryanodine. The activation of proteases or the generation of oxygen derived free radicals may contribute to CRC degradation. In vitro exposure of non-ischaemic CRCs to trypsin or singlet oxygen and superoxide radicals progressively reduced labelled ryanodine binding to functional SR vesicles and modified the activity of CRCs incorporated into bilayers. During exposure, the channels typically exhibited a transient increase in opening followed by an irreversible loss of activity.

We conclude that the CRC is a target for degradation early during ischaemia but that residual channels continue to function normally. CRC degradation may lead to increased permeability of the SR membrane during ischaemia and exacerbate cytosolic calcium overload. Subsequent reduction in the number of CRCs might impair calcium release from the SR and, therefore, contribute to the mechanism of reduced contraction in myocardial stunning.

**Myocardial potassium homoeostasis during hypoxia: role of ATP sensitive potassium channels**

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Potassium (K+) is lost from the ischaemic or hypoxic myocardium with a consequent rise in extracellular K+ concentration. The mechanism is unknown. Experiments were undertaken with arterially perfused rabbit interventricular septa (90 beats/minute, 32°C) to compare 86Rb+ and 42K+ fluxes under normoxic and hypoxic conditions and to determine the contribution of activation of the ATP sensitive K+ channel to the K+ efflux induced by hypoxia. Septa were labelled with isotope for 150 to 180 minutes, made hypoxic (substrate free) for 15 minutes, and then reoxygenated. Hypoxia caused an increased efflux of both 42K+ and 86Rb+. In eight control septa hypoxia caused a mean tissue net K+ loss of 4.03 (SE 0.62) mmol/kg wet tissue after 15 minutes (determined by 86Rb+ exchange), and this was similar to the increase in effluent K+ (n = 5), indicating that the tissue net K+ loss was due to increased efflux rather than decreased uptake. Barium (0-1 mmol/l and 1.0 mmol/l) was added, and did not affect the above findings. Neither barium (0-1 and 1.0 mmol/l) nor glibenclamide (0-1 mmol/l) affected myocardial 86Rb+ uptake during normoxic perfusion.

These data indicate that hypoxia causes an increase in 42K+ and 86Rb+ permeability and that part of the K+ efflux from the myocardial cells induced by hypoxia may be attributed to activation of ATP sensitive K+ channels, though other mechanisms are involved.
Dual control of tissue factor messenger RNA in human endothelium

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Tissue factor (TF) is the essential cofactor for activating the extrinsic pathway of coagulation by factor VII. In epidemiological studies raised factor VII concentrations correlate with an increased risk of cardiovascular events. Factor VII circulates in plasma unless induced in situations that have contact with the blood. Two intravascular cell types (monocytes and endothelium), however, may be induced to express TF. The control of TF expression in these cells is clearly of crucial importance. Total RNA was extracted from human umbilical vein endothelial cells (HUVEC) that had been exposed to bacterial lipopolysaccharide (LPS) 10 μg/ml or phorbol ester (PMA) 10 ng/ml. Northern blot analysis with panintein RNA probes labelled with phosphorus-32 showed rapid induction of TF messenger RNA (mRNA), detectable by 30 minutes and maximal at two hours after stimulation. In nuclear run on transcription assays nuclei from HUVEC exposed for one hour to either LPS or PMA showed a 10-fold increase in the level of transcription with PMA whereas little change was seen with LPS. Experiments to ascertain the half-life of the mRNA with actinomyycin D showed a 12-fold difference in the half-life of TF messenger RNA in cells exposed to LPS for either one or four hours (t1/2 = 2 hours, 10 minutes respectively). This suggests that LPS exerts its effects by increasing TF mRNA stability. In support of this cycloheximide produces rapid induction of TF mRNA without affecting the level of transcription.

Therefore TF messenger RNA concentrations in HUEC are controlled by changes in the level of transcription or in stability of the mRNA, or both.

Endocardial factors modulate myocardial contractile performance

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Selective removal of endocardium (2 seconds’ immersion in 0.5%, Triton X-100) from isolated heart muscle preparations exerts an unusual type of negative inotropic effect: it reduces contractile duration and peak isometric force without altering unloaded shortening velocity. Similar changes were induced in endocardium intact ferret papillary muscles (n = 22) with 0.1 mM 8-bromocyclic GMP and with 1 μM sodium nitroprusside, 0.4 μM atrial natriuretic peptide, and 1 μM substance P, which increased cyclic GMP concentrations by 472%, 329%, and 171%, respectively. Mechanical and biochemical effects of substance P were abolished by previous removal of endocardium or by haemoglobin (10 μmol/l), which inhibits endothelium derived relaxing factor (EDRF) (n = 11). Removal of endocardium, however, did not alter the cyclic GMP content (n = 6). Bioassay of the effect of effluent from superfused cultured porcine right ventricular endocardial cells on mechanical performance of pig coronary artery rings denuded of endothelium or ferret papillary muscles denuded of endocardium showed endocardial release of (a) a vasodilator identical to EDRF (n = 20) and (b) an unidentified stable substance (not endothelin), which reversed the mechanical effects of removal of endocardium (n = 6).

Thus endocardium can influence myocardial contraction by tonic release of a substance prolonging contraction and stimulated release of an EDRF-like factor abbreviating contraction.

Abnormal expression of class II major histocompatibility complex molecule on endocardium and cardiac endothelium: a marker of immune activation in dilated cardiomyopathy

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The inappropriate expression of major histocompatibility complex (MHC) class II molecules on endothelial and epithelial cells is a recognised marker of autoimmune disease. Expression of MHC molecules was studied in dilated cardiomyopathy (DCM) to investigate the role of autoimmunity in this condition. Fresh right ventricular endomyocardial biopsy tissue from 29 patients with DCM was compared with myocardium obtained at the time of cardiac surgery from 63 patients with other acquired cardiac disease and from 22 with congenital heart disease. Conventional immunofluorescence with monoclonal antibodies to lymphocytes and macrophage markers and to MHC class II molecules was performed. Double immunofluorescence with antibody to human factor VIII was used for identifying endothelial cells. MTC class II molecules were not found on myocytes in specimens from patients with congenital heart disease and were uncommon on endothelium (3/22) and endocardium (2/22). Class II molecules were expressed more frequently in DCM than in other acquired cardiac diseases on endothelium (28/29 vs. 19/63, p < 0.001) and on endocardium (22/29 vs. 11/63, p < 0.001) but were not expressed on myocytes. The finding of inappropriate expression of MHC class II molecules in DCM was not related to the presence of circulating organ specific cardiac antibodies, duration of symptoms, or their severity. In all the biopsy specimens examined from patients with DCM there was a hierarchy of class II subloci product expression (DR > DP > DQ); lymphocytic infiltrates and macrophage clusters were not seen.

The finding of inappropriate expression of MHC class II molecules on endocardium and cardiac endothelium in DCM suggests a possible pathogenic role for these cells in the initiation or perpetuation of this condition, or both.

Lack of relation of pretreatment streptokinase resistance titres and streptokinase IgG concentrations with hypotensive responses and coronary patency with thrombolytic agents containing streptokinase

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One hundred and twenty eight patients (101 men, 27
women, age range 31 to 70) were treated with either streptokinase (SK) 1·5 MIU infused over 60 minutes (n = 64) or anistreplase (A) 30 units by 5 minute injection, within six hours of onset of acute myocardial infarction. Pretreatment blood samples were analysed for streptokinase resistance titre (SKRT) in 96 patients (48 receiving SK, 48 receiving A) and specific SK IgG concentrations in 124 (60 receiving SK, 64 receiving A). Median IgG concentrations for each treatment group were similar (SK 1·19 ± 1·04 μg SK binding/ml, NS), but the median SKRT was significantly higher in the A group (50 ± 20 IU SK/ml, p < 0·05). Blood pressure was recorded at two minute intervals for 90 minutes after treatment. In the SK group 23/64 had a hypotensive response (defined as a blood pressure fall of at least 20 mm Hg lasting at least 6 minutes): 20 within the first 30 minutes, nine after 30 minutes, and six both. In the A group 33/64 had a hypotensive response: 26 early, 15 late, and six both (NS). Angiographic coronary artery patency was 53%, and 55% (NS) at 90 minutes with SK and A respectively and 87-5% and 81% (NS) at 24 hours. The infarct related artery was: left anterior descending (54 patients), right coronary (55), circumflex (12), and not determined (seven). No significant relation was found between pretreatment SKRT or SK IgG concentrations and coronary patency or hypotensive responses, nor between the infarct related vessel and hypotensive responses. Therefore these indices of previous exposure to streptokinase protein do not influence the thrombolytic efficacy or likelihood of hypotensive response to these SK containing thrombolytic agents, and the site of infarction is not related to hypotensive responses.

Placebo controlled trial of xamoterol versus digoxin in chronic atrial fibrillation

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Twelve patients with chronic atrial fibrillation and normal resting heart rate but exercise tachycardia and bradyarrhythmic episodes were randomised to receive xamoterol 200 mg twice daily, digoxin, or placebo in a double blind crossover study. Patients were assessed by symptom scores for dyspnoea, fatigue, and dizziness and by 24 hour ambulatory electrocardiographic monitoring and treadmill exercise testing. Maximum and minimum hourly heart rates and number and duration of ventricular pauses were measured. Combined symptom score results for xamoterol (4-9) were significantly lower than for digoxin (6-2) or placebo (6-2), (p < 0·05). Resting heart rate before exercise was lower (62 (5) beats/min) with digoxin than xamoterol (72 (5) beats/min), (p < 0·005) or placebo (70 (5) beats/min), (p < 0·01). Resting heart rate did not differ between placebo and xamoterol treatments. Maximum exercise heart rate was significantly slower with xamoterol (136 (10) beats/min) than with digoxin (150 (10) beats/min), (p < 0·005). Xamoterol increased the maximum hourly heart rate from 50 (4) to 59 (5) beats/min, (p < 0·05) but reduced the maximum hourly rate from 139 (8) to 132 (8) beats/min (NS). Digoxin reduced maximum heart rate to an equal extent (132 (8) beats/min (NS)) whereas the minimum heart rate declined (45 (3) beats/min, p < 0·001) compared with xamoterol. Xamoterol significantly reduced the maximum duration of ventricular pauses (1·8 (0·1) seconds) compared with placebo (2·3 (0·1) seconds) (p < 0·005) or with digoxin (2·5 (0·1) seconds) (p < 0·001).

We conclude from these data that xamoterol is effective in rate control and relief of symptoms in chronic atrial fibrillation, and may be preferable in patients with episodic bradyarrhythmia or ventricular pauses.

Effects of calcitonin gene related peptide on human coronary blood flow and epicardial vessel diameter

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Calcitonin gene related peptide (CGRP) is a potent dilator of epicardial coronary vessels in humans, but its effects on myocardial resistance vessels and coronary blood flow are unknown. The effects of CGRP on coronary artery blood flow and epicardial vessel diameter were investigated in seven patients (aged 40–57); six were men. Four had coronary artery disease, and three had normal coronary arteries. All had been admitted for routine coronary angiography for the investigation of chest pain. Left anterior descending vessel diameter, coronary sinus oxygen saturation (CSo2S), systemic blood pressure, and heart rate were measured during intracoronary infusion of increasing concentrations of CGRP (up to 200 ng/ml at 2 ml/min), followed by intracoronary adenosine (10^{-}6 M at 2 ml/min), and, finally, intracoronary glyceryl trinitrate (GTN) (5 μg/ml at 2 ml/min). CGRP dilated the left anterior descending artery by a mean of 23·0% (95% confidence interval ± 6·6%) p < 0·001, with only a small increase in CSo2S from 40·1 (±7·8%) to 47·3 (±5·1%), p < 0·01. Adenosine, a potent dilator of myocardial resistance vessels, caused no further increase in epicardial vessel diameter but a rise in CSo2S from 47·3 (±5·1%) to 76·0 (±5·8%), p < 0·01. GTN caused no further increase in epicardial vessel diameter. Myocardial work as assessed by heart rate x blood pressure product remained unchanged throughout the study; CSo2S can therefore be used as an index of myocardial blood flow. The CSo2S increased only slightly during CGRP infusion. That this rise in blood flow was not due to impaired coronary flow reserve was confirmed by the pronounced response to adenosine infusion.

These data indicate that CGRP, though a potent dilator of epicardial vessels, has little effect on myocardial blood flow in non-ischaemic myocardium in humans at rest.

Control of sick sinus syndrome by xamoterol

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Xamoterol has properties which might be beneficial in the sick sinus syndrome. We have studied its short term and long term effects on patients with mild to moderate symptoms. We entered 26 patients into a short term, double blind, randomised crossover trial of xamoterol versus placebo. Their response was assessed by symptoms, weekly Holter monitoring, and exercise testing. The 13 patients who improved were started with xamoterol for up to one year. All had symptoms, and seven had been referred for permanent pacing. Holter monitoring was repeated at
three monthly intervals during treatment and again two
days and two weeks after treatment was stopped. Treatment
was stopped early in five patients (two required permanent pacing, one developed ventricular tachycardia, one had worsening palpitations, and one died of bronchial carcinoma). The remaining eight patients took xamoterol for nine to 12 months, and the beneficial effects on symptoms and electrocardiography were maintained. On withdrawal of the drug all six patients who had paused while taking xamoterol displayed an increase in the number and duration of these; four noticed a deterioration in symptoms.

Xamoterol may improve sinoatrial disease for up to one year and might be an alternative to pacing in some patients.

Does antianginal treatment with atenolol, nifedipine, and isosorbide mononitrate confer more benefit than treatment with atenolol and nifedipine or isosorbide mononitrate in patients with stable angina and symptoms receiving atenolol?

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Twenty two patients with stable angina pectoris and proved coronary artery disease were evaluated subjectively and by maximal treadmill exercise testing (MET). They entered a randomised double blind crossover study of four weeks of atenolol 100 mg (A) and placebo (P), A and nifedipine slow release 20 mg twice daily (B), A and isosorbide mononitrate 20 mg twice daily (C), and all three active agents combined (D). Exercise time expressed in seconds of the Bruce protocol was significantly longer during treatment C (473 (21-2) than treatments P (427 (19-4)), B (438 (23-4)), or D (455 (22-6)) (p < 0.05). There was, however, no significant difference in maximum ST depression (mm) between treatment periods P (1-4 (0-70), B (1-39 (0-7), C (1-44 (0-77)) and D (1-54 (0-8))). The rate of angina attacks was reduced from 15-6 (2-3) with treatment P to 10-2 (2-2) with treatment B, to 11-3 (2-5) with treatment C, and to 12-5 (2-6) with treatment D. Nitrate consumption fell similarly.

The combinations of atenolol and isosorbide mononitrate or nifedipine slow release were equally effective with no obvious further benefit conferred by all three combined. Nitrate tolerance was not observed after four weeks of continuous treatment.

High coronary artery patency and plasma recombinant tissue plasminogen activator concentrations after bolus administration of alteplase in acute myocardial infarction

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Thirty three consecutive patients (23 men and 10 women, age range 40-74) suitable for thrombolytic treatment within six hours after onset of myocardial infarction detected on electrocardiography were treated with two intravenous boluses of 35 mg alteplase 30 minutes apart. Mean time to first bolus was 208 (75) minutes after onset of symptoms. Coronary angiography was successfully performed in 30/33 patients, starting 30 minutes after treatment with serial injections to 90 minutes and at 24 hours. The infarct related artery was left anterior descending in 12 patients, right coronary in 15, left main coronary artery in one, and circumflex in two. At first injection (49-4 (13-3) minutes) the rate of patency (TIMI grades 2 and 3) was 23/30 (77%, 95% confidence interval 61% to 92%), rising to 26/30 (87%, 74% to 99%) at 90 minutes. At repeat angiography at 24 hours 24/29 arteries were patent (83%, 69 to 97%). The rate of reocclusion at 24 hours was 3/29 (10%, 0 to 22%). Five patients had haematoma formation related to arterial cannulation, and three had minor spontaneous bleeding. Mean baseline plasma recombinant tissue plasminogen activator (rtPA) concentration (n = 24) was 20-1 (5-3) ng/ml, attaining peaks of 4451 (452) and 4124 (450) ng/ml after the two boluses of alteplase. Before the second bolus the mean rtPA concentration fell to 415 (56) ng/ml, and 90 minutes after the second bolus it fell to 130 (23) ng/ml.

These results show that the administration of two intravenous boluses of alteplase achieves brief, high plasma concentrations of rtPA, resulting in high coronary patency without serious adverse effects on bleeding or reocclusion.

Reduced myocardial efficiency in hypertrophic cardiomyopathy

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The common symptoms of chest pain and dyspnoea in hypertrophic cardiomyopathy (HCM) are often refractory to treatment, and the mechanisms which underly them are poorly understood. The severity of symptoms and impairment of exercise capacity (VO₂ max) are not closely related to the severity of left ventricular (LV) hypertrophy, to the presence of an LV outflow tract gradient, or to LV filling pressures. To investigate myocardial function at a more basic level in HCM we compared LV heat production, an index of myocardial mechanical efficiency, in five patients with HCM and five normal controls, at the time of cardiac catheterisation. All patients had normal epicardial coronary arteries. Energy supply to the myocardium, calculated from myocardial oxygen uptake, was higher in the patients with HCM compared with that in the controls (mean 6-3 (SD 2-5) W v 4-4 (2-5) W, NS). Proportionately more of the energy released by the metabolism of this oxygen, however, was 'wasted' as heat in the HCM group (mean LV heat production 4-6 (1-6) W v 2-5 (1-1) W, p < 0.05). Calculated myocardial efficiency was significantly lower in the HCM patients (0-23 (0-10) v 0-44 (0-10), p = 0-006).

It is not clear whether the observed reduction in mechanical efficiency of the myocardium in HCM is a consequence of the hypertrophy per se. Evaluation of the myocardium in other hypertrophic states is warranted.
Changes in human monophasic action potential during transient aortic occlusion

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The strong association between ventricular arrhythmia and ventricular dysfunction is unexplained. One possible mechanism may be a feedback limb of excitation-contraction coupling, whereby ventricular loading conditions influence the time course of repolarisation and hence refractoriness (contraction-excitation feedback). Although this has been shown in animal studies, and despite its potential arrhythmogenic importance, there is to date only limited evidence for the existence of this phenomenon in humans. We recorded monophasic action potentials during transient aortic occlusion from the left ventricular epicardium in 16 patients having routine coronary artery surgery. Peak systolic pressure was monitored using the routine radial artery pressure in 10 patients and left ventricular pressure by direct needle puncture in six. Aortic occlusion for between one and three beats was used to produce a transient increase in ventricular loading. In all patients during aortic occlusion the monophasic action potential duration at 90% repolarisation decreased (325 (SD 31) ms to 311 (29) ms, p < 0.0001). After release the monophasic action potential duration returned to initial values within three beats. In the six patients in whom intraventricular pressure was measured directly peak systolic pressure rose from 79 (18) mm Hg to a maximum of 139 (27) mm Hg (p < 0.0001) during the occlusion. In these six patients there was a strong correlation between beat to beat changes in peak systolic pressure and changes in monophasic action potential duration (r = 0.96, p < 0.0001). This study shows that changes in the timing of repolarisation in response to acute changes in ventricular loading occur on a beat to beat basis.

The results provide further evidence for the existence of contraction-excitation feedback in humans. Inhomogeneous contraction patterns could, by this mechanism, induce inhomogeneity of repolarisation and provide an ideal basis for arrhythmia.

Potassium concentration in cardioplegic solutions has a critical role in mediating endothelial damage in isolated rat heart

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We have previously shown that serotonin 5 hydroxytryptamine causes dose dependent vasodilatation of coronary circulation in isolated rat heart by releasing nitric oxide. We studied the effect of potassium concentration in cardioplegic solutions on the vasodilatation in rat heart induced by serotonin and glyceryl trinitrate (GTN). Forty eight rat hearts were perfused on a modified Langendorff preparation; after exposure to 10^-7 M serotonin and 10 μg/ml GTN they were perfused for 30 or 60 minutes with either St Thomas's solution or Bretschneider solution containing 20 mmol/l or for 30 minutes with either solution containing 30 mmol/l potassium (eight hearts each). Serotonin and GTN caused 39-0 (3-3)% and 39-7 (2-8)% increase in coronary flow respectively. After 30 or 60 minutes' perfusion with St Thomas's solution containing 20 mmol/l potassium there was little change in response to serotonin or GTN (43-1 (4-1)% 38 (3-2)% respectively). Similarly, perfusion with Bretschneider solution (20 mmol/l potassium) for 30 or 60 minutes did not alter the amount of vasodilatation (serotonin 39-2 (2-9)% GTN 38-0 (3-3)%). Perfusion with St Thomas's solution (30 mmol/l potassium) for 30 minutes, however, abolished the endothelial dependent serotonin induced vasodilatation (serotonin −1-6 (1-43)% GTN 36-9 (2-2)%. Perfusion with Bretschneider solution (30 mmol/l potassium) gave similar results (serotonin −2-1 (1-23)% GTN 36-4 (1-65)%).

We conclude that potassium concentration in cardioplegic solutions as used clinically is not detrimental to the endothelium. Increasing the concentration of potassium to 30 mmol/l, however, can cause endothelial damage.

Evidence for a role for nitric oxide in mediating endothelium dependent responses in human epicardial coronary arteries

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Endothelium dependent relaxations have been reported to be mediated through release of nitric oxide (NO) in animal vascular tissue. There has been no direct evidence, however, that NO is the endothelium relaxing factor in human vascular tissue. One hundred and thirty two ring segments of coronary artery were removed from 23 patients undergoing heart transplants for reasons other than ischaemic heart disease. The segments were suspended in 5 ml organ baths for in vitro recording of vascular smooth muscle relaxations. Substance P (SP) (10^-19 M to 10^-7 M) elicited a dose dependent relaxation of coronary artery segments. This action of SP is dependent on an intact endothelium. The maximum response of SP was equivalent to 89 (8-5)% of the maximum effect induced by 1 μg/ml glyceryl trinitrate (GTN). The action of SP was unaffected by the presence of 10^-4 M indomethacin. L-N G-Monomethyl arginine (10^-4 mol/l), a specific inhibitor of NO formation from L-arginine, antagonised the relaxations induced by SP, decreasing the maximum response of SP to 23 (7-8)% of the response with GTN. On application L-N G-Monomethyl arginine caused a further 29-3 (10-1)% increase in tension on preconstricted vessels, which was reversed with the addition of L-arginine but was unaffected by D-arginine.

It is concluded that the relaxations induced by SP on human epicardial coronary arteries is mediated by an endothelial derived factor, which our data indicate to be NO, cleaved specifically from L-arginine.

Eosinophils from hypereosinophilic patients damage endocardium of isolated heart muscle

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Clinically, hypereosinophilia is associated with endo-
cardial damage to the heart, but a causal relation is not established. We therefore studied the effect of eosinophil suspensions (containing 38–80%, "hypodense"—that is, activated—eosinophils) or eosinophil supernatants from eight untreated hypereosinophilic patients on contraction of isolated cat cardiac papillary muscle preparations (n = 16). Eosinophil suspensions (5–15 × 10⁶/10 ml tissue bath) or supernatants (prepared by overnight incubation of eosinophils at 37°C) induced within 30 minutes contractile changes identical to the previously reported and characteristic effects of selective endocardial damage—that is, reduced time to peak isometric tension (−6–6%, p < 0.05) and isometric tension (−8–6%, p < 0.05) but unchanged unloaded shortening velocity. Light and electron microscopic studies showed a specific pattern of damage to endocardial cells but an undamaged myocardium. Neither the eosinophils nor their supernatants induced any change in contraction of muscles denuded of endocardium (n = 3). Similarly prepared suspensions of eosinophils (containing no hypodense cells) or neutrophils from healthy volunteers caused no contractile or morphological changes in muscles with intact endocardium (n = 10).

Thus eosinophils from hypereosinophilic patients induce morphological and contractile changes in cat papillary muscles suggestive of a pathophysiological role in vivo mediated by endocardial damage.

Increased cough reflex in chronic heart failure independent of treatment with angiotensin converting enzyme inhibitor

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Dry non-productive cough is described as a symptom of chronic left heart failure (CHF). Cough is also a recognised side effect of treatment with angiotensin converting enzyme (ACE) inhibitor, and ACE inhibitors cause increased cough sensitivity to inhaled irritants, but cough reflex has not been studied in CHF. Bronchial hyperreactivity (increased bronchoconstriction to inhaled methacholine) has been reported in subjects with CHF not receiving ACE inhibitors, suggesting that airway abnormalities may be important. The cough response to inhalation of metered doses of z-capsaicin was studied in 10 patients with CHF not receiving ACE inhibitors and in 10 age matched controls. Subjects with CHF were aged 47–76, New York Heart Association grade II or III, and left ventricular ejection fraction was <45%. There was no history of pulmonary disease or atopy, and lung function (forced expiratory volume in one second, forced vital capacity, diffusing capacity for lung carbon monoxide, Kco) was >70%, of predicted normal values. Deep inspiration through a mouthpiece actuated the delivery of 6-25 nmol nebulised capsaicin in saline (0.02 ml, mass median diameter 4 μm). The number of distinct coughs was noted, and each subject was tested four times in succession on the same occasion. The mean number of coughs in subjects with CHF ranged from 35 to 10 (median 6.1) and in controls from 0 to 75 (3.9) (p < 0.01, two tailed Mann-Whitney test).

Increased cough reflex to inhaled irritants in CHF per se may reflect abnormal sensitisation of pulmonary airway receptors, which may contribute to the symptoms of this condition.

Systolic retrograde pulmonary venous flow as a new quantifiable index of mitral regurgitation

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Non-invasive quantification of mitral regurgitation (MR) by ultrasonography is difficult because many technical factors and haemodynamic variables influence the related area of turbulence detected on colour flow mapping (CFM). The most common index of severity—turbulent jet area measured as a proportion of left atrial cross sectional area—cannot usually be obtained by transoesophageal echocardiography (TEE), and it is unreliable in patients with very eccentric MR jets. These confounding factors do not, however, affect left atrial pressure events, which are the major determinants of pulmonary venous blood flow (PVF). As spectral Doppler recordings of PVF are readily obtained by TEE we investigated whether PVF Doppler velocity profiles can be used to measure MR. Pulsed Doppler recordings from the left upper pulmonary vein (LUPV), which is well aligned for Doppler studies, were obtained in 18 adult patients before and immediately after mitral valve reconstruction or mitral valve replacement for isolated angiographic grade III or IV regurgitation. The velocity profiles were digitised with a newly developed microcomputer programme, and the results were compared with conventional ultrasonographic indices of MR such as CFM jet width, depth, and area and the duration of regurgitation on the colour M mode recording. Before surgery 15 patients (83%), including all those with prolapse and an eccentric jet, had abnormal retrograde PVF during ventricular systole. No retrograde PVF was seen in three patients with an early systolic, central MR jet. The time velocity integral (TVI) of the velocity profile was 0.9 (SE 1.7) cm in systole and 8.2 (0.8) cm in diastole (p < 0.01). After surgery no patient had significant residual MR on CFM as judged by TEE. In five patients MR in early systole (colour M mode) was associated with minimal residual retrograde PVF flow. TVI in systole had increased to 8.7 (0.9) cm (p < 0.05) whereas TVI in diastole was unaltered, at 7.5 (1.0). The ratio of peak diastolic to peak systolic velocities was 0.55 (0.45) before surgery and 0.97 (0.13) afterwards (NS). Changes in PVF Doppler profiles correlated well with other indices and were helpful in assessing the outcome of surgery.

In conclusion severe MR causes systolic retrograde flow in the pulmonary veins, which resolves immediately after successful surgical repair. TEE analysis of PVF with calculation of systolic TVI seems to be a useful index of the severity of MR.

Echocardiographic assessment of mitral valve repair

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We report our initial experience with conservative mitral surgery since 1985. Fifty eight patients underwent mitral valve repair for mitral regurgitation (MR); 41 were men and 17 women, aged 48 to 79. Follow up ranged from two weeks to four years. One patient was lost to follow up. MR
was graded preoperatively by pulsed wave Doppler echocardiographic mapping. Preoperatively MR was moderate-severe and severe in 50 (86%). Seventy eight percent were in New York Heart Association (NYHA) functional class III-IV. In 42 patients MR was due to degenerative changes, in four to ischaemia, seven to rheumatic fever; one had congenital disease, one functional, and two had endocarditis. All but one patient had an annuloplasty ring inserted. Concomitant cardiac procedures included coronary artery bypass grafting (12), aortic valve replacement (seven), patch atrial septal defect repair (one), tricuspid valvotomy (one), and tricuspid annuloplasty (one). There were two deaths at four months after repair, which were unrelated to mitral valve repair. One patient required valve replacement. At follow up 95% of patients were in NYHA class I–II. MR was absent or mild in 52 (90%). Early and late postoperative ultrasonography showed that the septal movement was impaired in all but two patients, with abnormal or paradoxical motion. This is unexplained but limited the echocardiographic measurement of left ventricular function. Function of other myocardial regions seemed to be unimpaired. This initial satisfactory experience has led to earlier and increased referral of patients with MR for surgical treatment.

Does blood pressure response to the first dose of captopril predict response to subsequent doses in chronic heart failure?

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Captopril (CPT) is used increasingly in chronic heart failure (CHF), and it is common to start treatment with a low dose (6-25 mg). It remains uncertain whether a low starting dose is really necessary, and, furthermore, there is a paucity of data on the blood pressure (BP) response to subsequent doses. The aims of our study were twofold: firstly, to determine whether the first dose effect is different when different starting doses of CPT are given and, secondly, to determine whether the first dose response predicts the response to subsequent doses of CPT. Forty patients with stable, diuretic controlled CHF were recruited into a double blind placebo controlled study comparing either a high dose (25 mg eight hourly for four doses) or a low dose (6-25, 6-25, 12-5, and 25 mg) regimen. No patients withdrew from the study or complained of dizziness or hypotension. Mean BP fell significantly in both groups after the first dose of CPT. In the low dose group mean BP fell by 7 (4) mm Hg after placebo, 16 (4) mm Hg after 6-25 mg CPT, and 18 (4) mm Hg after 25 mg CPT (fourth dose). In the high dose group BP fell by 10 (4) mm Hg after placebo, 15 (4) mm Hg after 25 mg CPT, and 7 (4) mm Hg after CPT 25 mg (fourth dose). The maximum fall in BP after the first dose of CPT was significantly correlated with the fall in BP after the fourth dose in both groups (r = 0.51, p < 0.02; r = 0.58, p < 0.01). These results suggest that the fall in BP after the first dose of CPT is of the same magnitude and duration for either 6-25 mg or 25 mg of the drug. Furthermore the fall in BP to the fourth dose (25 mg) of CPT correlated significantly with that in the first and was in most cases of a lesser magnitude than the response to the first dose.

Hypotension after captopril occurs independently of plasma renin activity and sympathetic nervous activity in patients with primary autonomic failure

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We investigated the haemodynamic and hormonal responses to inhibition of angiotensin converting enzyme in 12 patients with primary autonomic failure (AF) (five with pure autonomic failure and seven with multiple system atrophy) and seven normal subjects. Measurements of blood pressure (BP), heart rate (HR) (Sentron), stroke distance (SD) and cardiac index (CI) (by continuous wave Doppler), forearm blood flow (FBF) (by strain gauge plethysmography), and digital skin blood flow (DSBF) (by laser Doppler flowmetry) were made non-invasively. Plasma renin activity (PRA) (determined by radio-immunoassay) and noradrenaline (NORAD) determined by high performance liquid chromatography were measured before captopril (50 mg oral) and at 30 minute intervals after. Basal supine BP was higher in AF compared with that in normal subjects (p < 0.05). After captopril mean BP fell in AF (117 (6) to 103 (5) mm Hg, p < 0.05) but not in normal subjects (99 (4) to 97 mm Hg, NS). HR was unchanged after captopril in both groups. The depressor response in AF was accompanied by a fall in SD (9.6 (1.2) to 7.6 (0.7) cm, p < 0.05) and in CI (676 (79) to 536 (65) cm/minute, p < 0.05). SD and CI were unchanged after captopril in normal subjects (SD 7.7 (3) to 7.4 (0.6) cm, CI 579 (117) to 571 (69) cm/minute, both NS). There was no reduction in forearm or digital skin vascular resistance after captopril in either group. Basal PRA in AF was similar to that in normal subjects but did not rise after captopril (691 (217) to 681 (221) pg/ml/h, NS), unlike in normal subjects (813 (103) to 1360 (290) pg/ml/h, p < 0.05). NORAD was unchanged after captopril in both groups.

We conclude that captopril lowers blood pressure in AF, unlike in normal subjects. The depressor response in AF occurs independently of renin levels and sympathetic nervous activity, suggesting that alternative mechanisms, including accumulation of bradykinin and prostaglandins are responsible.

Acute β blockade decreases cardiac noradrenaline spillover

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Cardiac and whole blood noradrenaline (NA) kinetics were used to assess the effect of short term administration of metoprolol on cardiac and overall sympathetic activity at rest and during dynamic exercise in 12 patients (mean age 58 (SD 3)) who had not received β blockers for at least seven days. Two periods of supine bicycle exercise were undertaken during infusions of either saline or metoprolol (10-35 mg bolus plus 150 µg/minute intravenously), and NA kinetics were measured before and during each period of exercise. During infusion of metoprolol heart rate decreased from 68 (5) to 61 (5) beats/min (p < 0.01) and coronary sinus (CS) plasma flow from 50 (5) to 37 (4) ml/minute (p < 0.001). CS NA (171 (21) µ 141 (15) pg/ml) and arterial NA (171 (15) µ 158 (16) pg/ml) both tended to
decrease, and cardiac NA spillover was significantly decreased during metoprolol (5-6 (0-8) to 3-4 (0-7) ng/minute, p < 0-05). Whole body NA spillover also tended to decrease during metoprolol (196 (23) v 172 (19) ng/minute/m²). Exercise resulted in increases in CS plasma flow, arterial NA, CS NA, and cardiac NA spillover during both placebo and metoprolol infusions. CS plasma flow during exercise was higher during infusions with placebo than with metoprolol (69 (6) v 52 (4) ml/minute), but cardiac and whole body NA spillover were not significantly different. Thus short term administration of metoprolol was associated with a striking decrease in resting coronary blood flow, attenuation of the increase in coronary flow with exercise, and a modest decrease in resting cardiac NA spillover.

The results suggest that, in addition to blocking cardiac postsynaptic receptors, β₁ selective adrenoceptor antagonists may decrease NA release from the cardiac sympathetic nerves.

Comparative study of the efficacy and safety of sotalol in prophylactic treatment of patients with paroxysmal supraventricular tachycardia

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One hundred and twenty six patients were entered into a randomised double blind placebo controlled multicentre parallel group comparison study to assess the relative efficacy of placebo versus sotalol 80 mg twice daily versus 160 mg twice daily in the management of paroxysmal supraventricular tachycardia (PSVT), including atrial fibrillation (AF), atrial flutter, atrioventricular re-entrant (AVRT), atrioventricular nodo-re-entrant (AVNRT), and paroxysmal atrial tachycardia (PAT). The frequency of episodes of PSVT was monitored during three baseline periods, the length of which were related to the frequency of symptoms and which could be one, two, or four weeks. There followed a one week dose escalation period in three parallel groups of placebo (n = 48), sotalol 80 mg twice daily (n = 35), and sotalol 80 mg twice daily (n = 46) increasing to 160 mg twice daily (n = 44). During the double blind phase PSVT events and symptoms were monitored as in the baseline phase using diary cards and "Cardiomemo" solid state recorders. The relative risk (Cox's proportion of hazard) of a recurrence of PSVT detected by electrocardiography (ECG) in the 95 patients completing the study was less in the treatment group (p = 0-042, p = 0-0009) with 80 mg and 160 mg respectively. After excluding 15 patients (four taking placebo, five 80 mg sotalol, and six 160 mg sotalol) without recurrence of PSVT on ECG or whose period in the double blind phase was too short according to the protocol 80 patients remained. Five of 26 (19%) of patients taking placebo, 11/23 (48%) taking 80 mg sotalol, 21/31 (68%) taking 160 mg sotalol experienced no recurrence of PSVT (p = 0-018, p = 0-0002 respectively by logistic regression). Subgroup analysis showed that sotalol was effective in suppressing attacks of PAC at both 80 mg and 160 mg twice daily (p = 0-017, p = 0-003 respectively (Fisher's exact test) but of AVRT or AVNRT only at the higher dose (p = 0-683, p = 0-032 respectively (Fisher's exact test). No significant unwanted effects were observed.

It is considered that sotalol is a useful and safe product in the management of PSVT.

Effects of theophylline, atenolol, and their combination on myocardial ischaemia in patients with stable angina pectoris

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The effects of theophylline (400 mg twice a day), atenolol (50 mg twice a day), and their combination on myocardial ischaemia were studied in nine patients with stable angina in a randomised, single blind, triple crossover trial. Placebo was given to the patients during the run in and run off periods. A treadmill exercise test and 24 hour Holter monitoring were obtained at the end of each treatment period.

Compared with placebo theophylline improved the time to the onset of myocardial ischaemia (1 mm ST segment depression) from 7-8 (3-7) to 9-5 (3-7) minutes (p < 0-03) and the exercise duration from 9 (3-4) to 10-1 (3-5) minutes (p < 0-04). During atenolol treatment and combination treatment the time to the onset of ischaemia and the exercise duration were similar (10-8 (4-2), 11-2 (3-2) minutes and 11-2 (3-6), 11-5 (3-2) minutes respectively) and longer than during theophylline (p < 0-05). Holter monitoring showed that during theophylline treatment the heart rate was higher than during placebo treatment throughout the 24 hours (p < 0-05). During atenolol treatment and combination treatment the heart rate was similar and in both cases lower than during placebo treatment (p < 0-05).

Compared with placebo theophylline decreased the total ischaemic time from 97 (110) to 70 (103) minutes (p < 0-05). During combination treatment the total ischaemic time (5-6 (8-5) minutes) was not statistically different from that during atenolol administration (18 (29) minutes), although it was significantly lower than that observed during theophylline treatment (p < 0-05).

Thus long term theophylline administration improves myocardial ischaemia but to a lesser degree than atenolol. The apparent lack of detectable additive effects, despite the fact that atenolol abolishes the undesirable chronotropic effect of theophylline and that theophylline probably reduces the undesirable increase of cardiac volumes caused by atenolol, suggests that these two drugs might share a common mechanism of action.

Rotational angioplasty for chronic coronary occlusions

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A new rotational angioplasty catheter system (ROTACS) has been developed at Frankfurt for use in chronic coronary occlusion. It consists of a smooth olive shaped tip with an oval cross section attached to a helical drive shaft that rotates at up to 300 rpm and is enclosed in a 5F catheter. Through the centre runs a hole large enough to take a standard (0-014) angioplasty guide wire. We have used the ROTACS in four patients. Patient 1 (aged 67) had previous coronary artery bypass graft (CABG) with a failed left anterior descending (LAD) artery graft. The LAD lesion was a chronic (three years) calcified, but subtotal occlusion, which was successfully passed by the guide wire, opened by the drill, and dilated with a 2-5 mm balloon. Patients 2, 3, and 4 (aged 59, 52, and 67 respectively) all had chronic total occlusions of the circumflex artery and all underwent
unsuccessful attempts to cross with conventional percutaneous transluminal coronary angioplasty systems. In patient 2 attempts to cross with the ROTACS were abandoned after the drive seized on to the guide wire. In patient 3 also the drive seized after some progress had been achieved, but a second device was used successfully. In patient 4 the occlusion was crossed and dilated without trouble. There were no complications. Patient 2 was referred for single vessel CABG; the other three procedures were angiographically and clinically successful.

We conclude that the ROTACS technique is not without technical difficulties but widens the scope for non-surgical intervention in coronary disease.

Silent myocardial ischaemia before and after coronary artery angioplasty in patients with stable and unstable angina

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Ambulatory ST segment monitoring was carried out in a series of 69 patients with stable (35) and unstable (34) angina pectoris undergoing successful, uncomplicated coronary artery angioplasty. The frequency, duration, and severity of ST segment depression was analysed to determine its relation to several angiographic features. Patients were monitored for 24 hours immediately before, after, and between 48–96 hours after angioplasty. All episodes of ST segment depression recorded were asymptomatic. Before angioplasty ST depression was seen in 12/35 (34%) of stable and 14/34 (41%) of unstable patients (NS). Immediately after angioplasty ST segment depression was still frequent in 8 (22%) and 11 (32%) of stable and unstable patients respectively. The mean duration and extent of ST segment depression was 38.9 minutes and 1.8 mm in the stable group and 26.2 minutes and 1.3 mm in the unstable group before dilatation. After angioplasty it was 92.4 minutes and 3.1 mm in the stable group and 192 minutes and 1.3 mm in the unstable group. At 48–96 hours after angioplasty ST segment depression was present in nine and six patients in the stable and unstable groups respectively. There was no association between the occurrence of ST segment depression at any time period and angiographic features.

Silent ST segment depression is a frequent finding in patients with both stable and unstable angina undergoing coronary artery angioplasty. The frequency of ST depression decreases after successful angioplasty (p < 0.05), but the duration and severity of ST depression is increased.

Urgent general practitioner referral to a cardiac centre: evaluation of a chest pain clinic

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In patients with chest pain of recent onset the value of an electrocardiographic reporting service is questionable, and full assessment may be preferred. Therefore after the introduction of an acute chest pain referral service 154 patients, referred by their general practitioners over a year, were reviewed. They comprised 105 men and 49 women (mean age 59, range 25 to 84). The mean duration of symptoms was 19 days (range one to 90 days), and all patients were seen within one day after referral. One hundred and eleven patients (72%) were assessed within one month after the onset of symptoms, and 59 (38%) were seen within seven days. The clinical diagnosis was of unstable angina in 37 patients (24%) and stable angina in 48 (31%). Four patients (3%) had acute infarction whereas 48 (31%) were considered to have non-cardiac pain. In 17 patients (11%) the cause of chest pain was uncertain. The resting electrocardiogram was normal in 83 patients, including 12 considered to have unstable angina. Thirty seven patients were admitted directly from the clinic; 73 patients (47%) underwent coronary arteriography, of whom 32 (44%), in whom the initial electrocardiogram was normal in 13, were investigated within one month. Of all patients investigated, 45 (62%) underwent intervention (percutaneous transluminal coronary angioplasty (23) and coronary artery surgery (22)), 16 within one month of presentation.

An electrocardiographic reporting system is not in itself enough to evaluate chest pain properly. This experience underlines the value, and illustrates the effect on facilities for early investigation and intervention, of a service offering a full assessment of patients with chest pain of recent onset.

How quickly is defibrillation performed in coronary care and other medical wards?

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When ventricular fibrillation occurs outside hospital response time is of major importance, but little accurate information is available on the timing of defibrillation in hospital. Response time (from cardiac arrest call to first defibrillation) was accurately measured in coronary care units (CCU) and medical wards. The precise time of the arrest call was recorded automatically by the hospital switchboard. Each defibrillator carried a modified tracker recorder, which recorded cardiac rhythm, elapsed time, and defibrillation markers automatically. No patient was further than 50 m from a defibrillator. In a year 66 fibrillation arrests (34 in CCU) were recorded in 48 patients; 19 patients survived to leave hospital. Response time <3 minutes was associated with improved survival (52% v 8%). Arrests in CCU were associated with shorter mean response time (35 seconds v 202 seconds) and improved survival (68% v 29%). In the medical wards mean time from arrest call to monitor connection was 125 seconds, and fibrillation was displayed for more than one minute before any defibrillation in 19 out of 32 arrests (maximum 235 seconds). Response times were not significantly longer at night.

Defibrillation outside CCU could be speeded up by obtaining the defibrillator more quickly and training nursing staff to use it.

Heart failure in a district general hospital

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The management of heart failure is an important consideration in allocating resources in a district general hospital
Effect of two laser and dynamic angioplasty devices on platelet reactivity

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Dynamic and laser atherectomy devices are being assessed for coronary angioplasty. Their interaction with arterial wall is the focus of many studies. Their effects on blood elements, however, are largely unknown. We investigated the influence of a dynamic angioplasty catheter with a fast rotating tip "Kensey catheter" (KC) and continuous wave neodymium-yttrium aluminium garnet (Nd-YAG) (1604 nm) laser (with sapphire tip) on in vitro platelet function. Blood from healthy volunteers was citrated and divided into 5 ml samples of whole blood (WB) or platelet rich plasma (PRP). These were exposed to Nd-YAG laser pulses of 10, 25, 50, or 100 J. Similar samples were exposed to the dynamic catheter rotating at 20, 40, or 80 thousand rpm. Control samples were exposed to the appropriate device without activation. Platelet count (PC), platelet aggregate ratio (PAR), and extent of platelet aggregation to collagen in WB and PRP were measured and compared with values in control samples. The KC caused inhibition of platelet aggregation in WB and PRP proportional to speed and duration ($r = 0.81, p < 0.001$). A similar effect was obtained with laser energies $> 10$ J ($r = 0.69, p < 0.001$); lower energies potentiated aggregation ($p < 0.01$). There was no change in PC or PAR to account for either phenomenon. Transmission electron microscopy showed no appreciable membrane disruption of platelets or release of granules.

Exposure to these angioplasty devices inhibits in vitro platelet function without apparent loss of the integrity of platelet structure. This phenomenon and its clinical implication for coronary angioplasty using these techniques justifies further study.

Blood velocity fields at arterial bifurcations: in vivo measurement by high frequency pulsed Doppler velocimetry

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Endothelial function depends on patterns of shear stress, intimately related to the blood velocity field. As this may be important in atherogenesis, which occurs preferentially at bifurcations, we measured velocity fields around eight surgically exposed canine iliofemoral bifurcations with 20 MHz 8 channel Doppler velocimetry. Peak Reynold's numbers ranged from 196 to 564 and frequency parameters from 2 to 4.1, suggesting flow with both viscous and inertial effects important. Geometry was assessed by casts, photography, and 25 MHz ultrasound imaging. The bifurcations were planar to within 5° and asymmetrical; vessel diameters were 3.2 (0.9) mm upstream; 3.4 (1.1) mm and 1.8 (0.4) mm downstream, and bifurcation angles were 58 (10°). Differences in measured velocities among dogs were unrelated to geometrical differences or flow distribution between daughter vessels, which was altered by variable rate pacing. Strong secondary flows were detected, and three dimensional velocity fields were reconstructed from measured vectors. The secondary flows caused profiles calculated on the assumption of parallel flow to be misleading.

The measured velocities indicated spatial differences in shear stress that may explain regional variations in endothelial function and plaque formation at bifurcations.

Central modulation of dyspnoea in chronic heart failure related to opioid axis

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The pathophysiological mechanisms of dyspnoea in chronic left heart failure (CHF) are poorly understood. The level of dyspnoea correlates only weakly with cardiac function and central haemodynamics. The perception of dyspnoea may involve similar mechanisms to the perception of pain: central modulation could explain differences in the severity of dyspnoea between individual patients and in the same patient at different times. The relation between exertional dyspnoea and pain threshold was studied in 40 patients with CHF, New York Heart Association (NYHA) grade II-III. Dyspnoea was assessed with visual analogue scales during maximal symptom limited treadmill exercise, and exercise capacity was measured as peak oxygen consumption ($V_{O2\text{max}}$). The effects of modulating the opioid axis were studied in 10 subjects with NYHA grade III CHF with dihydrocodeine 1 mg/kg and naloxone 0.5 mg/kg. The threshold times for cold immersion pain and for forearm ischaemic pain both correlated with indices of dyspnoea ($r = -0.41, p < 0.01$; $r = -0.37, p < 0.02$). Dihydrocodeine increased $V_{O2\text{max}}$ by 14% ($p < 0.05$) and reduced dyspnoea at a standard workload by 19%
Exonimone increased exercise time with the incremental test from 498 (91) to 573 (94) seconds after two weeks (p = 0.051) and to 572 (100) seconds after four weeks (p = 0.057). With the fixed test exercise duration increased from 252 (75) to 431 (98) seconds after two weeks (p = 0.011) and to 381 (85) seconds after four weeks (p = 0.01). The improvement with the fixed test was greater than that with the incremental protocol at weeks 2 and 4 (p = 0.01, p = 0.057). It improved the corridor walk test but had no effect on pedometer scores. It increased cardiac output during exercise (p = 0.01) and blood flow to the calf, and therefore to skeletal muscle, at rest and after exercise (p = 0.01).

Exonimone improves the exercise capability and haemodynamic variables in patients who have not responded adequately to diuretics and captopril. The magnitude of the effect depends upon the technique used to assess it.

Lignocaine aerosol anaesthesia and dyspnoea in chronic left heart failure

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Stimulation of J receptors and other intrapulmonary receptors has been postulated as the cause of dyspnoea in chronic left heart failure. We assessed the role of these receptors by observing the effects of inhaled small particle aerosols of local anaesthetic. Ten patients with New York Heart Association grade II–III chronic heart failure (CHF) without evidence of intrinsic pulmonary disease were studied. Aerosol with a mass median diameter of 1 μm was generated; 99mTc-diethylene trimine pentaacetic acid labelled aerosol was shown to deposit uniformly in the peripheral lung fields with a peripheral penetration index of 0.94 relative to krypton gas. Each subject performed maximal treadmill exercise limited by dyspnoea, once after lignocaine aerosol, and once after isotonic saline aerosol as control, given in random order. Exercise capacity was determined as peak oxygen consumption (V̇O₂max) from analysis of mixed expired gases. Lignocaine aerosol abolished the cough response to inhaled capsaicin without producing measurable blood concentrations. Gag reflex and phonation were unchanged. There was a minor (6%) fall in forced expiratory volume in one second after lignocaine aerosol. Exercise V̇O₂max after lignocaine aerosol was 10-6-22-2 (median 17-4) ml/kg/minute and after saline aerosol was 10-4-21-1 (17-6) ml/kg/minute. There were no significant differences in respiratory rate, peak ventilation, or visual analogue scores for dyspnoea.

These results suggest that, contrary to expectation, pulmonary airway receptors and J receptors are not major afferent sources for the sensation of dyspnoea in CHF.

**Effect of supine posture on lung mechanics in chronic left ventricular failure**

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The mechanisms of orthopnoea in heart failure are still not well understood, partly because of difficulty in obtaining reliable measurements of pulmonary mechanics in the
supine position. We adapted the forced oscillation technique to measure total respiratory resistance (Rrs) in the sitting and supine positions. Nine patients (8 men, mean age 61.6) with chronic left ventricular failure (New York Heart Association class II–III) and eight matched controls (7 men, mean age 61.5) were studied. Rrs, mid-tidal lung volume (MTLV), spirometry, oxygen saturation (SaO₂) and visual analogue scores for breathlessness (VAS) were recorded in the sitting position, after five minutes' supine rest, and five minutes after return to the sitting position. In the sitting position mean (SE) Rrs in the patients was significantly higher than in controls (3.54 (0.28) v 2.35 (0.33) cm H₂O/l/sec, p < 0.05). Lung volumes were reduced in the patients: total lung capacity (% predicted) was 81.5 ± 103.9, forced expiratory volume in one second (FEV₁) (% predicted) was 68.3 ± 106.1, and forced vital capacity (FVC) (% predicted) was 62.3 v 97.8 compared with controls (all p < 0.01). FEV₁/FVC% was 77.3 in patients v 75.9 in controls (NS). Rrs increased significantly more in patients than in controls on lying supine (85.4 (13.0) % v 39.1 (13.0)%, p < 0.01). Vital capacity declined more in patients than in controls (217 v 100 ml, p < 0.01). SaO₂ did not change in either group. There was a 79.5% increase in VAS dyspnoea scores in supine compared with sitting patients (p < 0.05). No control subjects experienced dyspnoea. In patients resuming the sitting position, all measurements reverted to initial sitting values.

We conclude that patients with chronic left ventricular failure show a substantial reversible increase in airways resistance accompanied by subjective dyspnoea on changing from the sitting to the supine position despite a small decline in MTLV.

Disclosure of increased free radical activity in heart failure by biochemical markers and proton nuclear magnetic resonance spectroscopy

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Free radicals (FRs) can cause myocardial dysfunction. Recurrent episodes of myocardial ischaemia, hypoperfusion-reperfusion cycles in other vascular beds and neuroendocrine activation may lead to increased FR generation in chronic heart failure (CHF). We sought evidence for this in two groups of patients with CHF. Group A (n = 15, age range 30–66) had CHF due to coronary artery disease (CAD); because CAD itself may be associated with increased FR activity (second group B), (n = 15, age range 27–79) with CHF and normal coronary arteries (no CAD) was also studied. Both groups had a comparable degree of systolic dysfunction on echocardiography and were similarly treated with diuretics, digoxin, and vasodilators. Lipid peroxides, markers of FR damage to lipids (where peroxides increase), and plasma thiols, markers of damage to proteins (where thiols decrease), were measured in peripheral venous blood. In normal controls (n = 13, age range 23–64) lipid peroxides were 7.6 (6.5–8.3) nmol/ml (median and interquartile range) and thiols 505 (492–590) μmol/l. Compared with controls both patient groups showed comparable abnormalities in FR markers: in group A (with CAD) lipid peroxides were 10.0 (8.6–11.0) nmol/ml (p < 0.01) and thiols 384 (351–451) μmol/l (p < 0.05); in group B (non CAD) lipid peroxides were 9.3 (8.85–10.3) nmol/ml and thiols 364 (339–418) μmol/l (both p < 0.01). In a further group of 10 patients proton nuclear magnetic resonance spectroscopy of erythrocytes showed a significant reduction in the signal for reduced glutathione, an intracellular FR scavenger.

These results show that CHF per se is associated with increased FR activity in humans. It is possible that FRs contribute to myocardial dysfunction in CHF.

Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease

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Impaired exercise capacity after successful mitral valve replacement (MVR) for rheumatic mitral valve disease (MVD) may result from prosthetic valve dysfunction, persistent pulmonary hypertension, or left ventricular dysfunction. This study reports that the late development of tricuspid regurgitation (TR) is also an important cause of impaired exercise capacity. We studied 19 patients who had previously undergone MVR for rheumatic MVD; nine with clinically significant TR and 10 without. The groups were matched for age and sex, preoperative New York Heart Association class, symptom duration, mean pulmonary artery pressure (PAP) and mitral lesion, and for mitral prosthesis. All had normal preoperative left ventricles and coronary arteries and no significant aortic or tricuspid valve lesion. Postoperative prosthetic mitral valve function was normal and systolic PAP and left ventricular function similar in both groups. Subjects were assessed by echocardiography and colour flow Doppler and maximal treadmill exercise; expired gas was monitored by mass spectrometry. Exercise tolerance was impaired in patients with TR: NYHA class (2.8 (0.6) v 1.2 (0.4), p < 0.001), exercise duration (6.6 (2) v 11.3 (3) minutes, p < 0.001), and peak oxygen consumption (10.8 (3.2) v 16.6 (3) ml/minute/kg, p < 0.001). Respiratory exchange ratio at peak exercise was similar (1 (0.2 (0.7) with TR v 1.07 (0.7) without), indicating maximal exercise in both groups. Patients with TR had smaller increases in systolic blood pressure at maximal exercise (5 (14) v 22 (19) mm Hg, p < 0.05), and minute ventilation at the same minute carbon dioxide production was greater in patients with TR (41 (9) v 33 (6) (4.2) l/minute, p < 0.01).

We conclude that clinically significant TR may develop after successful MVR for rheumatic MVD and have shown that this is associated with appreciable impairment of exercise capacity.

Does spatial orientation of the Björk-Shiley mitral prostheses affect hydraulic performance of the valve?

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We studied the influence of disc orientation in Björk-Shiley mitral prostheses (MVR), on the diastolic Doppler
flow characteristics and on the effective orifice area. Cross sectional echocardiographic studies with pulsed and continuous wave Doppler and colour flow imaging were performed in 37 consecutive patients aged 40 to 75 (mean age 57.2). Patients were divided into two groups according to the direction of the diastolic excursion of the disc. In group A (22 patients) the orientation of the disc was anterior, opening towards the ventricular septum whereas in group B (17 patients) it was posterior, opening away from the septum. MVR size (group A 28.6 (1.5) cm² v group B 29.2 (1.2) mm), left ventricular diastolic dimensions (51 (7) v 51.5 (7.7) mm), fractional shortening (28.9 (9.9) v 29.5 (5.8)) incidence (9/22 v 8/17), and severity (0.46 (0.6) v 0.59 (0.5)) cm² of aortic regurgitation were similar in both groups. Group A patients had higher peak transmitral gradients when compared with group B patients (9.8 (4.4) v 5.1 (1.3) mm Hg, p < 0.001). The effective mitral valve orifice area was consistently smaller than that of the manufacturers in both groups (group A 1.41 (0.8) cm² v group B 1.47 (0.64 cm²), NS) and did not depend on the size of prosthesis. It was not affected by the presence of aortic regurgitation.

It is concluded that in Björk-Shiley mitral prostheses at rest peak gradients are higher when the disc excursion is anterior, but the effective valve orifice area is similar in both orientations and unaffected by the presence of mild aortic regurgitation.

Abnormal leaflet apposition as a cause of mitral regurgitation: a new finding?
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Both transoesophageal and epicardial echocardiography can show the morphology and function of the mitral valve in much greater detail than is possible with conventional transthoracic ultrasonography. With these techniques in 67 patients with New York Heart Association grade III or IV heart failure who were undergoing mitral valve surgery we performed a detailed sequential analysis of the valve leaflets and the zone of coaptation. Absence of leaflet coaptation was identified as the cause of regurgitation in 30 patients. Eight patients had normal leaflet coaptation and apposition and central regurgitation caused by a dilated annulus. In the other patients (n = 29) the leaflets seemed to coapt along the whole closure line, from the anterolateral to the posteroomedial commissure, but there were eccentric regurgitant jets related to an asymmetrical overlap of one leaflet above the other—that is, abnormal apposition. These appearances were often mild, being present without echocardiographic criteria diagnostic of leaflet prolapse. This pattern has not previously been widely recognised as a substrate for mitral regurgitation. To study its possible mechanism eight hearts obtained at necropsy from patients who had died from non-cardiac causes were perfused under pressure retrogradely through the aortic valve, to fix the mitral valve leaflets in the closed position, thus simulating systole. The hearts were sectioned, and the minimum dimensions between the free edges of the leaflets and the border of the rough zone, corresponding to the width of normal leaflet apposition, were measured. The minimum dimension at any site along either leaflet was 1.5–4.0 mm (mean 2.9 mm).

These data suggest that asymmetrical apposition of the mitral leaflets, in which one leaflet protrudes towards the left atrium by 3 mm or more over the other leaflet at the zone of coaptation, may be sufficient to cause significant regurgitation. The probable mechanism is regurgitation under the reflected edge of the abnormal leaflet, between adjacent primary chordae tendineae. The identification and localisation of this problem will be of value in understanding the mechanism of regurgitation in particular patients, thereby allowing an appropriate mitral valve repair operation to be performed.

Infective endocarditis: Is it a transoesophageal echocardiographic diagnosis?
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The diagnosis of infective endocarditis (IE) and its major cardiac complications can prove difficult using conventional transthoracic echocardiography (TTE). To assess the role of transoesophageal echocardiography (TOE) we studied 60 consecutive patients with suspected IE by both TTE and TOE. TOE suggested IE in 24 of 27 patients in whom IE was subsequently confirmed. Valves affected included the aortic valve (AV) (seven native, nine prosthetic), mitral valve (MV) (seven native, two prosthetic), tricuspid valve (TV) (one patient), and both a TV and pulmonary valve (PV) (one patient). Vegetations were diagnosed by TOE in 17 patients (and confirmed in all five who subsequently underwent surgery) but in only five patients using TTE. In three patients, all of whom had persistent fever despite appropriate antibiotic treatment, TOE showed cavities consistent with aortic root abscesses; only one was seen with TTE. In another two patients TOE disclosed large cavities around the aortic root but underestimated the anterior extent of these compared with surgical findings. TOE disclosed a small mycotic aneurysm on the anterior MV leaflet in two patients and a fistula in a patient with an aortic root replacement; these had not been detected with TTE. TOE did not suggest IE in any of the 33 patients with other clinical diagnoses. TOE was limited in several respects: (1) the anterior aspect of the aortic root was not well visualised; (2) assessment of prosthetic AVs was limited by acoustic shadowing; and (3) TOE did not provide additional information in the patients with TV and PV IE.

We conclude that TOE provides important anatomical and functional insights in patients with documented IE but should not be used to exclude the diagnosis. Early use of TOE in suspected IE should increase the diagnostic yield and help reduce the morbidity and mortality associated with this serious condition.

Who refers patients for repeat valve operations?
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We have reviewed our experience of patients who required repeat valve replacement over four years, during which 286 tissue valves and 496 mechanical prostheses were inserted in our institution; 48 patients (16%) underwent repeat valve replacement. Of these, 30 patients (62%) had
previous tissue valves and 18 (38%) mechanical valves. Repeat valve replacement was necessary because of degeneration of the prosthesis in 22 patients (45%), endocarditis in 14 (29%), paraprosthetic leak in seven (15%), thrombotic occlusion in three (6%), dehiscence of valve ring in one (2%), and haemolysis in one (2%). Eleven patients were admitted with pulmonary oedema, and in only one case was this due to endocarditis. The pattern of re-referral for consideration for further surgery was surprising. Deterioration in the patient's condition was most often detected by the general practitioner despite the fact that all of these patients were under "routine" medical and surgical follow up: 70%, were referred back by general practitioners, 4% by cardiac surgeons, and 26% by cardiologists. Even excluding patients who were admitted as emergency cases with suspected endocarditis or jammed prostheses, further assessment for reoperation was initiated by general practitioners in 63% of cases.

These findings raise questions about the merits of hospital follow up of patients with heart valve prostheses.

Value of complete myocardial revascularisation in combined ischaemic and mitral valve surgery

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Operative and follow up data on 70 patients with combined myocardial revascularisation and mitral valve surgery (63 valve replacements, four repairs, and three replacements) were analysed to assess the early and late outcomes. The valve disease was ischaemic origin (ischaemic heart disease-IHD group) in 30 patients (43%) and non-ischaemic origin (non-IHD group) in 40 (57%). Thirty patients had surgery between 1977 and 1984 (17 IHD, 13 non-IHD) and 40 between 1985 and 1989 (13 IHD, 27 non-IHD). The operative mortality for the ischaemic group came down between the two periods (from 53% to 15%) and remained similar in the non-ischaemic group (7-6% vs 11%). Patients with complete myocardial revascularisation had a much lower operative mortality than those with incomplete revascularisation (20% vs 53%, IHD group; 6% vs 20%, non-IHD group). In the last 40 patients at the end of a mean of 18 months' follow up (range 2-62 months) two thirds of patients in the IHD group and one third of those in the non-IHD group were of New York Heart Association class I–II functional state.

Our results suggest that all patients with mitral valve disease should undergo coronary angiography before valve surgery, and to minimise the operative risk complete myocardial revascularisation is strongly recommended.

Early experience of a low speed drill for recanalisation of chronic total coronary occlusions

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The success rate of conventional angioplasty in chronic coronary artery occlusion is low (<50% and decreasing with age of occlusion). Low speed rotational coronary angioplasty (RA) has been shown to be safe, and primary success rates of up to 60% have been reported. We attempted RA with the rotational angioplasty catheter system (ROTACS) device on six occlusions (five right coronary, one circumflex) in six patients in whom attempts at conventional angioplasty had failed (five unable to pass guide wire; one unable to pass balloon over wire). Estimated duration of occlusion was five to 18 (mean 10) months. Mean length of occlusion was 2-4 (range 0-5–3-2) cm. Successful recanalisation followed by conventional balloon angioplasty was achieved in 2/6 (including the patient with successful passage of the guide wire). Three attempts to recanalise the right coronary artery were unsuccessful. On each occasion the ROTACS drilled along the full length of the occlusion, but it was impossible to pass a guide wire into the distal lumen. Simultaneous contrast angiography of right and left coronary arteries showed the exact position of the drill tip to be within 1 mm of the distal vessel lumen in each case. In the one attempt to recanalise a circumflex artery no progress could be made due to the tortuous nature of the proximal vessel, which prevented drill advancement.

Our experience shows a low success rate with RA when conventional angioplasty has failed. A major problem is failure to enter the distal lumen despite successful progress of the ROTACS past the occlusion.

Angioplasty of totally occluded arteries by a probing catheter

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A 21 mm probing catheter (USCI) was used in nine patients with chronic total coronary artery occlusion. Occlusion was present for five (two) months (range 1 to 10 months) in the left anterior descending artery (five patients), right coronary artery (one) and left circumflex artery (one). In two patients attempts to cross the lesion with a 2 mm low profile balloon and wire had failed. A standard 0-016 wire (USCI) and probing catheter successfully crossed the lesion in 8/9 arteries. After crossing the lesion distal coronary injection through the probing catheter lumen confirmed the presence of the catheter in the true lumen and outlined the distal artery. A probe balloon or low profile balloon was then passed through the inner lumen of the probing catheter and withdrawn to the site of the stenosis. Serial inflations were performed with a 2.5 or 3 mm balloon, or both, leaving a residual stenosis of 28 (18)% stenosis. In two patients further distal stenoses were also dilated. Only one complication was observed—a distal coronary embolus—and no patient developed infarction or required surgery.

The probing catheter facilitates dilatation of chronic totally occluded coronary arteries.

Intracoronary stents for angioplasty of stenoses of saphenous vein aortocoronary bypass grafts

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The success of percutaneous angioplasty of stenoses of saphenous vein aortocoronary bypass grafts is limited by a very high restenosis rate, up to 60% for proximal graft
Percutaneous angioplasty: from peripheral to coronary arteries

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Unlike angiography, angioplasty allows direct visualisation of arterial lumen. We used high resolution angioscopes percutaneously before and after angioplasty in peripheral and coronary arteries. The angioscopic features were compared with the corresponding angiographic findings.

In 14 patients with peripheral vascular disease 10 had total occlusion treated with Kensey atherectomy catheter (KC). In four with stenotic lesions balloon angioplasty was used. With saline flush, good views were obtained in 13/14 arteries before angioplasty and in 10/14 afterwards due to increased blood flow. Angioplasty revealed features often undetected by angiography and was superior in establishing the precise nature of occlusive pathology (thrombotic or atheromatous). KC did not seem to generate any more luminal disruption than conventional balloon. Encouraged by these results, we made 18 attempts (n = 18) at percutaneous coronary angioplasty before and after percutaneous transluminal coronary angioplasty (PTCA) in six patients (one left anterior descending and five right coronary arteries), with either a 0.5 mm diameter (n = 2) or 1.4 mm diameter (n = 4) angioplasty, or both (n = 12). The angioplasties were introduced through 9 F PTCA Judkins catheters. An intelligible view was possible in 7/10 attempts with the 1.4 mm diameter angioplasty but in only 2/8 with the 0.5 mm diameter angioplasty. Angina occurred during 3/10 attempts with the 1.4 mm diameter angioplasty. The 0.5 mm diameter angioplasty induced angina in 5/8; in one, this was associated with demonstrable coronary spasm. No rise in creatine kinase (heart type) activity was observed in any of the patients. After PTCA angioplasty revealed intimal flaps at all PTCA sites visualised, mural thrombus in one, and small dissection in another; neither was obvious on angiography. In one patient clinical and angiographic features suggested thrombotic pathology; angioplasty showed atheromatous occlusion with no thrombus.

From peripheral to coronary arteries: analysis of particles resulting from simulated dynamic angioplasty

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The Kensey catheter (KC) utilises a fast rotating cam and high pressure fluid jet to recanalise occluded arteries. We have successfully used 8 F KC in peripheral arteries, a 5 F size is proposed for coronary use. There has been some concern regarding the risk of embolism of particles resulting from this technique. A study was undertaken to investigate these particles and some of the factors that influence their size. Eighty four fresh endarterectomy specimens were inserted in a flow circuit and randomised to undergo a simulated procedure using a 5 F or 8 F KC at a range of predetermined cam speeds (CS) (20 000-80 000 rpm) and flow rates (FLR) (16-60 ml/min). The collected debris was mounted on slides, and all particles > 4 μm were measured with computerised edge detection technique. Most particles (median 90.8 (SD 3.4)) were < 35 μm in diameter. In those remaining (9.2 (3.4)) significant differences were found between the maximum particle size (MPS) in each group (from 170 to 985 μm). Increasing CS independently reduced MPS from 985 to 320 μm (p < 0.001). Increasing FLR and reducing catheter size had a smaller but significant effect on reducing MPS (p < 0.005 and p < 0.01).

In conclusion, although most particles resulting from the use of KC in atheroma were small, a low proportion of larger particles was also detected. Cam speed, flow rate, and catheter size had significant effects on MPS. These results may be particularly important for future use of KC in coronary arteries.

Coronary angioplasty of chronic total occlusions and tortuous vessels

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Percutaneous transluminal coronary angioplasty of chronic total occlusions or tortuous vessels has been attempted using a balloon on a wire dilatation catheter system (Buchbinder-Versiflex) designed so that the distal tip of the wire can be rotated and flexed through a control on the proximal end of the catheter, potentially allowing extra wire tip control. This is combined with a low profile (0.034 inches for the 2.0 mm diameter catheter). In 57 of 925 consecutive angioplasty procedures this system was used, 15 in the left anterior descending, 15 in the circumflex, and 27 in the right coronary arteries. Lesions were classified as total occlusions (TIMI 0 or 1) of duration less than three
months (21) or greater than three months (22), distal or difficult access due to tortuosity or acute angulation (eight) or acute occlusions after angioplasty (six). The system was used as first choice in 20 lesions and as either a second or third line system in the remainder. The success rate, defined as crossed, dilated with residual stenosis less than 50%, was 74% compared with an overall success rate of 92%. The success rate was higher in occlusions less than three months' duration (80%) compared with those greater than three months (64%). The system was successful in five lesions considered to be complex owing to severe tortuosity, acute angulation, or their distal nature. Six acute occlusions after angioplasty were successfully crossed when standard systems could not be reintroduced, four with sustained patency. Overall mortality was 0·5%, and two patients proceeded to urgent bypass surgery, all after acute occlusions with another system. The main disadvantages of the system are that it is not exchangeable over a guide wire and that the lesion needs to be recrossed to introduce a larger balloon. There is also no distal port for contrast injection to exclude a false channel, which occurred in three cases.

This system is an important adjunct to conventional "over the wire" or monorail systems. It is suitable as a first line approach to acute or chronic total occlusions and as a second line system for tortuous or angulated vessels not amenable to crossing with a conventional system and for acute occlusions occurring during angioplasty.

Delay to invasive investigation and revascularisation in coronary heart disease in South West Thames: cause for concern?
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The accessibility of invasive investigation and revascularisation procedures to the population of North West Surrey health district in South West Thames region was audited over the 10 years 1979-88. The mean catchment population during the period was 205,000, and cross boundary flow was balanced. Waiting time to investigation/intervention by the regional cardiac centre was compared with that of the private sector. Deaths of patients on the waiting list for investigation/operation were recorded. The regional centre favoured in the first five years was St Thomas's Hospital, Lambeth, and in the second five years St George's Hospital, Tooting. A total of 823 patients aged 34-80 were referred for investigation of ischaemic heart disease (including 15 with concomitant valvar heart disease), 204 to the private sector. After some initial vacillation the mean waiting time for coronary angiography after referral increased from 68·2 (SE 6·85) days (range 23 to 153 days, n = 42) in 1984 to 114·3 (12·1) days (range 22 to > 430 days, n = 98) in 1988 in the public sector, but remained unchanged over 10 years in the private sector, at 15·8 (0·16 days) (range 1 to 62 days, n = 204). Mean waiting time to elective surgery in the public sector increased from 107·9 (15·4) days (range 12 to 240 days, n = 26) in 1984 to > 274·8 (24·2) days (range 22 to > 506, n = 60) in 1988, but the waiting time for emergency angiography remained static at 4·7 (0·07) days (range 0 to 24 days, n = 132) over 10 years and for surgery 26·1 (1·02) days (range 0 to > 400 days, n = 103). In the private sector the overall waiting time to angiography was 15·8 (0·16) days (range 1 to 62 days, n = 204) and for surgery 22·8 (0·52) days (range 2 to 152 days, n = 124), both taken over 10 years. There were 15 cardiac deaths in patients with ischaemic heart disease alone, all of whom were on the public sector routine waiting lists for catheterisation and surgery. This exceeded the overall surgical mortality (1·4%). Fifty three (8·6%) patients on the public sector waiting list for surgery waited for longer than a year and required reinvestigation, 36 in 1987-8.

Prolonged waiting times to investigation and surgery in the public sector reflect underprovision of service which seems to be worsening in South West Thames region. This exposes these patients to unfair and unjustifiable risks in terms of morbidity and mortality.

Changes in practice of cardiopulmonary resuscitation have not affected outcome
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The United Kingdom Resuscitation Council has modified the guidelines for drug usage in patients with asystolic cardiac arrest. Atropine is recommended as the drug of first choice, calcium is no longer recommended, and sodium bicarbonate should be reserved for patients in whom an acidosis had been reported. We audited the asystolic cardiac arrest rates for 1982 (n = 55), 1986 (n = 67), and 1988 (n = 57) that occurred outside the cardiac care unit (CCU). Atropine use increased, from 29% to 52% to 61% over the six years. Bicarbonate use did not change from 1982 (74%) to 1986 (74%) but fell in 1988 (35%). Calcium use was similar to that of bicarbonate in 1982 (73%) and 1986 (61%) and fell in 1988 (24%). Adrenaline use has remained unchanged at 72%, 63%, and 65% over the same period. Survival from asystolic arrests (hospital discharge) has remained unchanged at 5·4% (1982) v 3·0% (1986) v 3·5% (1988) (NS). We also audited the total cardiac arrests (not in CCU) for 1982 (n = 120), 1986 (n = 153), and 1988 (n = 150). Of these, 11·6%, 7·2%, and 8% (NS) were discharged from hospital. Drug usage for all arrests for the three respective years were: bicarbonate 67·5%, 71·2%, and 28%; calcium 59·2%, 58·1%, and 16·9%; adrenaline 51·5%, 74·6%, and 44%; atropine 15·8%, 55%, and 51·8%; and lignocaine 13·3%, 35·3%, and 21·9%. Asystole as a primary event in the CCU was uncommon, occurring in 13 of 956 (1·3%) patients with a myocardial infarction between 1986 and 1988. Seven patients had received atropine as the first drug, and six had attempted emergency pacing. No patient survived to be discharged home. Over the same period there were 43 cardiac arrests in CCU due to ventricular fibrillation (VF), 11 patients having had an anterior myocardial infarction and 12 an inferior one. Of those with VF, 67% were discharged from hospital, with 48·8% known to be alive six months subsequently.

Although the United Kingdom Resuscitation Council guidelines for the management of asystole are becoming assimilated by the resuscitation teams, changing drug usage has not affected outcome. This audit also shows that survival from cardiac arrest has remained constant from 1982 to 1988.
Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting

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This study was designed to assess aspects of anxiety, depression, and social adjustment in patients awaiting coronary artery surgery. Patients on the waiting list for routine surgery were sent a series of questionnaires designed for this purpose. One hundred and nine questionnaires were sent, and 68 (62%) were returned. Anxiety and depression were assessed with the hospital anxiety and depression (HAD) scale. Social functioning was assessed by means of several nine point rating scales, on which the patients were asked to indicate the extent to which their work, family relationships, social activities, private leisure activities, and home management were impaired. Patients were also asked to indicate their present severity of clinical cardiac symptoms with the New York Heart Association's classification. On the HAD scale 19 (28%) of patients scored in the clinically significant range for anxiety. Time on the waiting list was positively and significantly related to anxiety (p = 0.05). Thirty two (47%) of patients scored in the clinically significant range for depression. Time on the waiting list was positively and very significantly related to depression (p = 0.005). Positive and significant relations were found between time on the waiting list and impairment of work (p < 0.0001), family relationships (p < 0.0001), private leisure activities (p < 0.0001), and social activities (p = 0.004). No relation was found between any of the above variables and severity of clinical symptoms.

This study highlights the social and psychological consequences of the long waiting lists for coronary artery bypass grafting in this country.

Heartstart Scotland: initial experience of a nationwide scheme for out of hospital defibrillation by ambulance crews

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Widespread provision of out of hospital defibrillation in Britain has been limited by the rate at which ambulance crews can undergo extended training, including tuition, in recognition of electrocardiograms. We attempted an alternative approach in the Scottish Ambulance Service, training ambulance crews in basic life support and in the use of a semiautomatic defibrillator (Laerdal 2000). Between 1 October 1988 and 30 September 1989, 96% of the 2000 vehicle crews completed an eight hour training programme. A total of 268 defibrillators were purchased by public subscription during the study period, resulting in a cumulative availability of 5548 defibrillator weeks. During this period crews equipped with defibrillators recorded data on 1111 cardiac arrests, in which defibrillation was undertaken in 602 (54%). Data on outcome were obtained for all 602 patients from the receiving hospital; 180 patients (29.9%) reached hospital with a spontaneous pulse, and 75 (12.5%) were discharged alive. Extrapolation to the Scottish Ambulance Service's total of 395 ambulances would yield a hospital discharge rate of 278 a year.

Pre-hospital defibrillation with semiautomatic defibrillators is feasible and can be introduced rapidly owing to the limited staff training requirements.

Interpretation of electrocardiograms in the accident and emergency department

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To determine the accuracy with which casualty officers interpret electrocardiograms (ECGs) in patients presenting to the accident and emergency department with anterior chest pain we conducted a prospective double blind study in which casualty officers' interpretation of electrocardiograms was compared with that of a consultant cardiologist. Three hundred and fourteen consecutive patients attending the department with anterior chest pain over a two month period were studied with respect to the percentage of attenders who complained of anterior chest pain, the accuracy with which the casualty officers interpreted normal and abnormal ECGs, and the rate of inappropriate management. Of all those attending the accident and emergency department, 4% presented with chest pain; 90% of normal ECGs were correctly interpreted by casualty officers and 43% of abnormal ECGs were incorrectly interpreted by casualty officers; and 96.5% of patients with chest pain were managed correctly in casualty.

Senior house officers in the accident and emergency department, although good at identifying the presence of an abnormality of an ECG, are less good at defining the nature of the abnormality. This may result in inappropriate management of some patients. Audit of all ECGs should be undertaken by someone with experience of their interpretation. New accident and emergency staff should receive training in the interpretation of ECGs.

Invasive cardiological assessment and intervention: an audit of health district activity

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The requirement for invasive cardiological assessment and intervention in a defined health district in South West Thames region was studied prospectively over the 10 years from 1979 to 1988. The mean population was 205 000 and cross boundary flow of referrals was balanced; private patients were included. A total of 1000 catheterisation procedures were performed, 823 for coronary artery disease and 177 for valvar heart disease (VHD). Subsequently 497 patients underwent coronary artery bypass grafting (CABG) and 140 patients valvar surgery with or without CABG. With the exception of 1984, growth in the need for investigation of coronary artery disease and revascularisation has been continuous. Thus whereas the 10 year mean district requirement for coronary angio- graphic was 401 procedures/million population/year the 1988 requirement was twice that (848). Likewise, whereas the 10 year mean requirement for bypass grafting was 242
operations/million population/year the figure for 1988 was 395 (estimated). Valvar investigation and surgery showed little change over the period; 18 (SE 1.9) patients were investigated annually, and 14-3 (1-3) underwent surgery. Figures/million population/year are 88 and 70 respectively.

North West Surrey has a standardised mortality ratio (SMR) of 0-78 for ischaemic heart disease and of 1-0 for VHD. Extrapolation towards the current national need for invasive investigation seems to approach 1200 procedures/million population/year. The extrapolated current need for coronary artery surgery approaches 500 operations/million population/year. As the mean age of the population of the district is lower than the national average the predictions for valvar heart disease may be skewed. The national target for 1990 for CABG is 300 operations/million/year.

Comparative study of left ventricular structure and function in elite athletes

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Adaptations to left ventricular (LV) structure and function in athletes seems to be dependent on the type, intensity, and duration of exercise training. We therefore studied two clearly defined groups of elite athletes by M mode and Doppler echocardiography, with a group of sedentary subjects as controls. All groups were age and sex matched. Group 1 comprised 10 elite endurance athletes with mean maximal oxygen consumption (VO2max) 74-7 (SD 4-8) ml/kg/minute. Group 2 comprised 10 elite weightlifters with mean maximal VO2max 45-3 (6-6). Group 3 comprised 10 sedentary individuals with VO2max 44-5 (7-0). Left ventricular end diastolic dimension was significantly higher in group 1 (5-72 (0-23)) than in group 2 or 3 (5-29 (0-29), 5-19 (0-31) respectively, p < 0-001). Left ventricular mass index was significantly higher in groups 1 and 2 (156-4 (19-8), 138-6 (24-1) respectively) than in group 3 (104-1 (10-5), p < 0-001). Percentage fractional shortening was used as an index of systolic function, and no significant difference was found between the groups. Doppler E/A ratio was taken as an index of diastolic function and was significantly raised in group 1 at rest (3-37 (0-81)) compared with groups 2 and 3 (2-12 (0-76), 1-99 (0-34) respectively, p < 0-003). On exercise the E/A ratio in group 1 was significantly higher than in group 3 (1-95 (0-48) and 1-23 (0-16), p < 0-001) and tended to be higher than in group 2 (1-68 (0-49), NS).

These data show that both modes of intense training produce left ventricular hypertrophy. Diastolic function is enhanced in the endurance trained athletes but not in the weightlifters.

Myocardial flow and function in microvascular angina

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Patients who have typical anginal chest pain but who have angiographically normal coronary vessels present a major clinical problem. Ten patients, three male and seven female, with typical exertional angina and abnormal exercise thallium scans underwent angiography and were found to have entirely normal vessels with no evidence of coronary artery spasm. Myocardial flow was assessed using xenon washout. Xenon was injected into the coronary artery under direct vision, and scans were obtained with a mobile gammacamera fitted with a biplane collimator. Distribution within the myocardium was assessed, and flow was calculated from washout curves using peak to 30 seconds and applying the Kety formula. At rest right coronary artery and left coronary artery distribution and flows were within normal limits; RC flow 55-5 (8-8), left anterior descending 66-6 (11-3), and circumflex 62-3 (9-9) ml/100 g/minute. With atrial pacing to a heart rate similar to that achieved during exercise, chest pain occurred in all patients. Distribution volume fell in at least one coronary distribution in all patients, and this was associated with reduced coronary flow by a mean of 28-6 (9-4)% (p < 0-05). By gating the scans to the electrocardiogram and reconstructing list mode data into a representative cardiac cycle, wall motion can be obtained from the same data that produced the washout curves. Areas of reduced distribution and flow were associated with reduced wall motion in all 10 patients.

These results suggest that in these patients a combination of reduced myocardial flow and associated wall motion abnormalities constitutes an ischaemic response, presumably at the microvascular level.

Interaction between cycle length and ventricular loading conditions on repolarisation

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Alteration in the normal time sequence of ventricular repolarisation encourages arrhythmia formation. There is evidence that the timing of ventricular repolarisation is not only dependent on cycle length (restitution process) but also on loading conditions (contraction-excitation feedback). This study aimed at examining a possible interaction between the two by comparing the timing of repolarisation of premature beats (cycle length 350 mseconds) with that of paced steady state beats (cycle length 700–850 mseconds) under altered conditions of ventricular loading. We recorded monophasic action potentials from the left ventricular endocardium as a measure of the time course of repolarisation with a catheter that incorporates a micro-manometer sensor for recording ventricular pressure. The Valsalva manoeuvre was employed to alter ventricular loading whereby forced expiration impedes venous return and peak systolic pressure falls. Our observations were made during the early part of the Valsalva manoeuvre, before significant autonomic effects occur. Steady state atrial pacing was established. An early beat of cycle length 350 mseconds was interposed during a steady state pacing train before the start of the procedure and again during the low pressure phase. Peak systolic pressure for the steady state beats fell from 134 (SD 23) to 97 (30) mm Hg and for the early beats from 97 (23) to 66 (28) mm Hg. Under control conditions before the Valsalva manoeuvre monophasic action potential duration as measured at 90% repolarisation was shorter in the premature beats than in
the control beats by 9 mseconds (298 (17) v 289 (13) mseconds). During the Valsalva manoeuvre at the lower pressures monophasic action potential duration was shorter in the premature beats than the preceding beats by 22 mseconds (303 (14) v 281 (20) mseconds).

Our results show that changes in ventricular loading alter the normal differences in repolarisation in response to an abrupt shortening in cycle length. These findings may be important in the genesis of arrhythmias initiated particularly by premature beats.

Postprandial hypotension and splanchic vasodilatation are prevented by octreotide in patients with primary autonomic failure

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We studied the haemodynamic responses to a liquid meal in eight patients with primary autonomic failure before and after octreotide (SMS 201-995), which inhibits the release of gastrointestinal peptides. Subjects were studied while supine, in a temperature controlled laboratory (23 (1)°C), after a 12 hour fast. Saline placebo (0-5 ml) or octreotide (50 µg) was injected subcutaneously 30 minutes before a balanced liquid meal (66 g carbohydrate, 22 g fat, and 18 g protein), and measurements were made for 60 minutes. Blood pressure (BP) heart rate (HR) (Sentron), cardiac index (CI, assessed with continuous wave Doppler ultrasound (Exerdrop)), forearm blood flow (FBF, assessed with strain gauge plethysmography), digital skin microvascular flow (LDF, assessed with laser Doppler flowmetry (Periflux, PFB2b)) were measured non-invasively. Superior mesenteric artery blood flow (SMABF) was measured by a real time sector scanner and pulsed Doppler flowmeter (Ultramark 8 ATL). After placebo and the meal mean arterial pressure (MAP) fell (122 (8) to 99 (9) mm Hg, p < 0.05). SMABF rose (0-41 (0-05) to 0-743 (0-148) l/minute, p < 0.05) and superior mesenteric artery vascular resistance (SMAVR) fell (371 (94) to 167 (33) units, p < 0.05). There were no other haemodynamic changes. After octreotide there was a transient rise in MAP (118 (6) to 135 (8) mm Hg, p < 0.05). SMABF fell (0-497 (0-03) to 0-40 (0-03) l/minute, p < 0.05) and SMAVR rose (240 (19) to 370 (26) units, p < 0.05). There was no change in HR, CI, FBF, and LDF. After octreotide, ingestion of food did not change MAP (127 (7) to 125 (9) mm Hg), SMABF (0-373 (0-04) to 0-323 (0-04) l/minute), SMAVR (352 (19) to 386 (31)), or other haemodynamic variables.

We conclude that in patients with autonomic failure ingestion of food increases SMABF and reduces SMAVR, which probably contributes to the fall in BP, especially as there is no compensatory rise in HR, CI, and FVR, as observed in normal subjects. Octreotide prevents superior mesenteric artery vasodilatation and postprandial hypotension, probably through inhibiting the release of vasodilatory gastrointestinal peptides.

Changes in ultrafilterable and non-filterable serum magnesium concentrations after acute myocardial infarction

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To describe changes occurring in the free and protein bound plasma magnesium concentrations after acute myocardial infarction, 30 patients admitted with a diagnosis of suspected acute myocardial infarction (AMI) had serum total magnesium (Tmg) and ultrafilterable magnesium (UMg) concentrations estimated on five separate occasions over two days. Fourteen patients were subsequently shown to have had an AMI whereas the remaining 16 with an alternative diagnosis formed a control group. At the time of admission mean (SE) Tmg concentration was 0-853 (0-025) mmol/l in the control group and 0-774 (0-018) mmol/l in the infarct group, representing a deficit of 9-26% (p < 0.02). Mean UMg concentration at admission was 0-638 (0-019) mmol/l in the control group and 0-585 (0-014) mmol/l in the infarct group, a deficit of 8-31% (p < 0.05). Mean non-filterable magnesium (NfMg) concentration was 11-68%, lower in the infarct group, though this difference was not significant (p < 0.10). In patients with AMI mean Tmg concentration rose by 0-072 mmol/l (9-3% (p < 0.02) and NfMg concentration by 0-02 mmol/l (10-6%, p < 0.05) over the first 48 hours while no significant change in UMg concentration was noted. In contrast, Tmg concentration fell by 0-044 mmol/l (5-2%, p < 0.02) in the control group with no change in UMg and NfMg concentrations being observed. Mean venous H+ concentration fell by 6%, from 48-8 (1-31) mmol/l to 4-10 (0-86) mmol/l in patients with AMI. This change showed a significant negative correlation with the observed increase of mean NfMg concentration (R = 0-903; p < 0.05).

In contrast to the previously reported changes occurring in Tmg concentration after AMI, we found that the physiologically active ultrafilterable magnesium component remains stable during the early postinfarct period. Our data additionally suggest that displacement of Mg2+ from its protein binding sites, by H+, may be important in producing buffering of UMg.

Platelet activating factor antagonist protects the heart from arrhythmias and limits the extent of myocardial infarction during early ischaemia

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There is increasing evidence that platelet activation aggravates the effects of coronary artery occlusion (CAO). To investigate this we examined the effects of inhibition of platelet activating factor (PAF) during 30 minutes' CAO in the rabbit on haemodynamics, infarct size, and arrhythmias. Infarct size was measured in four left ventricular (LV) sections of equal thickness and was expressed as percentage zone at risk (obtained in 10 separate hearts after 90 minutes CAO). In the control group (n = 10) CAO produced an immediate decrease in arterial pressure (100 (2) mm Hg to 91 (3) mm Hg, p < 0.01) while heart rate (HR) remained unchanged (NS) and half developed ventricular fibrillation (VF). The extent of infarction in each section was 52 (2)% 54 (2)% 44 (2)% and 35 (2)% from base to apex and 46% of total LV. After pretreatment with the PAF antagonist BN 50739, 10 mg/kg intravenously (n = 10), CAO produced little change in arterial pressure (93 (3) mm Hg to 86 (5) mm Hg) and HR (both NS), and a fifth developed VF. The extent of infarction was significantly reduced in each section (36 (1)% 43 (2)% 32 (1)% and 26 (1)% from base to apex and 34% of total LV (p < 0.001 v untreated group).
These results indicate that use of a PAF antagonist can attenuate the extent of myocardial necrosis and the incidence of ventricular arrhythmias during early stages of acute myocardial infarction.

Differential expression of ventricular proto-oncogenes in three models of cardiac hypertrophy

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Various stimuli, including pressure and volume overload, result in cardiac hypertrophy. To investigate the role of proto-oncogene products in signal transduction in myocardial growth we compared hypertrophy in three rat models with changes in ventricular H-ras, c-myc and c-fos messenger (m) RNAs measured by hybridisation to specific complementary (c) RNAs. Left ventricular (LV) pressure overload induced by aortic constriction increased heart weight and LV proto-oncogene mRNAs at three days compared with controls (H-ras 1-5 (0-2) v 0-6 (0-2) optical density (OD) units/total mRNA, p < 0-01; c-myc 1-3 (0-2) v 1-0 (0-1), p < 0-05; c-fos 2-9 (0-5) v 1-0 (0-1), p < 0-05; mean (SE), n = 8). In genetically hypertensive rats, despite established hypertrophy, no changes in LV mRNAs were found at five or 12 weeks, but right ventricular (RV) mRNAs were reduced compared with controls (H-ras five weeks, 0-14 (0-07) v 0-96 (0-04), p < 0-01 and 12 weeks 0-03 (0-01) v 0-22 (0-04), p < 0-01; c-myc five weeks 0-29 (0-12) v 0-97 (0-04), p < 0-01 and 12 weeks 0-06 (0-007) v 0-22 (0-03), p < 0-01; n = 8), suggesting reduced RV load. Marked LV and RV hypertrophy resulting from thyroid hormone treatment (triiodothyronine 50 μg daily for 14 days) was associated with increased LV c-fos (0-63 (0-1) v 0-33 (0-08), p < 0-05) and RV myc and fos (c-myc 0-95 (0-09) v 0-43 (0-13), p < 0-01; c-fos 0-8 (0-04) v 0-32 (0-03), p < 0-01, n = 8), consistent with continuing changes in LV and RV volume load.

Cardiac refashioning is associated with different effects on pretranslational expression of specific proto-oncogenes in the left ventricle and right ventricle, while established hypertrophy can be found without maintained proto-oncogene stimulation. These findings provide insight into the mechanisms of cardiac growth and potential for controlling the hypertrophic process in disease states such as hypertension.

Effects of captopril on arrhythmias and cellular electrophysiology during low flow ischaemia and reperfusion

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Treatment with captopril reduces the ventricular arrhythmias recorded from patients with severe heart failure and is associated with improved mortality. To investigate the cellular electrophysiological (CEPT) effects of captopril we studied isolated guinea pig hearts paced at 3-3 Hz and perfused at 32°C with oxygenated Krebs solution contain-

Do monounsaturated fatty acids have a role in restenosis after coronary angioplasty?

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Recent work has suggested that a diet enriched with fish oils may reduce restenosis after coronary angioplasty. The object of this study was to determine whether there was any association between the long term intake of fatty acids, as reflected by the fatty acid composition of subcutaneous fat, and restenosis after percutaneous transluminal coronary angioplasty. Eighty two patients who had undergone successful single vessel angioplasty were studied. All underwent angiographic follow up. The fatty acid composition of the subcutaneous fat was determined by gas liquid chromatography. Restenosis occurred in 37 (48%). The concentrations of the monounsaturated fatty acids were lower in those who had restenosis. The percentage of palmitoleic acid was 5-8 (2-28)% in those who had restenosis, and 7-1 (2-44)% in those who did not (p < 0-001). The percentage of oleic acid was 41-0 (3-3)% in those who had restenosis and 42-5 (4-18)% in those who did not (p = 0-08). The percentage of the saturated fatty acid palmitic acid was increased in those who had restenosis compared with those who did not (24-7 (2-92)% and 23-7 (2-23)% respectively, p = 0-06). There were no other differences in the subcutaneous fatty acid composition of the two groups.

These results lend support to the recent suggestion that monounsaturated fatty acids may have a protective role in relation to the development of coronary arterial disease.
Antiarrhythmic benefits of left ventricular preload reduction

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Ventricular stretch may play an important part in arrhythmogenesis in heart failure. Though stretch is known to influence action potential duration in isolated muscle strips, it remains uncertain whether haemodynamic changes in the whole heart can influence action potential duration. We studied the effects of left ventricular pressure changes in an isolated working heart preparation. Guinea pig hearts (n = 23) were perfused via the left atrium, ejecting against an aortic afterload. Left ventricular diastolic and systolic pressures were varied independently. Intra-cellular potentials were recorded from the epicardium of the left ventricle using microelectrodes. An increase in left ventricular end diastolic pressure from 2.2 to 8.2 mm Hg, at constant systolic pressure, shortened action potential duration by 10.2 (SE 2.1) ms (p < 0.001). After a change in pressure action potential duration reached a new steady state after 30 seconds. Changes were fully reversible. Increase in left ventricular peak systolic pressure from 60 mm Hg to 100 mm Hg, at constant diastolic pressure, caused a lesser degree of shortening of action potential (2.7 (0.6) ms, p < 0.002). The gradients of the regression lines relating the shortening of action potential duration to the increase in end diastolic pressure and peak systolic pressure were −1.70 mssec/mm Hg and −0.07 mssec/mm Hg respectively.

Our findings show that changes in whole heart haemodynamic variables do influence action potential duration. They show a mechanism whereby changes in ventricular stretch may contribute to arrhythmogenesis in heart failure and suggest that preload reduction is more likely to prevent arrhythmias that afterload reduction.

Characterisation of the calcium release channel from human cardiac sarcoplasmic reticulum

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Release of calcium from the sarcoplasmic reticulum (SR) is central to excitation-contraction coupling in the mammalian heart and is controlled by the gating of a specific ion channel. The purpose of this study was to characterise the calcium released channel from human tissue by incorporating functional SR vesicles into artificial planar phospholipid bilayers and recording their conductance under voltage-clamp conditions. An additional objective was to investigate the possibility that the altered function of these channels contributes to the impairment of SR calcium release, previously reported in humans with end stage cardiac failure. Tissue was obtained from the explanted hearts of six patients (three with coronary disease and previous infarction and three with normal coronary arteries) undergoing transplantation for refractory cardiac failure, and preparations enriched with junctional SR membrane vesicles were isolated. A calcium channel was identified with a conductance of 101pS in 67 mM Ca²⁺. Gating was modulated by alterations to the medium at the cytosolic face of the channel. Elevation of the Ca²⁺ concentration across the range 0-1-100 μM increased channel opening, as did the addition of millimolar ATP or caffeine. Millimolar magnesium or micromolar ruthenium red reduced channel opening. The plant alkaloid ryanodine bound irreversibly to the channel to produce a fixed open state with a reduced conductance (about 40%) relative to the unblocked open state. The ryanodine sensitive channel identified in this study has properties consistent with a role in excitation-contraction coupling through a process of calcium induced calcium release and is similar to equivalent channels from normal animal tissue.

We conclude that alterations to the properties of single calcium release channels do not seem to contribute to the abnormalities of SR function observed in heart failure.

Effect of low dose fish oil supplements on contraction and relaxation in the resistance artery

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There are conflicting reports on the effects of fish oil in hypertension and ischaemic heart disease. To date, animal studies have tended to use high doses of fish oil of little relevance to the amounts recommended in humans. Accordingly, we examined the effect of low dose (0.4% of total dietary calories) fish oil supplementation of a 40%, mainly saturated, fat diet (typical of Scottish eating habits) on α₁ adrenoceptor stimulated contractile function in resistance arteries. Two groups (n = 10) of male Sprague-Dawley rats were fed for eight weeks, one group receiving fish oil daily. This dose of fish oil significantly increases tissue phospholipid eicosapentaenoic acid concentration (138-8 (21-0) v 24-2 (6-5) μg/g, p < 0.01). Femoral resistance arteries were dissected and mounted as rings in a myograph. Rats in the fish oil group showed a highly significant increase in sensitivity to noradrenaline (estimated doseₜ₀ 2-2 v 4-2 x 10⁻³ M, p < 0-001) in the presence of 10⁻³ M timolol and 10⁻⁷ M yohimbine. Acetylcholine induced relaxation of preconstricted arteries was also significantly enhanced in the fish oil group (maximum relaxation 36%, v 27%, p < 0-05).

These data indicate that fish oil can effect both contractile and relaxing functions of resistance arteries in doses comparable to those given to humans.

Perception of angina in diabetes: relation to somatic pain threshold

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Patients with silent myocardial ischaemia may have a generalised non-segmental hyposensitivity to pain. It is not known, however, whether more subtle alteration in the perception of angina, as measured by anginal perceptual threshold, also reflects generalised hyposensitivity to painful stimuli. We exercised 45 patients (19 diabetic and 26 non-diabetic) to measure anginal perceptual threshold (the
time from onset of 0.1 mV ST depression to onset of angina). Somatic pain threshold was measured by calf sphygmomanometry. The cuff was inflated rapidly until pain occurred, with six repeat inflations to test reproducibility. Because there was no significant difference between measurements (coefficient of variation 0.16) the mean value in each patient provided a measure of somatic pain threshold. The median value for anginal perceptual threshold was higher in the diabetic patients with a broader interquartile range (125 (100 to 163) v 12 (0 to 40) seconds, p < 0.01). In the diabetic group there was a significant linear relation between anginal perceptual threshold and somatic pain threshold (r = 0.5, p = 0.03), those patients with a higher somatic pain threshold having greater prolongation of the anginal perceptual threshold. In the non-diabetic patients, however, the range of values was lower, and no relation could be shown between these variables.

Thus, like patients with silent ischaemia, diabetic patients in whom the perception of angina is impaired have a generalised hypersensitivity to pain which, based on earlier observations, is caused at least in part by diabetic neuropathy.

**Electrocardiogram correlates of early coronary artery patency and myocardial perfusion after thrombolysis**

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An early fall in the ST segment is recognised in patients receiving thrombolytic treatment. The sensitivity and specificity of this fall in detecting reperfusion remain controversial and require further validation in a large patient group. One hundred and four patients (82 men, 22 women, age range 31-69) with acute myocardial infarction of ≤6 hours’ duration received thrombolytic treatment (anistreplase 30 mg (n = 53), 1.5 MU streptokinase (n = 51)). Coronary angiography at 90 minutes showed a patent artery (TIMI 2,3) in 64 of the 104 (61.5%) and occlusion (TIMI 0,1), in 40 (38.5%). Twelve lead electrocardiograms (ECGs) were performed before and two and four hours after thrombolysis. Data from each ECG were digitised and the parameters stored on computer. Fractional change (FC) (% fall in ST segments) was calculated for the single lead with maximal ST elevation and for the ST elevation across all leads. An FC value ≥0.5 calculated at two hours from a single lead was more sensitive in detecting reperfusion than FC2 calculated from the ST elevation (81% v 75%) and more specific (60% v 55%). All arteries performed well (FC2 sensitivity and specificity respectively: left anterior descending 81.5% and 55.5%; right coronary, 81.5% and 67.5%; circumflex, 83% and 50%). Ten patients with an occluded artery at angiography had collateral supply to the distal infarct related artery and four of them had an FC ≥0.5, suggesting adequate perfusion of myocardium despite no anterograde reperfusion.

An FC value ≥0.5 two hours after starting treatment calculated from a single lead suggests (re)perfused myocardium and is helpful in directing further treatment.

**Cardiac reserve and prognosis in cardiogenic shock**

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The hypothesis that the prognosis in patients with cardiogenic shock is primarily dependent on cardiac pumping reserve was tested in a prospective study of consecutive patients with a clinical diagnosis of cardiogenic shock treated medically. Twenty eight patients were included, and their haemodynamic state was assessed with thermodilution Swan–Ganz catheters and arterial cannulas. The cardiac pumping reserve was evaluated by the response of the failing heart to graded incremental dobutamine infusion (2.5–40 μg/kg/minute) after optimising left ventricular preload. The patients were followed up for at least one year: 11 survived longer than one year, and the rest died within that period. The patients were indistinguishable by clinical and basal haemodynamic criteria. When the responses to dobutamine stimulation were considered, however, clear separation of the cardiac reserve of survivors and non-survivors was obtained. All patients with limited reserve—that is, with peak stimulated cardiac power output of <1.0 W or peak left ventricular stroke work index of <0.25 J.m⁻²—died, and all patients with values above both these levels were able to survive longer than the one year follow up.

Thus this study showed that haemodynamic evaluation of cardiac reserve can provide objective criteria for predicting the prognosis of individual patients with cardiogenic shock. The availability of such a prognostic indicator will be invaluable in formulating management plans for these patients.

**Angiographic findings and prognosis in unstable angina associated with T wave inversion in anterior chest leads**

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It has been proposed that the presence or development of deep symmetrical T wave inversion in the precordial leads in patients with unstable angina is indicative of critical reduction of flow in the left anterior descending (LAD) coronary artery. This has been associated with a poor short term prognosis, and therefore early investigation and revascularisation have been advocated. We report the angiographic appearances in 53 patients with this condition attending two centres. A very severe stenosis was found in the LAD artery in all except one patient; 62%, had single vessel disease, 25% double vessel disease, and 11% triple vessel disease. One patient had an occlusion of the right coronary artery only. Urgent revascularisation of such patients has not been routinely practised at one centre. We have reviewed 26 patients admitted to the coronary care unit there between 1984 and 1989 with these clinical characteristics and electrocardiographic pattern (16 of whom had undergone coronary angiography) who were treated medically during their initial admission. Of these, 13 were still alive and had not progressed to infarction (mean follow up 41 months). Seven patients had had
Human α calcitonin gene related peptide improves exercise workload to ischaemia and dilates stenoses of the epicardial coronary artery

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Six patients (aged 54–67) with effort angina and normal left ventricular function received intravenous infusions of placebo and human α calcitonin gene related peptide (CGRP) (50 pmol/minute for 10 minutes) before and during treadmill exercise testing. Rate-pressure product (RPP) at 0.1 mV ST segment depression was 201.4 (46.0) and 241.0 (90.7) beats/min/mmHg/10⁻² (p < 0.05) and at peak exercise was 238.2 (83.7) and 264.0 (80.5) beats/min/mmHg/10⁻² (p < 0.05) with placebo and CGRP respectively. Exercise duration to 0.1 mV ST segment depression and peak exercise were similar on both infusions. Cardiac catheterisation was performed with right atrial pacing at a rate up to 20 beats/min above the resting rate; aortic, pulmonary artery, right atrial and pulmonary wedge pressures, left ventricular end diastolic pressure (LVEDP) and its rate of change (dP/dt) were recorded during consecutive intravenous infusions of placebo and CGRP for 10 minutes at the same rate as before. Systemic vascular resistance index was lower with CGRP compared with placebo (34.6 (15.6) v 44.6 (14.4) units m⁻¹, p < 0.05). Cardiac index was greater (p < 0.05) with CGRP (3.84 (0.5) l/minute/m²) compared with placebo (3.38 (0.5) l/minute/m²). There was no significant change in aortic pressure, LVEDP, dP/dt, or pulmonary vascular resistance index. Incremental atrial pacing to angina or 0.2 mV ST segment depression disclosed no difference in RPP at 0.1 mV ST segment depression with placebo and CGRP. Quantitative analysis of selected coronary artery stenoses showed an increase in stenosis diameter from 1.14 (0.16) to 1.57 (0.33) mm (p < 0.05) and in reference diameter from 2.16 (0.30) to 2.54 (0.37) mm (p < 0.05) with placebo and CGRP respectively.

Thus intravenous CGRP increases cardiac workload to 0.1 mV ST segment depression and peak exercise, which implies an increase in the coronary flow reserve on exercise, not present on pacing. It dilates both stenosed and normal segments of the coronary arteries at rest.

Exercise testing after thrombolytic treatment in acute myocardial infarction: reciprocal ST changes and diagnostic specificity

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Thrombolytic treatment modifies the evolution of myocardial infarction, but its effect on the exercise electrocardiogram (ECG) for risk stratification is unknown. We analysed predischarge exercise ECGs in 40 patients with acute infarction (23 anterior and 17 inferior) treated with streptokinase. Coronary arteriography within two weeks confirmed disease of the infarct related artery in every patient, with additional remote disease (>70%, stenosis) in 45% of patients. The exercise ECG showed ST depression (>0.1 mV) in 30 patients, only three of whom experienced angina. Exertional ST elevation in the infarct territory was common, occurring in 26 patients, 18 of whom had additional ST depression in the contralateral territory. Of these, only seven had remote coronary disease and in the remainder ST depression occurred as a purely electrical phenomenon. Thus the sensitivity of exertional ST depression for the diagnosis of coronary disease remote from the infarct related vessel was 76%. The specificity was, however, only 25% because of the high incidence of false positive reciprocal ST depression.

In conclusion, exertional ST elevation in the zone of infarction occurs commonly after thrombolytic treatment. It is often associated with reciprocal ST depression, although remote coronary disease is found in fewer than 40% of these patients. Thus the specificity of exercise electrocardiography for coronary disease remote from the zone of infarction is reduced by thrombolytic treatment while sensitivity is largely unaffected. These data indicate a need for reappraising exercise ECG criteria for risk stratification after acute myocardial infarction treated with thrombolytic agents.

Evaluation of cardiac transplantation for cardiomyopathy in children

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Thirty seven children underwent cardiac transplantation for cardiomyopathy (dilated 26, hypertrophic eight, restrictive three) and were followed up for a minimum of one year. The age at transplantation ranged from 6 months to 14 years (mean 7.4 years). Nine patients were less than 2 years of age. The hospital survival was 86% (32/37). Causes of death were right side heart failure secondary to increased pulmonary vascular resistance in four and hyperacute rejection in one. Immunosuppression consisted of cyclosporin and azathioprine treatment without routine steroids. Routine biopsy was not performed in children below 12 years of age. There were three late deaths at 1, 31, and 4 years. The 29 survivors, with a mean follow up of 36.6 (12–64) months, were free of symptoms (New York Heart Association class I). Renal dysfunction requiring discontinuation of cyclosporin treatment occurred in only one patient. Two patients were given long term antihypertensive treatment. Two patients developed B cell lymphoma, which was localised to the abdomen in one and to the tonsils in the other; both lymphomas regressed completely with a reduction in level of immunosuppression and intravenous acyclovir concentration. Annual cardiac catheterisation showed normal left ventricular function and absence of angiographic coronary artery disease. Change in aortic root dimension towards the appropriate size for age and weight of the child was shown by echocardiography. The majority of patients showed a satisfactory growth pattern. Cognitive function was within the normal range, but the rate of late behaviour disturbances was higher than the
normal population (25% v 10%). Twelve of the 13 children of school age returned to school.

We conclude that medium term results of cardiac transplantation for cardiomyopathy in children are encouraging.

Class II major histocompatibility complex molecules on cardiac endothelium: an early biopsy marker of rejection in the transplanted human heart

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The role of major histocompatibility complex (MHC) class II molecule expression in the rejection of the transplanted human heart is controversial. To assess whether MHC class II expression precedes histological evidence of rejection we studied 63 sequential endomyocardial biopsy specimens from 13 patients 24-390 days after orthotopic cardiac transplantation. Histological rejection was graded according to Stanford criteria. MHC class II expression on endothelial cells was assessed by double immunofluorescence with monoclonal antibodies to class II molecules and antiserum to human factor VIII as endothelial cell marker. Class II molecule expression was independently scored as absent (0), low (1+), or high (2+). Rejection grade was 0 in 38 endomyocardial biopsy specimens (60%), 1 in 18 (28%), and 2 in seven (11%). Class II expression score was 0 in 19 biopsy specimens (30%), 1+ in 27 (43%), and 2+ in 17 (27%). There was no relation between the 63 MHC scores and the severity of histological rejection in the corresponding biopsy specimen. The MHC scores of the 38 endomyocardial biopsy specimens with no histological rejection were compared with the histological grade of biopsy specimens taken in the following two to four weeks; 8/9 with a high MHC score (2+ or 3+) were subsequently rejected v 5/29 with absent or low MHC expression (score 0, +1) (p < 0.001). The sensitivity, specificity, predictive value, and accuracy of MHC score 2+ as a predictor of rejection was 61%, 96%, 89%, and 84%, respectively.

High grade MHC class II molecule expression on cardiac endothelial cells is an early biopsy marker of subsequent rejection and may be a useful adjunct to routine histological assessment. Cardiac endothelial cells expressing MHC class II molecules may have an active role in first set allosensitisation and initiation of rejection of the cardiac allograft.

Coronary angioplasty in cardiac transplant recipients

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Accelerated coronary artery disease continues to be one of the most important problems after cardiac transplantation. Because of the diffuse nature of the disease the only treatment applied to date has been retransplantation. We performed balloon angioplasty on nine patients with coronary artery disease judged suitable for revascularisation at a mean of 36 months (range 15-87 months) after orthotopic transplantation; the mean age of the patients was 42 (range 21-58). This constitutes 18% of transplant recipients with significant coronary disease at our institution. Two patients had symptoms of angina, both developing ST segment change on exercise testing. Three patients had significant disease (> 50% luminal narrowing) in one vessel and the remaining six had three vessel disease. A total of 16 lesions were dilated, angioplasty being undertaken in the left anterior descending artery in seven patients, the right coronary artery in two, and the circumflex artery in four. Single lesion dilatation was performed in three cases, two lesion dilatation in five, and three lesion dilatation in one. Primary angiographic success was achieved in 15 lesions. Revascularisation was unsuccessful in one lesion, and one patient developed ventricular fibrillation during balloon inflation. After 13 months of follow up (range 5-51 months) one patient had recurrent angina. Seven patients were restudied, of whom two developed restenosis. One underwent a second successful angioplasty and the other had bypass surgery.

These data indicate that coronary angioplasty in transplant recipients can be successfully undertaken with an apparent low restenosis rate. The influence of this procedure on the ultimate prognosis remains to be determined.

Resolution of pulmonary hypertension after single lung transplantation

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The benefits of single lung transplantation on pulmonary haemodynamics and right ventricular function have not previously been described. Five patients underwent cardiac catheterisation at a median of 18 months after transplantation for fibrosing alveolitis. Four had preoperative data for comparison. Mean pulmonary artery pressure fell by 46% (33-25 (3-75) to 17-75 (1-25) mm Hg; p = 0.039) and peak right ventricular systolic pressure by 38% (32-75 (5-11) to 20-5 (1-66) mm Hg; p = 0.013). There was no significant change in pulmonary artery wedge pressure or cardiac output. Total pulmonary resistance fell by 52% (6.33 (0.85) to 3.04 (0.17) Units; p = 0.022) and pulmonary arteriolar resistance by 62% (5.01 (0.8) to 1.92 (0.25) Units; p = 0.021). In all patients there was an improvement in right ventricular function assessed by contrast ventriculography, and all were normal after transplantation. A fifth patient, who was not catheterised preoperatively, had normal pulmonary pressures, arteriolar resistances, and right ventricular function.

This study shows that even in patients with moderate pulmonary hypertension and impaired right ventricular function due to lung disease single lung transplantation may be performed with success. In such patients, right heart pressures, pulmonary resistances, and right ventricular function return to normal.

Total and differential blood flow measurement in pulmonary arteries of patients with single lung transplantation: a magnetic resonance study

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Magnetic resonance imaging was used to measure total and differential pulmonary arterial blood flow in nine patients with single lung transplantation and in nine volunteers matched for age and sex. Spin echo images were acquired in transverse and oblique planes parallel and perpendicular to the mean pulmonary artery and right and left pulmonary arteries. Magnetic resonance velocity mapping was used to measure velocity profile and to estimate pressure gradient across the anastomoses. Quantitative blood flow was also measured in the mean, right, and left pulmonary arteries. Arterial blood flow to the transplanted lungs was 2.07 (0.45) l/min/m² in the group with right side transplantation and 2.43 (0.60) l/min/m² in the group with left side transplantation compared with 1.22 (0.22) l/min/m² and 1.27 (0.41) l/min/m² in the control groups respectively. The ratio of blood flow in the transplanted and the native lungs in all patients studied was 2.8 (0.83). The estimated pressure gradient across vascular anastomoses was 4–25 mm Hg.

The flow patterns in the pulmonary arteries of transplanted and native lungs are of particular interest. The flow pattern in transplanted lungs has a wide forward flow during systole and most of diastole, whereas in native lungs has a narrow forward flow with early systolic peak and a reverse flow during late systole and most of diastole. This differential flow and its pattern is related to the relative resistance in the two lungs. Sequential studies of pulmonary blood flow using this non-invasive technique could be useful in managing patients with single lung transplantation.

**Feasibility and acceptability of day case permanent pacing**

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Fifty patients requiring permanent pacing or generator change were randomly assigned to either conventional inpatient management or same day discharge day case management. Twenty-four (mean age 73.2 years) were managed conventionally and 26 (mean age 73.7 years) as day cases. Two in the day case group could not be discharged on the same day, one because of haematoma and one because the family refused. Mean hospital stay in the remainder was 5.7 days (day case) and 7.0 days (conventional). There was only one other complication in the day case group—an electrode dislodgement after discharge. In the conventional group there were two electrode dislodgements (one atrial displacement and one ventricular threshold rise assumed to be secondary to a microdislodgement), one infection requiring the procedure to be redone, and one pneumothorax. One patient in the conventional group died of ruptured aortic aneurysm five days after discharge. A questionnaire designed to assess how acceptable patients found the procedure gave an equal result (8.8/10) for each group. There were no significant differences between the two groups in the number of consultations with general practitioners in the month after pacing or in acceptability (Mann-Whitney U test). To assess the significance of the complication rates sample size calculations indicate the study would have required 2500 subjects. The saving per patient with day case management was between £400 and £650.

Day case pacing is feasible in the United Kingdom, is acceptable to patients, and has considerable economic advantages.

**Randomised double blind crossover study of four rate responsive pacing modes**

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Rate responsive pacing has known haemodynamic advantages over fixed rate but no direct comparison of modern RR modes has been undertaken. Twenty-two patients aged 18–81 years (mean 52) had activity sensing DDDR pacemakers (PM) implanted. All showed second or third degree atrioventricular block, seven with retrograde ventriculo-atrial conduction and 17 with sinus node incompetence at implantation. Patients were randomised to VVIR, DDIR, DDD, or DDDR for four week periods in a double blind crossover design. They were then assessed subjectively, with symptom and functional state questionnaires and visual analogue scales, and objectively, by graded exercise treadmill testing and while performing standardised daily activities continuously monitored electrocardiographically. Five patients demanded early crossover, all from VVIR mode. Most patients (13) preferred DDDR, four preferred DDIR (three after His ablation), four pre-
ferred any dual mode, and one patient with poor left ventricular function preferred VVIR. Perceived general wellbeing was worse in VVIR than DDD (p < 0.05) and DDDR (p < 0.01) but not than DDIN (NS). Subjective exercise capacity was worse in VVIR than in dual chamber modes (p < 0.05). Objective assessment showed, however, that mean exercise treadmill times were similar in all modes. Percent change in heart rate during standardised daily activities was also similar in all modes, except during mental stress when VVIR significantly underresponded (p < 0.001).

Thus, most patients prefer DDDR, but objective exercise and standardised daily activity parameters are similar in all four RR modes.

Complications associated with retained defunct pacemaker leads

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The incidence and type of complications associated with retained, defunct pacemaker leads is reported in 118 patients seen at this unit between 1978 and 1989. Sixty-four women and 54 men (mean age 66 years, range 9–94) were classified according to the reason for intervention resulting in lead retention as (a) lead failure (group A, 65 patients) or (b) infection of the pacing system (group B, 53 patients). Follow up ranged from 1 month to 192 months (mean 67) in group A and from 5 months to 162 months (mean 62) in group B. Total mortality was 28% in each group; pacemaker related mortality was 0 in group A and 5.7% (3 patients) in group B (all three patients died of septicemia). Major complication occurred in one patient (1.5%) in group A and in 22 patients (42%) in group B: one patient in group A and 10 patients in group B had recurrent local infection requiring surgery under general anaesthesia or cardiopulmonary bypass; nine patients in group B had septicemia and three patients in group B had the superior vena cava syndrome. Minor complication occurred in two patients (3%) in group A and five patients (9%) in group B: one patient in group A and three patients in group B had recurrent local infection, one patient in each group had lead extrusion, and one patient in group B required further intervention.

Our data suggest (a) that non infected pacemaker leads can be safely left in situ if removal is difficult and (b) that pacemaker lead removal is essential when the change in pacemaker system is dictated by infection.

Improved physiological sensitivity of the QT sensing, rate adaptive pacemaker with a non-linear algorithm

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The physiological sensitivity and specificity of rate adaptive pacing systems depend on the attributes of the bio-sensor and the algorithm that translates the input from the sensor into changes in pacing rate. In this study we describe the electrophysiological basis of a new non-linear algorithm for the QT sensing pacemaker and compare the pacing rate responses during treadmill exercise with simultaneous measurement of oxygen consumption (Vo2) in 11 patients (mean 59 years, six females) randomly programmed to one month periods in the linear and non-linear algorithms by a double blind, crossover design. The time to a 10 beats/min increase in rate was significantly less with the non-linear algorithm (126 s v 255 s; p = 0.025) but there were no significant differences in exercise duration, peak pacing rate, or peak Vo2. The slopes of the individual regression lines for the pacing rate and Vo2 relation, which indicated the amount of pacing rate change per unit change in oxygen consumption, showed a significant improvement in four cases. Rate oscillation occurred in seven patients in the linear algorithm and in two patients in the non-linear setting. Initial deceleration of the pacing rate at the onset of exercise occurred in seven patients in the linear algorithm and in four patients in the non-linear setting.

In conclusion, the non-linear algorithm results in a faster response time during exercise, fewer instances of rate instability, and a qualitative improvement in the pattern of pacing rate change as gauged by metabolic indices in 36% of patients. The problem of an initial fall in rate, however, remains and is a function of the sensor rather than the algorithm.

Rate response to intravenous isoprenaline is an accurate predictor of chronotropic incompetence in sinoatrial disease

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Rate responsive pacing may be valuable in patients with chronotropic incompetence. A rapid, sensitive method of identifying which patients with sinoatrial disease have chronotropic incompetence would facilitate selection of patients that may benefit from implantation of rate responsive systems. This would have economic advantages. We gave isoprenaline in incremental doses up to 0.075 gg/kg/min to 14 patients with sinoatrial disease who had received AAIR systems. On repeated exercise testing with the Cleveland chronotropic adequacy exercise programme five showed chronotropic incompetence (maximum heart rate < 115/min at peak exercise). In each case patients graded the peak exercise level as “hard” or above on the Borg exercise grading scale. The eight other subjects showed a sinus tachycardia at peak exercise of 130/min or above. All patients with chronotropic incompetence failed to show an acceleration of their heart rate in sinus rhythm in response to isoprenaline to a peak of 100/min (range 70–96). Two patients with chronotropic incompetence developed accelerated nodal rhythms and two remained paced at 30/minute throughout. The eight patients who showed chronotropic “competence” all developed a sinus tachycardia in response to isoprenaline (range 110–150/min). The difference in peak sinus rate in response to isoprenaline between the two groups was highly significant (p < 0.001).

A peak rate in sinus rhythm < 100/min in response to 0.075 gg/kg/minute of intravenous isoprenaline is a sensitive (100%) and specific (100%) marker of chronotropic incompetence in sinoatrial disease.