WEDNESDAY 19 MAY 1993

from 8.15 Registration. Coffee available in the Exhibition Hall from 8.30

9.00 Grand Hall
Plenary Session: Revascularisation, restenosis and RITA
(chairmen: Prof Keith A A Fox and Mr John Parker)
(a) Restenosis: an update on cellular pathways important for the development of arterial lesions (Prof Michael A Reidy (Washington))
(b) Restenosis: Achilles’ heel or Pandora’s box (Prof Patrick Serruys (Rotterdam))
(c) Randomised Intervention Treatment of Angina (RITA): Results and implications (Dr E Sowton (Guy’s Hospital, London) and Dr R Henderson (Wythenshawe Hospital, Manchester))
(d) Panel and audience discussion

Avon III
Paediatric Cardiology (General)
(chairman: Dr E Silove)
Papers 43–48

Severn I & II
Audit
(chairman: Dr G C Sutton)
Papers 49–54

Avon I
British Pacing and Electrophysiology Group
Case Conferences in Pacing and Arrhythmias
(chairman: Dr Richard Sutton)
Discussants: Dr Richard Charles, Dr J Campbell Cowan, Dr Wyn Davies, Dr Janet McComb, Dr Edward Rowland

10.30–11.15 Coffee in the Exhibition Hall—Poster viewing 159–238

11.15–12.45 Grand Hall
Stents
(chairman: Dr M Rothman)
Papers 55–59

Avon II
CVS Pathophysiology, Basic and General
(chairman: Prof S G Ball)
Papers 60–65

Avon III
Paediatric Intervention I
(chairman: Prof M Tynan)
Papers 66–71

Severn I & II
Echocardiology
(chairman: Dr L Shapiro)
Papers 72–77

12.45–2.15 Lunch and Poster Viewing in the Exhibition Hall
159–238 Authors present

1.00–2.00 Exhibition Hall
Moderated Posters 145–158 Authors present
(Prof R W F Campbell)

from 2.15–3.45 Grand Hall
Arrhythmias VT/VF
(chairman: Dr M Rothman)
Papers 78–83

Avon I
British Nuclear Cardiology Group
(a) Debate: The use of nuclear techniques after myocardial infarction
For: Dr J Caplin (Hull Royal Infirmary)
Against: Dr K Jennings (Aberdeen)
(b) Debate: The use of nuclear techniques after revascularisation
For: To be announced
Against: To be announced

Avon II
Vascular Biology
(chairman: Dr P Weissberg)
Papers 84–89

Avon III
Paediatric Intervention II
(chairman: Dr B R Keeton)
Papers 90–95

Severn I & II
Coronary Disease Thrombolysis
(chairman: Dr D P de Bono)
Papers 96–101

3.45–4.30 Tea and Poster Viewing in Exhibition Hall

4.30–5.30 Grand Hall
Keith Jefferson Lecture
Myocardial Perfusion Imaging in Clinical Cardiology
Dr George A Beller (USA)

5.30–6.30 Grand Hall
Annual General Meeting for Members of the British Cardiac Society only
**CRITICAL AORTIC STENOSIS - PROGNOSIS IN PATIENTS WHO SURVIVE INITIAL INTERVENTION**

D Kitchiner, Sreean N, Maliya N, Jackson M, Paetl I, Walsh K, Arnold R.
Cardiac Unit, Royal Liverpool Children's Hospital.

We studied 70 patients with critical aortic stenosis (AS) born between 1979 and 1992. 13 died before intervention, 44 within a month of intervention and 43 patients (61%) survived for more than 1 month after initial intervention (surgery = 41; balloon valvuloplasty = 2). All those alive were reviewed prospectively and their current status assessed. The median duration of follow-up was 3 years (range 0.5 - 14.4 years).

Eleven patients had a good result with mild AS with or without mild regurgitation (AR); 16 had a moderately good result with moderate AS or AR; 7 had a poor result with severe AS or reoperation; and 9 died at a median age of 19 months (range 2.6 - 81.2), giving a late mortality of 21%.

Seven patients required reoperation at a median age of 37 months and 2 patients had a third operation. Two reoperations were performed for AR. The mortality from reoperation was 57%. Aortic balloon valvuloplasty was performed on 10 occasions in 9 patients. Survivors presented at a median age of 21 days (range 1-90), and there was no difference in those with good or poor result, but those who died later presented at a younger age (median = 4 days; range 1-20). Factors found to be insignificant in terms of prognosis after initial survival were whether the patient had arterial duct dependency or acidosis at presentation, whether the patient required ventilation before initial intervention and whether the patient had other cardiac lesions.

**CONCLUSIONS**

The late survival after successful intervention for critical aortic stenosis is almost 80%. Sixty three percent have an acceptable medium term result, but the mortality in those requiring reoperation is high. Most factors which predict initial survival are unhelpful in predicting late results.

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**THERAPEUTIC USE OF INOTROPES IN COMPLETE HEART BLOCK IN THE FETUS**

Alison M. M. Groves, Lindsey D Allan, E. Rosenthal, Fetal Cardiology, Guy's Hospital, London

A total of 33 fetuses with congenital complete heart block and structurally normal hearts have been seen in the department of fetal echocardiography since 1980. Initially the prognosis was thought to be favourable if the pregnancy was carefully managed, but with greater experience this has not proved true in all cases, particularly those who develop intracardiac cardiac failure. There have been 9 spontaneous losses related to CHB in this series, 8 of the 9 associated with fetal hydrops.

A series of 3 patients with isolated complete heart block, one with fetal hydrops, were given a trial of inotropes to assess the effect on the fetal heart. All mothers were seropositive for anti-Ro antibody. All fetuses showed an increase in heart rate and improvement in ventricular function on salbutamol, but no significant change with isoprenaline. Salbutamol was maintained until delivery in the mother of the hydropic fetus, resulting in resolution of hydrops. All 3 fetuses treated were delivered close to term, two of three requiring pacing in the neonatal period.

We conclude that salbutamol can be effective in the treatment of fetal complete heart block and should be considered in patients with this condition and any evidence of deteriorating cardiac function.

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**RECURRENT SUPRAVALVAR MITRAL STENOSIS: A PREVIOUSLY UNRECOGNISED COMPLICATION FOLLOWING RESECTION.**

RMR Tulloh, ID Sullivan.
The Hospital for Sick Children, Great Ormond St, London

Supravalvar mitral stenosis (SVMS) is uncommon. There are no guidelines for the follow-up or management of this lesion. Twenty-six patients were found to have SVMS between August 1978 and November 1992. Of the 26, two had mild left ventricular outflow obstruction not requiring surgery and three had severe mitral valve abnormalities requiring valve replacement. Therefore 21 children (12 male, 9 female), mean age 3.3 years (range 0.1-13) underwent complete resection of SVMS. Associated intracardiac abnormalities (number) included abnormal mitral valve morphology (8), ventricular septal defect (13), subaortic stenosis (9), coarctation of the aorta (8), left superior vena cava to coronary sinus (6), aortic valve stenosis (2) and atrial septal defect (2). Follow-up was for a mean of 58 months (range 0.5-216). Four developed recurrent SVMS and have undergone re-operation: 3 are well but one has required mitral valve replacement and did not survive. There have been 5 other deaths during follow-up. The mean age at the time of initial resection of SVMS was less for those who died or developed recurrent SVMS (1.1 years compared to 5.4 years, p<0.05). All who developed recurrent SVMS were < 1.6 years at initial resection as were 5/6 who died. Subaortic stenosis was associated with recurrent SVMS (3/4 with recurrence, 1/8 who are alive without recurrence, p<0.05). An abnormal flow pattern as blood crosses a small or abnormal left ventricular inlet may be responsible for the generation of fibrous tissue and development of SVMS. Even after the fibrous ridge is resected, the stimulus for fibrosis may persist in the smallest patients. All children who have SVMS resected should be carefully followed up. Special attention should be paid to those who are less than 2 years of age at surgery or who have subaortic stenosis because of the high risk of death or recurrent SVMS.

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**DEATHS IN GROWN-UP CONGENITAL HEART PATIENTS**

Jane Somerville, Susan Stone
Royal Brompton National Heart & Lung Hospital, London

325 grown-up patients (pts.) with congenital heart disease (GUCH) cared for by the Unit died between 1972-1992 aged 12-74 (mean 24) years. Case notes and all available evidence were reviewed retrospectively by two independent observers. Ability Index (A.I.) at last assessment before final illness, previous cardiac surgery and complications, evidence of state, diagnosis made by doctor if seen, and necropsy material when available were assessed. Death for each individual pt. with inappropriate or suboptimal management was designated avoidable, when inevitable, unavoidable and managed optimally unavoidable, and if uncertain 'avoidable'. 65% of deaths occurred before age 25 years. Unavoidable deaths occurred in 237 (73%), avoidable in 64 (20%) and 'avoidable in 24 (7%).' Reoperation was the commonest precipitating cause (34%) particularly below age 30 years in avoidable and unavoidable groups, followed by 'sudden' unexpected (24%), first definitive repairs (17%) and terminal failure (12%) excluding transplant deaths (7 pts.). The A.I. was 1/2 (well) before death in 40% of unavoidable deaths and 52% of avoidable deaths with 60% A.I. 3/4 (sick) before unavoidable death. Avoidable deaths were precipitated by cardiology errors, ie, poor arrhythmia management, missed coronary disease, pacemaker box change problems with inexperienced operators, underestimation of pulmonary vascular disease, missed endocarditis and late diagnosis of cerebral abscess and late referral to specialist centre. "Surgical" deaths were related to intracardiac mistakes and careless post-operative care. Deaths also resulted from "neglect" of cardiac problems in relation to extracardiac surgery or other system's medication in "at risk" patients. Particularly at risk of avoidable death were the atheros, Eisenmenger, Mustard and operated aortic valve disease. This highlights the importance of informed super-specialist care for the GUCH pts. and the need for physicians to consult and refer.
Isoprotenerol (IP) is thought to uniformly shorten the QT interval in normal persons. We tested the hypothesis that children with Tilt test proven syncope have an abnormal QT response to IP by measuring the effect of a bolus of IP (1-4 mcg) on QT and QTc (TQTcR) in 39 children. Each had syncope and a normal heart. Their ages ranged from 4-21 years, median 13. None had documented arrhythmias or long QT syndrome. Tilt testing reproduced symptoms of syncope (Tilt +) in 20, did not (Tilt-) in 9. Presuming that the Tilt- group was "normal", QT and QTc were compared at baseline and after IP for each tilt group.

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<th>Results (mean ± SD)</th>
<th>QT ms</th>
<th>QTc ms</th>
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<td>Baseline</td>
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<tr>
<td>IP</td>
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<tr>
<td>Tilt -</td>
<td>391 ± 7</td>
<td>419 ± 24</td>
</tr>
<tr>
<td>Tilt +</td>
<td>381 ± 32</td>
<td>414 ± 32</td>
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<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
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</table>

While baseline QT and QTc were similar between the 2 groups, Tilt + patients had a significantly higher QT and QTc than Tilt - patients after IP. QTc was prolonged in both groups but more so in the Tilt + group. Conclusion: Children with Tilt + syncope show no shortening of QT and significantly greater prolongation of QTc after IP. This is in contrast to normal children and to Tilt - patients. This finding may have relevance in the etiology of syncope in children.

EVALUATION OF THE CORONARY CARE STEP-DOWN UNIT IN THE ROYAL INFIRMARY OF EDINBURGH

I Wiczerek, C Simpson, NA Boon
Department of Cardiology, Royal Infirmary, Edinburgh

The aim of this study was to evaluate a new Coronary Care Step-Down Unit (CCSDU) in the Royal Infirmary of Edinburgh. In the past patients had been transferred from the CCU to a general medical ward after an initial period of approximately 24 hours. In the new unit patients remained under the same team of doctors and nurses and underwent a vigorous programme of physical and psychological rehabilitation. A group of 52 consecutive patients who suffered an uncomplicated myocardial infarction and were subsequently transferred from the CCU to the CCSDU (Group A) were compared with a group of 59 consecutive patients with the same diagnosis who had been transferred from the CCU to a medical ward during an equivalent period a year before (Group B). A group of 7 patients who had experienced both forms of care were also surveyed (Group C). The length of stay in the CCU was comparable in both groups but overall hospital stay was significantly shorter in Group A (7 ± 0.2 vs 8.9 ± 0.4 days, p<0.005). Assessment of quality of care and patient satisfaction was performed by means of a specially designed questionnaire and revealed that: (1) patients in Group A were significantly more satisfied with the quality of care and counselling they received (p<0.005), (2) general knowledge about risk factors and coronary heart disease was significantly higher in Group A (p<0.005). A similar satisfaction pattern was found in Group C also. The CCSDU compared with the medical wards (p<0.005). In addition, patients in Group A had significantly fewer readmissions during the 6 months of follow-up (19% vs 39%, p<0.05). Crude cost benefit analysis showed that the new unit offered considerable savings, although it had been opened in conjunction with a high dependency progressive care area the introduction of the complete package was achieved without any increase in overall expenditure. CONCLUSIONS: The introduction of a coronary care step-down unit may result in a shorter length of hospital stay, greater patient satisfaction and improved remote clinical outcome. This system of care can be offered as a part of an extremely cost effective care package.

Variations in the use of coronary angiography

David Gray and John R. Hampton, Division of Cardiovascular Medicine, University Hospital, Nottingham NG7 2UH

We investigated the use of coronary angiography in the management of patients with suspected coronary artery disease in a Region-wide audit. Patients were identified from postcode as residing in one of the three cities designated as a Regional referral centre. 675 patient records were reviewed to obtain information on the indication for the procedure, preceding investigations and outcome. Most patient were investigated for chronic stable angina. Catheterisation showed 12-18% normal coronary arteries, 7-12% left main disease, 40-49% proximal LAD disease and 11-33% three vessel disease.

Age of patients and duration of symptoms were similar in patients from each of the centres. Highly significant differences were found in:

a) the severity of symptoms- centres A and B investigated patients predominantly with NYHA grade 1 to 2; most from centre C were grade 3 to 4.
b) the use of angiographic medication most patients in centres A and B were taking 1 or 2 anti-anginal drugs; most from centre C were taking 3 drugs.
c) planned management of patients after catheterisation- no coronary intervention was proposed for 38% in centre A, 55% in centre B and 23% in centre C.

Variability of clinical practice appeared to relate to different attitudes among doctors providing angiographic facilities. For purchasers, the end-product of variation is uncertainty as to who provides the best service.
(51) IS CORONARY ARTERY BYPASS SURGERY APPROPRIATENESS EXPERT PANEL DEPENDENT?
TJ Bowker and F Cluzeau, Clinical Epidemiology, National Heart & Lung Institute, London.

The opinion of expert panels in medical audit may vary from panel to panel. To audit the same CABG operations using the opinion of different panels, 7 adult cardiologists and 3 cardiac surgeons (all London consultants) rated 483 hypothetical clinical scenarios (subdivided hierarchically by symptom level, angiographic findings, PTCA candidacy etc.) in which CABG might be indicated, from 9 (maximally appropriate) to 1 (maximally inappropriate). The median value of the panel's ratings was used to categorise each indication into 1 of 3 levels of appropriateness—"appropriate" (median 9 - 7), "equivocal" (median 8.5 - 3.5) & "inappropriate" (median 3 - 1). A sample of 200 was drawn randomly from the 1632 CABG operations performed during 1989 at the National Heart & Chest Hospitals. By retrospective case note review, the 200 were each allocated blindly by a separate panel of researchers to one of the 483 indications, the appropriateness of which the case was then awarded. Similar allocation was performed using appropriateness levels previously prepared from a Trent Health Region panel and made available to us by the University Hospital, Nottingham.

TRENT:

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<tbody>
<tr>
<td>Appropriate</td>
<td>109</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>LONDON:</td>
<td></td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td>Inappropriate</td>
<td></td>
<td>0</td>
<td>12</td>
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Although the proportion rated as appropriate, equivocal and inappropriate were respectively 58%, 31% & 11% by the London and 58%, 28% & 14% by the Trent panel, there was inter-panel concordance on only 160 (80%) of cases, but no extreme discordance. Of those rated inappropriate, 28% were not PTCA candidates, 18% had had one or two vessel CAD, 29% of whom were symptomatic on maximal medical therapy. Identification of such sub-groups will aid completion of the audit cycle but appears panel dependent.

(52) DO PATIENTS ON NITRATES NEED INVESTIGATING?
K W Clarke, D Gray, J R Hampton
Cardiovascular Medicine, University Hospital, Nottingham.

In 1985 the prevalence of ischaemic heart disease (IHD) in the Nottingham Health District was calculated to be 1.5% by General Practitioners (GP) prescribing of nitrates. 499 of these patients were studied in detail and few had been investigated. We aimed to follow-up these 499 patients and assess their rates of investigation and referral to hospital. Of the original 499 patients 463 were identified and their hospital and/or general practice records examined. Since 1985, 197 patients (43%) have been admitted to hospital. 105 (21%) were admitted with chest pain but as some were admitted on more than one occasion, there were a total of 192 admissions with chest pain. A further 61 patients have been referred to medical outpatients, making a total of 258 (56%) patients known to the hospital. A further 127 (27%) of patients have had an ECG, 25 (5%) an exercise test and 26 (6%) an angiogram. 200 patients (43%) have died. Over 7 years only 23% of the patients were admitted to hospital with chest pain, and many of these did not have myocardial infarctions. The rate of investigation remains low. Nearly half the patients have died, ~30% of these from cardiac causes. It would seem that patients who are treated for IHD with nitrates largely are not referred to hospital. ~30% of patients were on more than one anti-anginal drug, and these may be the people who were investigated. Patients on nitrates do not appear to place a high demand on Cardiology Services and remain under the care of their GP.

(53) THE ECONOMIC IMPACT OF HEART FAILURE ON THE NATIONAL HEALTH SERVICE
J McMurray & "W Hart, Department of Cardiology, Western Infirmary, Glasgow.

Heart failure (HF) is an increasingly common illness in industrialised countries. The morbidity caused by HF is high, many patients require treatment with a variety of drugs, and hospitalisation is frequent and often prolonged. All of these factors suggest that the economic burden of HF is likely to be high. We therefore undertook an evaluation of the cost of HF to the National Health Service (NHS).

Estimates of prevalence, health care utilisation and costs were, wherever possible, obtained from published reports. Estimates of referral rates, hospital out-patient clinics and prescription data were obtained from General Practitioner surveys. In all cases conservative estimates were used. The table shows the estimated cost of heart failure to the NHS in the UK in 1990/91.

<table>
<thead>
<tr>
<th>Economic cost of HF to NHS in UK 1990/91</th>
<th>£ million</th>
<th>percentage of total cost</th>
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<tbody>
<tr>
<td>GP consultations</td>
<td>16.6</td>
<td>5.1</td>
</tr>
<tr>
<td>GP referrals to hospital</td>
<td>2.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>213.8</td>
<td>65.5</td>
</tr>
<tr>
<td>Hospital outpatient follow up</td>
<td>16.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Investigations</td>
<td>44.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Drug treatment</td>
<td>23.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Surgery</td>
<td>8.9</td>
<td>2.7</td>
</tr>
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</table>

TOTAL: £ 326.4M, 100.0%

Though a conservative estimate, £326 million represents 1.1% of total NHS expenditure and 8.7% of NHS expenditure on diseases of the circulatory system. Analysis of this type give insights into the patterns of spending, and the categories of spending, for an illness, that might be modified to reduce expenditure. Hospitalisation accounted for the greatest proportion of the total cost of HF. ACE inhibitor treatment can reduce the need for hospitalisation in HF but is not widely employed. More effective use of ACE inhibitors represents a strategy that may reduce the economic impact of HF on the NHS.

(54) AUDIT OF CARDIOLOGY SENIOR HOUSE OFFICER WORK - TIME WELL SPENT?
MJ Griffith, DS Reid, SF Furniss, Cardiac Department, Freeman Hospital, Newcastle.

Junior staff are an increasingly scarce and therefore valuable resource. We audited our five cardiology senior house officer's time using a continuous worksheet, which they filled in during their choice of 14 activities during their routine daily activities for a week. On call work was not included. They worked a mean 43% (range 40-49) hour week, with 4.62 hours (11%) spent in breaks. They spent 6.5 hours (15%) a week clerking routine admissions, 5.1 hours (11%) supervising exercise tests and 3.5 hours (9%) a week in the anticoagulation clinic. On the wards 4 hours (10%) were spent on emergency admissions, 4.3 hours (10%) on their own ward rounds and 5.2 hours (12%) on ward rounds with a senior team member. Filling in forms took 1.95 hours (5%), discharge summaries 1.9 hours (4%), result chasing and booking tests 1.5 hours each (3%) and telephone 0.3 hours (1%). Only 0.8 hours (2%) of the week was taken up by formal teaching and invasive procedures were performed for 1.5 hours (3%).

Three activities, (routine clerking, exercise test supervision and the anticoagulation clinic) were felt to be of low training value and represent 35% of the working week. This is a total of 75 senior house officer hours, or £40,354 in salary costs. Re-organization, with outpatient clerking, nurse supervision of exercise testing and computer run anticoagulant clinics, could remove these activities from the senior house officer timetable without service disruption. This would either allow more time for training or fewer senior house officers doing a job with a higher training value. In conclusion, audit of our cardiac senior house officer's time allowed identification of three activities of low training value which occupy 35% of their working week. Re-organization could allow these services to continue without senior house officer involvement, reducing the requirement for senior house officers while improving the training value of the job.
SELF EXPANDING STENTS FOR EMERGENCY TREATMENT OF ABRUPT CLOSURE FOLLOWING PTCA: IMMEDIATE AND LONG-TERM RESULTS.

J E Nordrehaug, K A Priestley, N A F Chronos, A F Rickards, N P Buller, U Sigwart
Department of Invasive Cardiology, Royal Brompton National Heart & Lung Hospital, London

Coronary stents may be used to treat acute coronary occlusion after balloon angioplasty. We report the results of emergency implantation of a self-expanding stent (Wallstent) in 39 patients (33 men), mean age (±SD) 60±8 years. Acute occlusion occurred in the left anterior descending in 15 patients, the circumflex artery in 5 and the right coronary artery in 19. The mean stent length was 23.4±5.1mm (range 10.0-31.0mm), mean stent diameter 3.8±0.7mm (range 3.0-6.0mm). One patient suffered a Q wave and 8 a non-Q wave infarction post-procedure, one died. Thrombotic stent occlusion occurred in 5 patients (13%). Femoral artery bleeding occurred in 4 patients (10%), 2 required surgery. Emergency coronary artery bypass surgery was required in 2 patients. Thirty-four patients (89%) underwent angiographic restudy for recurrent symptoms or after 5-23 months if asymptomatic. Stent restenosis (>50% reduction in luminal diameter) was detected in 4 patients (12%), all were symptomatic. No further patients became symptomatic during one year of follow up. We conclude that stenting is an attractive alternative to emergency surgery for acute coronary occlusion following balloon angioplasty with low morbidity and encouraging long-term results.

CLINICAL EXPERIENCE WITH THE PALMAZ-SCHATZ STENT

K A Priestley, J S R Gibbs, L Denne, N A F Chronos, A F Rickards, N P Buller, U Sigwart
Department of Invasive Cardiology, Royal Brompton National Heart and Lung Hospital, London

We report our total experience of 70 Palmaz-Schatz stents used in 52 patients at the Royal Brompton Hospital. The indications for stenting were emergency bailout during a failed angioplasty procedure in 21 stents, 30% (Group I); unsatisfactory angioplasty result (ie. residual stenosis >40% or marked local dissection) in 21, 30% (Group II); restenosis in 8, 11% (Group III); and primary stenting in 20, 29% (14 in vein grafts, 6 in native vessels)(Group IV). Five half stents were used and 4 "doubles" (2 stents sited simultaneously). Sixty-one stents (87%) were successfully deployed with a good angiographic result in all but one. Six stents were not sited and 3 were wrongly sited. In 39 patients (75%) of patients) one stent was used, 2 stents in 9, 3 in 3 and 4 in one patient. Six of 17 patients (35%) in Group I suffered major complications during stenting (one death, 3 emergency coronary artery surgery, 2 Q wave infarction); one of 35 patients (3%) in Groups II-IV required emergency surgery. Later complications in hospital occurred in 10 of 52 patients (19%); one death, 4 acute stent occlusions, 3 major femoral artery problems, one gastrointestinal haemorrhage and one sepsis. Six month angiographic follow up has been obtained in 20 of 22 eligible patients. Six patients (30%) had restenosis within the stent, in particular 3 of 4 patients (75%) in Group III had restenosis compared with 3 of 16 (19%) in Group I, II and IV. These data suggest that elective use of the Palmaz-Schatz stent for an unsatisfactory angioplasty result or primary stenting is associated with a low risk of procedural complications and may reduce restenosis.

RESTENOSIS AND CLINICAL EVENTS AFTER CORONARY STENTING.

SW Davies, J Dean, SJ Winterton, I McCool, M Preston, MT Rothman
The London Chest Hospital and The Royal London Hospital.

Intracoronary stents are increasingly used to treat coronary dissection and acute occlusion during conventional balloon angioplasty, and in an attempt to reduce restenosis. However there remain problems with stent thrombosis and haemorrhage. We report the outcome in the first 53 patients treated with the Palmaz-Schatz stent. Stenting was performed urgently for acute closure in 19, for non-occlusive dissection or a poor result in 11, and electively in 23. 36/53 had multivesel disease, 32 had previous PTCA and/or CABG, and 8 had LVEF <45%. All had angiography at 6 months, and the first 30 again at 12 months. At discharge 1 m 3 m 6 m 12 m
Total number 53 53 53 53 30
Alive 52 50 48 46 24
Dead 1 3 3 4 4
Not asceterated (overseas) - - 2 3 2
Recurrent angina grade I, II 3 6 8 7 5
grade III, IV 0 2 3 1 0
Further intervention 1 2 4 8 5
Event-free 51 48 44 38 19
Event-free and free of angina 48 42 35 33 16
(94%) (91%) (83%) (72%) (79%)
(91%) (79%) (66%) (62%) (67%)
One death occurred at 3 days from heart failure, one from stent thrombosis at 10 days, one from acute infarction at 1 month, and one at 6 months from unrelated renal failure and sepiactia.
At 6 months there was restenosis (>50% diameter) within the stented segment in 6, minor stenosis in 2, and progression of disease at other sites in 2. At 12 months there was one additional mild restenosis within a stent.

EARLY MOBILISATION FOLLOWING CARDIAC CATHETERISATION USING COLLAGEN PLUG HAEMOSTASIS.

JPM Foran, D Palet, J Brooks, RJ Wainwright
Brook Cardiac Unit, London, SE18 4LW.

Day-case cardiac catheterisation is now commonplace, but prolonged patient immobilisation is required following femoral artery cannulation to control local bleeding complications. A novel biodegradable collagen-based haemostasis device is now available to secure haemostasis at the end of the procedure. We conducted a prospective study to investigate the potential of this device to allow early mobilisation (at one hour or two hours) in a series of 63 patients after a variety of invasive diagnostic and therapeutic procedures.

Successful placement of the device was achieved in 57 of 63 consecutive patients (90.5%). Six (9.5%) patients did not receive the haemostat because of femoral artery perforation by the tissue dilator (n=3), inability to compress the femoral artery proximal to the site of delivery (n=1), pre-existing haematoma (n=1), or patient withdrawal from the study (n=1). Uncomplicated mobilisation within two hours of investigation was possible in 54/57 (94.7%) patients. A significant haematoma (>5x5 cm) prevented early mobilisation in the remaining three patients. Mobilisation was uncomplicated in 32/34 (94.1%) patients mobilised at two hours and 22/23 (95.6%) patients at one hour (p:NS). One patient who was mobilised early without complication later developed claudication in the treated leg. Femoral angiography revealed a discrete obstruction, presumed to be a collagen plug, which was subsequently treated successfully with angioplasty. Sheath size, arterial pressure, the use of aspirin, heparin or warfarin, and body mass index did not influence patient outcome.

We conclude that the biodegradable collagen haemostat is a relatively safe and effective device which allows earlier patient mobilisation than conventional haemostasis after diagnostic and therapeutic interventions involving a percutaneous femoral artery approach. These results have important implications for patients undergoing investigation in mobile X-ray units or in hospital based day-case units.
INTERNATIONAL MULTICENTRE CLINICAL EVALUATION OF THE RX FLOW SUPPORT CATHETER

J.S. Gibbs, U Sigwart, N.P. Buller for the RX Flow Support Catheter Clinical Investigators
Royal Brompton National Heart and Lung Hospital, London

The RX Flow Support Catheter (FSC) (ACS Inc. USA) is a temporary stent device which was developed for the management of coronary dissection complicating coronary angioplasty. The FSC consists of a 30 mm collapsible metal cage on a 3.7 Fr rapid exchange catheter. We report the results of the initial clinical evaluation in 12 centres performed over an 18 month period from 1991-92. Fifty-five patients with coronary artery dissection causing impaired coronary flow and angina were recruited. Placement of the FSC across the culprit lesion was achieved in all cases. The cage restored antegrade flow (TIMI 2-3) and relief of angina in all cases.

Coronary dissection after FSC removal was improved in 56% of cases and resolved in 17%. Subsequent management involved a further percutaneous intervention in 20 patients and coronary artery surgery in 16 patients. Major events comprised 14 non-fatal myocardial infarctions and 1 death. Two month follow-up, completed in 35 patients, showed 5 patients underwent coronary surgery and 1 sustained a non-fatal myocardial infarction. In conclusion the FSC restores and maintains blood flow after severe dissections and abrupt closure after coronary angioplasty, providing adequate time to institute secondary treatment. Complete resolution of dissection occurred in the minority of cases. The device provides a successful bridge to surgery.

THE ANTI-ARRHYTHMIC ACTION OF ISCHAEMIC PRECONDITIONING DOES NOT INVOLVE FUNCTIONAL INHIBITORY G PROTEINS IN RAT HEARTS

C.S. Lawson, D.J. Collart and D.J. Hears. Departments of Cardiovascular Research and Cardiology, St Thomas Hospital, Lambeth Palace Road, London SE1 7EH

Brief episodes of ischaemia and reperfusion (ischaemic preconditioning) protect the heart against ischaemia-induced injury. It is not clear, however, if protection against myocardial necrosis and arrhythmias occur by the same molecular mechanisms. Previous studies have suggested that protection against necrosis may be mediated via inhibitory G (Gi) proteins. The aim of the present study was to determine whether functional Gi proteins are required for the anti-arrhythmic action of preconditioning. To address this issue, rats (n=24/group) were randomised to receive either pertussis toxin (25µg/kg, i.v) or saline. 48 hrs later their hearts were isolated, perfused with blood from untreated support rats and further randomised to undergo either: (i) 30 min aerobic perfusion (controls-C), or (ii) 3 cycles of 5 min regional ischaemia and 5 min reperfusion (preconditioned-PC) induced by tightening and releasing a snare around the left coronary artery. Subsequently all hearts underwent 30 min regional ischaemia and 10 min reperfusion. Cardiac rhythm was recorded continuously. In saline perfused hearts, preconditioning markedly reduced the severity of ischaemia-induced arrhythmias with reductions in the incidence of ventricular tachycardia (VT) from 100% to 33% and the mean number of ventricular premature beats (VPBs) from 164±42 to 23±14; each p<0.05. Pretreatment with pertussis toxin completely abolished the bradycardic response to acetylcholine and adrenaline but had no influence on the degree of antiarrhythmic protection afforded by preconditioning with reductions in the incidence of ventricular tachycardia from 83% to 33% and the mean number of ventricular premature beats from 267±56 to 62±32; each p<0.05. Preconditioning also reduced the incidences of ischaemia-induced ventricular fibrillation (VF) and reperfusion-induced VF; and VT; against these were unaffected by pertussis toxin pretreatment. We conclude that the anti-arrhythmic effect of preconditioning in isolated blood-perfused rat hearts does not require functional Gi proteins.

ABNORMAL RELAXATION AND THE ONSET OF PULSUS ALTERNANS IN THE INSITU PIG HEART


The onset of pulsus alternans in the context of ventricular dysfunction often indicates a poor prognosis. This study assessed myocardial segment behaviour before the onset of pulsus alternans as this may have implication with regard the cellular mechanisms of mechanical alternans. Twelve open chested pigs, anaesthetised with 1% halothane in a 1:1 mixture of nitrous oxide and oxygen, were subjected to stepwise changes in right atrial pacing to induce pulsus alternans. Left ventricular pressure was measured with an apically inserted fluid filled catheter. Regional mechanical performance was measured in three areas of left the ventricle using epicardially based tripodal devices. Control pressure-length loops were normal (fig 1a). At shorter cycle lengths alternation in the diastolic or relaxation phase of the loop (a) was seen in one or more areas in 11 out of 12 pigs (fig 1b,c,d). This abnormality preceded the onset of marked alternans in developed pressure (fig 1d).

There is now good evidence that mechanical alternans is caused by alternating calcium release from the sarcoplasmic reticulum. However, the mechanism behind this is not understood. These data point to a primary abnormality in the relaxation process as being responsible for resetting calcium cycling and release. Abnormal relaxation is a common feature of ventricular dysfunction of varied aetiology. This may provide a link to explain the prevalence of pulsus alternans in heart disease.

ANTIBODIES TO ACETALDEHYDE ADDUCTS OF HUMAN HEART IN PATIENTS WITH ALCOHOLIC HEART MUSCLE DISEASE

*Clinical School, Addenbrookes Hospital, CAMBRIDGE.
+Institute for Liver Studies, *Cardiac Department, Kings College Hospital, and *Department of Clinical Pharmacology and Toxicology, St Mary's Hospital, LONDON

The mechanism by which ethanol induces alcoholic heart muscle disease (AHMD) is unknown. Acetaldehyde, an ethanol metabolite, may render proteins antigenic. Patients with AHMD were therefore investigated for the presence of antibodies to acetaldehyde modified cardiac proteins. Sera were studied from 14 patients with AHMD (prolonged consumption of >80 units average alcohol weekly, moderate to severe left ventricular dysfunction and normal coronary angiography) and 39 controls, (20 idiopathic dilated cardiomyopathy, 8 ischaemic heart disease and 11 normal individuals) who drank less than 21 units(males) or 14 units(females) weekly. Eight patients with alcoholic liver disease were also studied. Cytosolic and microsomal fractions were prepared from homogenised normal human myocardium and incubated with or without acetaldehyde in the presence or absence of cyanoborohydride (which stabilises acetaldehyde adducts). Samples were resolved on polyacrylamide gels and transferred onto membranes by Western blotting. Blots were indirectly immunostained with the test sera. Four of 14 patients with AHMD (28%) had detectable antibodies against acetaldehyde modified cytosolic protein (p<0.05), detected only against samples incubated with acetaldehyde and cyanoborohydride. Antibodies were of IgG class in 3 patients, one of whom also had an IgA antibody. An IgM antibody was detected in the fourth patient. No control samples had these antibodies. Patients with IgG antibodies also had antibodies of the same isotype against microsomal protein. Thus, some patients with AHMD possess circulating antibodies against acetaldehyde modified cardiac cytosolic and microsomal proteins, which are not found in the sera of controls. It is suggested that acetaldehyde may play a role in the pathogenesis of AHMD via the humoral immune system.
INDUCTION OF NITRIC OXIDE SYNTHESE IN MEGAKARYOCYTES OF PATIENTS WITH SEVERE CORONARY ATHHEROSCLEROSIS.

A de Belder1,2, M Radomski, R Lechuk, S Moncada, J Martin2. Depts. of Cardiology1 and Medicine2, King's College Hospital, London, and Wellcome Res. Labs. Beckenham, Kent.

Human platelets of normal subjects contain the constitutive but not the inducible nitric oxide (NO) synthase which regulates platelet aggregation. Cultured megakaryocytic cells express the inducible NO synthase when stimulated with cytokines. We investigated the constitutive and inducible NO synthase activities in megakaryocytes isolated by an immunomagnetic technique from freshly taken bone marrow of 2 groups of patients: 1) 18 patients with severe multivessel coronary artery disease (CAD) requiring, at least 3 bypass conduits, 2) 8 age-matched patients undergoing valve surgery who had normal coronary arteries at angiography. The results are shown below:

Thus, the inducible NO synthase is expressed in megakaryocytes of patients with severe CAD. We are investigating the antithrombotic significance of these findings.

EXPRESSION OF ANGIOTENSINOGEN, RENIN AND ANGIOTENSIN-CONVERTING ENZYME GENES IN HUMAN ATRIAL TISSUE


Departments of Clinical Cardiology, Histochemistry and Cardiothoracic Surgery and MRC Lipoprotein Unit, RPPMS, Hammersmith Hospital, London.

Individual components of the renin-angiotensin system have been identified in the heart of several mammals, however, the expression of angiotensinogen, renin and angiotensin converting enzyme (ACE) has not been demonstrated together in the same cardiac tissues. We have examined the expression of the components of the renin-angiotensin system in a series of 30 human surgical samples of right atrial appendage using reverse transcriptase - polymerase chain reaction (RT-PCR) amplification. mRNA was isolated directly from pieces of snap-frozen atrial appendage (57.6 ± 3.8 mg) and first-strand cDNA synthesised by random-primed AMV reverse transcription. cDNA fragments of predicted size were amplified by 2 rounds of PCR (45 to 60 cycles) using nested oligonucleotide primers. Controls included the omission of the RT step and Southern blotting of PCR products. Angiotensinogen expression was detectable in more than 90% of the samples, at a level ~2 orders of magnitude less than that of atrial natriuretic peptide. ACE expression was demonstrated in the same proportion of samples, but at a level 10 to 20-fold lower than angiotensinogen expression. Renin transcripts were detected in ~60% of samples, the relative level of expression being ~50-fold lower than that of angiotensinogen. An intrame deletion mutation was identified in the angiotensinogen coding sequence of one patient resulting in a deletion of 66 codons (+350 (Gly) to +415 (Glu)), corresponding to the last 18 codons in exon 3 and the whole of exon 4. Variations, over at least a 15-fold range, were reproducibly detected in the relative level of specific gene expression between individuals, possibly reflecting tissue specific gene expression, disease status or drug therapy.

The results demonstrate the co-expression of renin-angiotensin components in human cardiac tissue and individual differences in the relative level of gene expression. The frequency and significance of the angiotensinogen deletion mutation is not known but in view of the genes conserved structure it is likely that this could influence angiotensin metabolism.

INCREASED PLASMA FIBRINOGEN LEVELS IN PATIENTS WITH CHRONIC AND PAROXYSMAL ATRIAL FIBRILLATION: A MECHANISM FOR THROMBOEMBOLIC RISK?

G Y H Lip, M J Metcalfe, "A Rumley, "G D O Lowe, F G Dunn Department of Cardiology, Stobhill General Hospital; and "University Department of Medicine, Royal Infirmary, Glasgow.

Paroxysmal atrial fibrillation carries an intermediate risk of thromboembolic events when compared to patients in chronic atrial fibrillation and those in sinus rhythm. Epidemiological studies have established that plasma fibrinogen levels are associated with an increased incidence of cardiovascular events and stroke. We, therefore, measured plasma fibrinogen levels (CLAUSS) in 57 consecutive patients with chronic atrial fibrillation (Group 1) and 19 with paroxysmal atrial fibrillation (Group 2). They were compared to 18 patients with ischaemic heart disease with normal left ventricular function (hospital controls) and 157 healthy population controls, all of whom were in sinus rhythm. Group 1 had higher median levels of plasma fibrinogen when compared to Group 2 (3.83 vs 3.15±g; p<0.05), hospital controls (3.93 vs 2.82±g; p=0.0001) and population controls (3.93 vs 2.60±g; p<0.0001). The median plasma fibrinogen level in Group 2 was increased when compared to hospital controls (3.15 vs 2.82±g;p<0.05) and population controls (3.15 vs 2.60±g; p<0.001). This study, therefore, provides rheological support for the increased risk of thromboembolism in all patients with atrial fibrillation. In addition, patients with paroxysmal atrial fibrillation have intermediate levels of plasma fibrinogen when compared to patients in chronic atrial fibrillation and those in sinus rhythm. This is in keeping with a thromboembolic risk which is graded between paroxysmal and chronic atrial fibrillation.

AXILLARY ARTERY CUT DOWN FOR INTERVENTIONAL CARDIAC CATHETERISATION IN INFANTS

M E C Blackburn, J L Gibbs, J M Parsons, D F Dickinson Paediatric Cardiology, Killingbeck Hospital, Leeds.

The axillary artery provides an alternative approach to the femoral artery for interventional left heart catheterisation and is now the approach of choice in our unit for infants. Over an 18 month period we have performed 21 interventional procedures in 17 infants via axillary artery cut down, median age 3.5 months (range 1-26), median weight 3.2 kg (range 2.2-6.6). Procedures were angioplasty for recoarctation (2), aortic valvoplasty (10) and ductal stenting (9). The axillary artery was cannulated under direct vision using the Seldinger technique and the arteriotomy repaired by suture. Axillary artery cutdown led to successful arterial access in all cases. In 3/3 cases it was possible to enter the artery a second time 1-24 weeks later. Total procedural time for aortic valvoplasty was 1 - 1.5 hours. Significant haemorrhage occurred in 4/21, involving complex interventions. 1 neonate developed an axillary haematoma which was surgically drained. Distal pulses were absent in 2/21 at the end of the procedure which in one case was due to a stent obstructing the subclavian artery. Delayed loss of pulse in another case required revascularisation with a vein graft. 3 children were treated with heparin for 24-48 hours because of diminished distal pulses and 1 child received streptokinase. There were 2 cases of transient Erb's palsy, one in the child with the axillary haematoma and the other following vigorous attempts to retrieve the stent lodged in the subclavian artery. In conclusion, axillary artery cut down provides a reliable and relatively simple means of arterial access in infants undergoing interventional left heart catheterisation and has a vascular complication rate comparable to that seen with the femoral approach.
PALLIATION IN HYPOPLASTIC LEFT HEART SYNDROME


Neonatal transplantation for hypoplastic left heart syndrome is limited by lack of availability of donor hearts. Conventional surgical palliation has a very high mortality. A programme of atrial septectomy/septostomy, transcatheter stenting of the arterial duct and bilateral pulmonary artery banding was developed in the hope of offering better palliation and increasing the chance of finding a donor.

Seven neonates were considered suitable. Four had septostomy and stenting (day 4-27) with banding on day 11-24. Two had atrial septectomy and pulmonary artery banding (day 27-33) followed by stenting on day 31-55. Septostomy was satisfactory in 4 of the 5 cases attempted. Septostomy was satisfactory in all 3 cases where it was performed. Stenting of the arterial duct was technically satisfactory in 5 of 7 patients. Stenting was not possible in one baby and he underwent the first stage Norwood procedure and is now at home awaiting transplant. One stent was deployed too far proximally with resultant stenosis at the distal end of the duct. Bilateral pulmonary artery banding was satisfactory in 3 of 7 patients. In 3 patients pulmonary blood flow was still excessive and there was continuing heart failure. In one patient the left pulmonary artery was occluded. Three patients survived to leave hospital. Two underwent heart transplant at 4 and 6 months of age and both died perioperatively. Electron microscopy of the stent at 6 months demonstrated complete endothelialisation.

Stenting and pulmonary artery banding offers realistic hope of survival to receive a transplant in this group of patients but continuing refinement of both techniques is required.

LONG TERM FOLLOW-UP OF RESIDUAL SHUNTING AND POTENTIAL COMPLICATIONS AFTER TRANS-CATHETER OCCLUSION OF THE DUCTUS ARTERIOSUS


From October 1987 to July 1992, a total of 140 patients have had attempted implantation of the Rashkind double umbrella occluder for a ductus arteriosus. Ages were from 0.5-78 years (median 3.8) and weights from 6.8-74 kg. (median) 13.8. The causes and outcome of residual shunts and the potential of the device to produce obstruction to flow in the sorts and left pulmonary artery were assessed by angiographic examination at the time of occlusion and thereafter prospective clinical and echocardiographic evaluation. Overall rate of successful occlusion was 94% including 7 re-occlusions; a total of 6 devices embolised at the time of the procedure (4, 3%)

Three were anatomical factors that statistically precluded a poor outcome, but sub-optimal device positioning was associated with a significantly higher incidence of residual shunts (p < 0.001). Four patterns of residual shunting were identified by doppler colour flow mapping (CFM).

1. Broad continuous high velocity jet n = 8 patients.
2. Narrow non-continuous high velocity jet n = 22 patients
3. Peri-device colour flow n = 4 patients.
4. Low velocity "flare" n = 2 patients. Seven of the 8 patients in Group 1 have required insertion of a second device. In contrast 21 patients in groups 2-4 have demonstrated late spontaneous closure. Encroachment of device legs produced statistically (p < 0.001) but not clinically significant increases in left pulmonary artery doppler velocities, which diminished with time.

Conclusion: Residual shunts associated with broad high velocity jets on CFM require a second device. The device itself does not produce significant disturbances to flow in the pulmonary arteries or sorts.

RADIOFREQUENCY THERMAL BALLOON ANGIOPLASTY OF THE ARTERIAL DUCT IN NEONATAL LAMBS PRODUCES LONG TERM PATENCY.

SE Ahrnsen*, KF Walsh*, M Diamond*, MJ Clarkson*. Cardiac Dept*, Royal Liverpool Childrens Hospital and Veterinary Field Station*, University of Liverpool.

The ability to produce long term arterial duct (AD) patency using a catheter intervention offers many potential therapeutic advantages for babies both with duct-dependent congenital conditions who cannot undergo surgical reconstruction in early life. We treated the AD of 28 lambs, mean age 38 hrs (12-120 hrs), mean weight 3.8 kg (2-8 kg), with radiofrequency thermal balloon (RFTB) angioplasty. 4 lambs had angioplasty alone. In anaesthetised lambs, a 5mm (n=12) or 6mm (n=16) diameter RFTB catheter was passed transvenously across the AD. The RFTB was inflated to 4 atmospheres and radiofrequency applied to produce balloon temperatures for 15 secs at 85°C (n=2), 75°C (n=2), 85°C (n=10), 100°C (n=6), 120°C (n=6). Lambs were recatheterised at intervals to assess patency and pulmonary artery (PA) pressure.

Immediate results show a mean rise in PA systolic pressure of 12±8mmHg and an angiographic AD appearance of a uniform, smooth walled tube. Mean ratio of balloon size to lung size of 1:1.4. With up to 29 weeks (mean 17.8) follow up (FU), 3 of 4 (75%) control ADs, and 8 of 28 (18%) treated ADs (18%) have closed (p<0.05). All closures occurred before 2 months. Mean PA systolic pressure at last FU was 29±11mmHg. Angiographic stenoses were present but lumen diameter at last FU is mean maximum 6±3.2mm, mean minimum 5±1.8mm. One lamb developed a ductal aneurysm, 2 died within 24 hrs from heart failure.

CONCLUSION: RFTB angioplasty maintains AD patency in lambs for up to seven months without causing pulmonary hypertension. Restenosis occurs and warrants further investigation.

PRIMARY TRANSCATHETER CLOSURE OF PERIMEMBRANOUS VENTRICULAR SEPTAL DEFECTS

Michael L Rigby, Andrew N Redington. Department of Paediatric Cardiology, Royal Brompton National Heart & Lung Hospital, Sydney Street, London SW3 6NP.

Nine infants and children underwent attempted primary closure of a perimembranous ventricular septal defect using a Bard ductal umbrella. There were five infants (aged 3 weeks to 6 months; weights 1.8-5.4 kg) presenting with congestive heart failure and failure to thrive, and three children (ages 2, 5 and 16 years; weights 12.5, 13 and 45 kg) who were breathless on exertion and had a pulmonary to systemic flow ratio greater than three to one. The procedures were performed under general anaesthesia and guided with simultaneous transeophageal echocardiography. A 17 mm ductal umbrella was positioned successfully in 5 patients and a 12 mm umbrella in two. In one infant the procedure was abandoned when a 17 mm umbrella embolised to the pulmonary artery because the VSD was too large. In the smallest infant (1.8kg) the umbrella was opened in the left ventricular outflow tract. The early effect of closure was a fall in the mean RV to LV systemic pressure ratio from 0.75 to 0.35 and a reduction in Qv/Qs from a mean of 4.1 to 1.6:1.

One infant died one month after the procedure because of congestional pulmonary lymphangectasia. At autopsy the VSD was completely occluded by the 12 mm device and was partially endothelialised. The mean follow-up in the remainder is 8.5 (1-19) months. Four patients have a small residual left to right shunt and one patient has mild and insignificant tricuspid regurgitation demonstrated by Doppler echocardiography. No arm fracture of the umbrellas has been observed on radiographic screening.

Transcatheter umbrella closure of perimembranous VSDs is technically feasible and can be therapeutically successful.
DELETERIOUS HAEMODYNAMIC EFFECTS OF BALLOON ATRIAL SEPTOSTOMY IN INFANTS WITH LEFT ATRIOVENTRICULAR VALVE ATRESIA.

N Seeram, K Walsh.

Alder Hey Children’s Hospital, Liverpool, England.

In infants with left atrioventricular valve (LAVV) atresia, pulmonary venous drainage to the left atrium reaches the systemic circulation through an interatrial communication which is often restrictive. In five consecutive infants (median age 3 days; range 1-42 days) with LAVV atresia diagnosed on echocardiography, transcatheter balloon atrial septostomy was performed as the initial palliative procedure. The gradient across the atrial septum fell from a median of 14 (range 7-16) to 3 (range 2-3) mm Hg; p<0.01, following the procedure. Clinical and biochemical deterioration occurred in all patients within 48 hours of septostomy (and <24 hours in 3 infants). The arterial oxygen saturation rose from 86% (75-90) to 92% (90-95) without any change in inspired oxygen concentration; p<0.05. This was associated with a fall in arterial pH from 7.37 (7.26-7.43) to 7.14 (6.8-7.3), and an increase in base deficit from -6 (-6 to +12) to -16.5 (-28 to +5); p<0.05. In three patients there was an acute fall in systolic arterial blood pressure from 70 (55-70) to 35 (30-50) mm Hg, and all required mechanical ventilation and inotropic therapy.

The associated with oxygen extraction of five consecutive patients (median 50) were performed at a median of 6 days (4-12) after septostomy. In conclusion, in infants with LAVV atresia and without associated pulmonary stenosis, effective balloon atrial septostomy results in a redistribution of the cardiac output, with a relative increase in pulmonary flow (reflected by the improved systolic arterial oxygen saturation and relative systemic hypoperfusion (with metabolic acidosis and hypotension). Pulmonary artery banding should therefore be performed in close proximity, to avoid the deleterious haemodynamic effects of balloon septostomy.

QUANTIFICATION OF LEFT TO RIGHT ATRIAL SHUNTING AND DEFECT SIZE AFTER BALLOON MITRAL COMMISSURITOMY USING BIPLANE TRANSESOPHAGEAL ECHOCARDIOGRAPHY, COLOUR FLOW DOPPLER MAPPING, AND THE PRINCIPLE OF PROXIMAL FLOW CONVERGENCE

Dymitr Ratto

Department of Cardiology, Western General Hospital, Edinburgh.

Flow convergence regions (FCR) are zones of progressive laminar velocity acceleration that can be imaged by colour Doppler proximal to restrictive orifices. Theoretically, FCR proximal to a discrete circular and planar orifice, such as a hemispheric aortic orifice in isovelocity shells. Using the continuity principle, orifice flow rate (Q) can be calculated as $2 \pi r V_r$ where $V_r$ is the velocity at a radial distance $r$. To determine whether these principles can be applied to quantify arterial shunt flow and defect size after mitral balloon commissuritomy, 36 consecutive patients were examined by transesophageal echocardiography (TOE) within 24 hours of the procedure. FCR was maximised by reducing Nyquist velocity to 11 cm/s. Peak velocity (Vp) of the shunt jet and its velocity-time integral (VTI) were obtained by pulsed Doppler. Defect flow area was derived as Qm/Vp, where Qm is the maximum Q derived from FCR. Anatomical area was calculated from 2-D echo using formula of an ellipse. Hence FCR shunt flow = flow area x VTI x heart rate. TOE identified shunting in 33/36 patients; FCR was imaged in 31. Oximetry identified shunting in 11 (Group 1) and no shunting in the other 25 (Group 2).

Qm (mL/min) Flow area (mm²) VTI (mm) Qm/Vp (mL/min/mm²)

Group 1: 38.1 ± 26.5 22.1 ± 11.2 22.6 ± 10.4

Group 2: 5.3 ± 2.7 4.4 ± 2.0 4.2 ± 2.3

Qm correlated strongly with oximetric shunt flow (r = 0.89-0.94, p < 0.001) and shunt ratio (r = 0.91-0.94, p < 0.001). Flow and anatomical area showed excellent agreement (r = 0.92-0.94, p < 0.001). Similarly FCR shunt flow agreed closely with that derived from oximetry (r = 0.94-0.98, p < 0.001). Correlation ranges indicate results from transverse and longitudinal plane imaging. The flow convergence method combined with TOE is a powerful new technique that can accurately quantify atrial shunt flow and defect size after balloon mitral commissuritomy.

LEFT VENTRICULAR FORCE DEVELOPMENT IN PATIENTS WITH CHRONIC AORTIC REGURGITATION

GD Young, M St John Sutton

Royal Brompton, National Heart Hospitals.

Ejection phase indices of left ventricular (LV) function are difficult to interpret in aortic regurgitation (AR) because they are dependent on LV load and shape and become normal only late. LV force, the product of mass and acceleration, is an index of myocardial performance that is independent of LV loading and configuration. We quantitated LV force, end-diastolic and end-systolic volumes, ejection fraction (EF) and LV mass in 28 patients with AR (19 male, mean age 50) and in 14 normals (9 male, mean age 41) using 2D Doppler echocardiography. 2D echo images of the LV short and long axes and LV outflow tract (LVOT), and Doppler velocity signals from the LVOT were recorded. LV volumes, mass and EF were calculated using the 5/6(short axis area x long axis length) method. Cross sectional area (CSA) of the LVOT was calculated from the diameter; r(D/2)². Velocity signals were digitized to obtain flow velocity integrals during acceleration (AT-PVI), peak velocities (PV) and acceleration times (AT). LV force was calculated as the product of mass (CSA x 1.05) (AT-PVI) and acceleration (PV/AT). LV force in patients with AR was greater than controls (67±1 vs 35±4.2; p<0.001). LV force correlated with end-diastolic (r = 0.85), end-systolic (r = 0.83) volumes and LV mass (r = 0.76; all p<0.05) but poorly with EF (r = 0.48). When LV force was normalized to unit LV mass the relationship with LV volumes became inverse, suggesting progressive myocardial dysfunction with increasing chamber size.

Conclusion: LV force correlates strongly with the clinical severity of AR in terms of LV size and hypertrophy. Force may provide an early recognition of myocardial dysfunction in patients with AR and normal EF.

DOBUTAMINE ECHOCARDIOGRAPHY PREDICTS ISCHAEMIC EVENTS IN PATIENTS WITH CORONARY ARTERY DISEASE AND AN INTERMEDIATE PROGNOSTIC TREADMILL SCORE

P Mazelaar, A Madedzin, Cella M Oakes

Clinical Cardiology Unit, Hammersmith Hospital, London.

Risk stratification of patients with coronary disease (CAD) is a major goal of noninvasive testing and affects later management. The prognostic treadmill score (PTS), exercise duration in min - 15 x maximal nonupsloping ST segment shift in mm - 4 x treadmill ansia index (HASI) has been validated in large groups of patients with CAD and enables their separation into high (score < - 10), moderate (- 10 to - 4) and low ( > - 4) risk.

An additional important concern with the principle of inducible regional ischaemia on dobutamine stress echocardiography (DSE) as a predictor of ischaemic events in those at intermediate risk, 56 patients aged 55 (9, 40) men with preserved ventricular function and a PTS of - 3±6.5 (range -10 to 4) were studied using stepwise doses of up to 20 mcg/kg/min. Images were analysed by calculating a wall motion score index (WMSI); normal = hypokinesia = 2, akinesis = -3, dyskinesia = 4 based on an 11 segment model: 50% of segments were interpretable at peak stress.

Over 38(5) months (range 24-45) of follow up 15 patients had events (2 cardiac death, 5 myocardial infarction, 8 unstable angina) and 41 were event free. Infusion duration, proportion with a positive dobutamine ECG (7/15 vs 14/41; p<0.05) and the proportion with induction of painful versus silent ischaemia were similar in these 2 groups (p>NS). A positive DSE was seen in 12/15 (80%) with and 17/41 (41%) without events (p<0.01); sensitivity 80%, specificity 59%, positive predictive value 61%, negative predictive value 89%.

The change in WMSI from baseline (0.08 ± 0.05; n=36) to peak dose (0.32 ± 0.10 x 0.17 ± 0.08, p<0.05) and WMSI at peak dose (1.14 ± 0.11 vs 1.25 ± 0.07, p<0.05) were significantly greater in those with coronary angiographic correlates (n=51) indicated that DSE tends to detect patients with severe multivessel CAD (minimal lumen diameter < 1 mm). The DSE was not predictive of cardiac risk in this cohort. DSE appears to refine risk assessment and provide additional prognostic information in patients with CAD and an intermediate PTS. It is a useful tool for coronary angiography and prognostic revascularisation and is especially suitable in patients unable to exercise.
**British Heart Journal**

**COMPARISON OF DOPLER DERIVED HEMODYNAMICS AND SIMULTANEOUS HIGH FIDELITY PRESSURE MEASUREMENT IN SEVERE PULMONARY HYPERTENSION**

S J Brecker, J S B Gibbs, M H Yacoub, D G Gibson
Royal Brompton National Heart & Lung Hospital, London

Doppler echocardiography is widely used to assess pulmonary hypertension (PH) and right ventricular function. It is increasingly used to estimate peak rates of ventricular pressure rise and decline. It is well known that correlations between right ventricular pressure (RVP) and the characteristics of tricuspid regurgitation (TR) have been recorded. Simultaneous right heart pressure measured with a transducer-tipped catheter and Doppler echocardiography in 8 patients with severe chronic PH (mean pulmonary artery pressure 69±11 mmHg). TR signals and pressure recordings were digitised for analysis peak-to-nil optimally -- a) peak pressure differences and absolute RV and their differentials. Peak right ventricular -- atrial pressure drop underestimated both the peak RVP by a mean of 33±20 mmHg, and by 20±33 mmHg when the Doppler value was added to the measured right atrial pressure (p values <0.05). This discrepancy was greater, the higher the pulmonary artery pressure. The timing of peak RVP differed with the Doppler value consistently shorter (mean difference 20 ms, p<0.05). Mean values from catheter and the root mean square (RMS) differences with Doppler for peak +ve and -ve Dp/dt, and the time intervals peak +ve and peak -ve Dp/dt and pulmonary closure to the end of the pressure pulse: were:

<table>
<thead>
<tr>
<th>Description</th>
<th>Mean</th>
<th>RMS Difference</th>
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<tbody>
<tr>
<td>Peak +ve Dp/dt (mmHg/s)</td>
<td>685</td>
<td>165</td>
</tr>
<tr>
<td>Peak -ve Dp/dt (mmHg/s)</td>
<td>822</td>
<td>193</td>
</tr>
<tr>
<td>Q wave peak +ve Dp/dt (ms)</td>
<td>85</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary closure end of pressure pulse (ms)</td>
<td>115</td>
<td>15</td>
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Left ventricular filling was abnormal (isovolumic relaxation time: 85±20 ms, A/E ratio 2.61±1.31), associated with high right atrial pressure at the instant of atrial opening (53±21 mmHg). Thus: Doppler echocardiography significantly underestimated both the peak RVP and the time interval to peak RVF in PH, particularly when severe. Digiisation of Doppler records of TR provides useful semiquantitative estimates of absolute values and timing of peak +ve and -ve Dp/dt. Clinically significant differences may exist however, and must be considered in individual cases.

**IMPROVED DOPLER EVALUATION OF VALVULAR HEART DISEASE USING SHU 508A, A NEW TRANSPULMONARY ECHO CONTRAST AGENT**

M.J. Stewart, P.J. Gibb-Peris, L.N. Gordon, G.R. Sutherland Department of Cardiology, Western General Hospital, Edinburgh

A poor signal to noise ratio of continuous wave and colour Doppler recordings may prevent full echocardiographic assessment of left heart valvular disease. The new transpulmonary, saccharide-based ultrasound contrast agent SHU 508A (S) has been shown to enhance left heart Doppler signals after intravenous injection. We have therefore evaluated the role of this agent in patients referred for assessment of aortic stenosis (n = 11), mitral regurgitation (n = 3), and mitral prosthesis function (n = 8). All underwent Doppler echocardiographic evaluation before and for 10 minutes after the intravenous injection of 3.2 G of S, recording continuously on videotape which was later assessed independently by two observers. All patients had a physical examination, electrocardiogram and full laboratory evaluation performed prior to, 1 hour and 24 hours after the study. Administration of S was well tolerated with no significant adverse events and no change in heart rate or blood pressure. Doppler signal enhancement was evident in all patients, with a maximal increase seen within 20 seconds and decreasing effects apparent for up to 600 sec (mean 204 ± 121). The continuous wave Doppler envelope improved in all retrograde and antegrade jets. Increased Doppler peak velocity was recorded in 6/11 patients with aortic stenosis who had vague pre-contrast velocity envelopes, but no increase in peak velocity was evident in those patients with satisfactory baseline recordings. Four patients with mitral prosthesis regurgitation detected at baseline all had increased retrograde flow measured after injection of S, and in 3/4 patients with no retrograde flow at baseline prosthesis regurgitation was detected after catheterised S, and in 3/4 patients with no retrograde flow at baseline prosthesis regurgitation was detected after catheterised S. Increased retrograde flow was also measured in 1/3 patients with native mitral valve regurgitation. Signal to noise ratio in pulsed Doppler recordings allowed quantification of measurements of pulmonary and aortic regurgitation in only 3/12 patients at baseline but in 7/12 after contrast enhancement. Conclusion: SHU 508A is a safe left heart ultrasound contrast agent which achieves significant enhancement of spectral and colour Doppler modalities, improving the quantitative assessment of aortic stenosis and pulmonary vein flow, and enabling improved identification and quantification of regurgitant jets through both mitral valve protheses and native valves.

**VARIABLE OVERESTIMATION OF CORONARY BLOOD FLOW VELOCITY WITH SIDE-MOUNTED DOPLER FLOW PROBES**

DR Holdright, D Clarke, KM Fox, PA Poole-Wilson, P Collins. Royal Brompton National Heart & Lung Hospital, London, UK

Coronary blood flow velocity can be measured using an intracoronary Doppler flow probe, available commercially with either end-mounted or side-mounted crystals. We assessed the importance of crystal location in a specially-designed rig. End-mounted (E) and side-mounted (S) probes were tested in a silastic tubing rig (internal diameter 5mm) using a roller pump and reperfusion blood at flow rates from 0 - 521 ml/min. Velocities measured with the side-probe were corrected for the crystal angle. Measured velocities (cm/s) were compared with calculated true values using the Bland and Altman method to determine the mean difference (measured - true velocity (cm/s)) and the standard deviation (SD) of the difference.

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<th>Description</th>
<th>Mean Difference</th>
<th>± SD</th>
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<tr>
<td>E probe</td>
<td>-2.5</td>
<td>0.9</td>
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<tr>
<td>S probe</td>
<td>23.7</td>
<td>52.0</td>
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E probe velocities agreed closely with calculated true velocity in the 6 probes considered overestimated true velocity. In an attempt to understand the significant discrepancies with the S probe, the flow experiment was repeated with randomly-selected S probes, following which magnified images (x80) of the crystal were made for calculation of the true crystal mounting angle for each of the S crystals range from 30 - 42° (mean 34.8°). In contrast to the quoted angle of 45°, velocities corrected for the individual mounting angles agreed more closely with calculated true values. Although results expressed in relative terms (eg ratios) will be similar for both probes, absolute values will be erroneously high for probes with side-mounted crystals and will vary between catheters.

**THE VALUE OF PHYSICAL SIGNS IN THE DIAGNOSIS OF VENTRICULAR TACHYCARDIA**

CJ Garratt, MJ Griffith, G Young, N Curzon, AF Rickards, AJ Camm
Royal Brompton and St. George's Hospitals, London and Freeman Hospital, Newcastle

Although the use of physical signs for the diagnosis of ventricular tachycardia (VT) was described in the early 1900s, their value in this role has never been systematically assessed. Using a blinded, randomised protocol, we examined the ability of 26 clinicians to detect ventricular-atrial (VA) dissociation during cardiac pacing in 21 patients with both atrial and ventricular temporary pacing wires in situ (flowing successful ablation of accessory pathways. In protocol 1 (10 patients) pacing was randomised to either ventricular pacing alone (simulating VT) or to atrioventricular sequential pacing (simulating supraventricular tachycardia or VT with intact VA conduction) at rates of 150 or 180 beats per minute. The presence of VA dissociation during ventricular pacing alone at these rates had previously been established for each patient at electrophysiology study. Each patient was examined by 4 clinicians blinded to the pacing mode. Clinicians were asked to make a diagnosis of "VT" or "not VT" after looking for variability of amplitude of the arterial pulse (AP), jugular venous pulse (JVP), and variability of the first heart sound (HS). A diagnosis of "VT" was made in 21 of 40 observations, with a specificity of 77%, sensitivity of 71% and a positive predictive value (PPV) of 71%. In protocol 2 (11 patients) randomisation of pacing mode was performed between examination of each of the 3 physical signs (the ability of each sign was assessed individually. The results for the diagnosis of VT are presented below from a total of 132 observations (44 for each sign):

<table>
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<tr>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
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<tbody>
<tr>
<td>Arterial pulse</td>
<td>61%</td>
<td>71%</td>
<td>70%</td>
</tr>
<tr>
<td>JVP</td>
<td>96%</td>
<td>75%</td>
<td>82%</td>
</tr>
<tr>
<td>First HS</td>
<td>58%</td>
<td>100%</td>
<td>100%</td>
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It is concluded that, in patients with a regular tachycardia of uncertain origin, clinically detectable variations in the first heart sound and JVP are highly specific and sensitive indicators, respectively, of a diagnosis of VT.
MAGNETIC RESONANCE IMAGING DETECTS CARDIAC ABNORMALITIES NOT VISUALISED BY ECHOCARDIOGRAPHY AND ANGIOGRAPHY IN PATIENTS WITH IDIOPATHIC VENTRICULAR TACHYCARDIA

Cardiological Sciences, St George's Hospital Medical School and MRI Unit, Royal Brompton Hospital, London.

Background: Abnormalities of cardiac chamber dimensions and function are detectable in a proportion of patients with idiopathic ventricular tachycardia (VT) by echocardiography (ECHO) and angiography. This study examines whether magnetic resonance imaging (MRI) will improve the detection of cardiac abnormalities in this group of patients.

Patients and Methods: Sixteen patients with idiopathic ventricular tachycardia (all of right ventricular origin) mean age 35 ± 11.8 years, 9 males, were studied by ECHO, angiography (including right ventricular angiography), MRI (including a cine-loop) and right ventricular cardiac biopsy. Angiography was not performed in 3 patients and cardiac biopsy was not performed in 5 patients for clinical reasons.

Results: Abnormalities were detected in a greater proportion of patients by MRI scanning than both ECHO and angiography. In all cases, the MRI scan was abnormal where ECHO or angiography was abnormal.

ECHO Angiography Biopsy

<table>
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<tr>
<th>Norm</th>
<th>Abnor</th>
<th>Norm</th>
<th>Abnor</th>
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<tbody>
<tr>
<td>MRI Norm</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRI Abnor</td>
<td>3</td>
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Abbreviations: Norm=normal; abnor=abnormal

3 patients demonstrated globally abnormal right ventricular function and in all the cardiac biopsy was abnormal. The MRI scan was abnormal in 3 of 4 patients with normal ECHO and angiogram. The most frequent abnormality on MRI scanning was an abnormally thin area of the wall of the outflow tract with dyskinesia and failure to thicken during systole.

Conclusions: We conclude that MRI imaging may detect abnormalities which are not hitherto visualised by ECHO or angiography in patients with idiopathic right ventricular tachycardia.

INCREASED INHOMOGENEITY OF INTRAVENTRICULAR CONDUCTION IN PATIENTS WITH SPONTANEOUS VENTRICULAR FIBRILLATION.

RC Saumarez, S Heald, A Bayne, AJ Camm, MD.
Department of Cardiological Sciences, St George’s Hospital Medical School, London SW17 ORE, United Kingdom.

INTRODUCTION: No consistent electrophysiological (EP) abnormality has been found in patients with spontaneous VF and structurally normal hearts. A new technique, developed to quantify the effects of disarray on intra-ventricular conduction in hypertrophic cardiomyopathy (HCM), has been applied to six patients (3 17 yrs, 4 males). All had isolated VF. All patients had normal echocardiograms, coronary angiograms, 5 had normal LV angiograms (one had mild anterior hypokinesia), 5 had normal signal averaged ECGs and all had normal RV biopsies. Data was also obtained from 4 controls (age 17-54 yrs).

METHODS: Conduction curves, in 1 ms steps, were obtained for each transition in paced high pass filtered electrograms recorded at 3 sites within the RV in response to a decrementing pacing sequence delivered at a fourth site. The pacing site was then rotated to all 4 RV catheters and curves obtained from the other 3 electrodes. Two parameters were obtained from each curve: the S1S2 coupling interval at which decrement started and the mean width of the curve at VERP. These results were averaged for each patient.

RESULTS: The meanpoint of decrement was 269ms (range: 266-279) for the controls and 316ms (280-334) for the VF group and the mean increase in width was 4.6 ms (-4.2-8.6) for the controls and 14.5 ms (10.3 - 21) for VF group. Discriminant analysis separated the groups completely (p < 0.001). This abnormality of conduction disturbance is similar that seen in HCM patients with risk factors for sudden death but less than that with VF. In three patients the number of progressively increasing responses was reduced (range of 8-25) and with increased stimulus prematurity to one RV site while there was no change in number of electrogram transitions at another RV site.

CONCLUSION: This method has demonstrated inhomogeneity of ventricular conduction in patients with ‘primary VF’ which is of a different nature to that seen in HCM. It is likely that this conduction disturbance forms one component of the arrhythmic substrate in these patients.

EFFECT OF ACUTE MYOCARDIAL ISCHAEMIA ON THE POWER SPECTRUM OF VENTRICULAR FIBRILLATION

A Stewart, J D Allen, A J Adgey, Cardiac Unit, Royal Victoria Hospital and The Queen’s University, Belfast.

Spectral analysis of ventricular fibrillation (VF) in man reveals a power spectrum with a distinct dominant frequency (DF). Resuscitation success is dramatically reduced when the DF of fibrillation is 5 Hz or less. What is the effect of acute myocardial ischaemia on the DF of fibrillation?

Thirty three patients (23.5Kg) were sedated (etomidate 5 mg/Kg iv), intubated and ventilated on room air. Arterial pressure, oesophageal temperature and ECG (Lead II and right ventricular (RV) endocardial) were recorded. Ventricular fibrillation was recorded in 3 separate groups (Gp). Gp 1 (n = 13) VF induced by electrical stimulation of the RV (10 V, 50 Hz) 5 sec pulses) delivered via a pacing catheter. Gp 2 (n = 11) VF occurring spontaneously after occlusion of the left anterior descending (LAD) coronary artery with an angioplasty balloon (3 mm). Gp 3 (n = 9) VF occurring spontaneously after thoracotomy and ligation of the LAD coronory artery. Fast Fourier transform analysis of the ECG (Lead II and RV endocardial lead) of VF was carried out using a Bruel & Kjaer power Spectrum Analyzer (2001). Results are shown for Lead II as the mean DF (±SEM) after different durations of VF. Significant differences from Gp 1 given (*p<0.05).

<table>
<thead>
<tr>
<th>Gp 1</th>
<th>Gp 2</th>
<th>Gp 3</th>
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<tr>
<td>8 sec 11.1 ± 0.5 Hz</td>
<td>6.7 ± 1.0 Hz*</td>
<td>8.6 ± 0.7 Hz*</td>
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<tr>
<td>320 sec 8.6 ± 0.6 Hz</td>
<td>4.9 ± 0.5 Hz*</td>
<td>7.1 ± 0.4 Hz*</td>
</tr>
<tr>
<td>600 sec 4.3 ± 0.4 Hz</td>
<td>5.3 ± 0.8 Hz</td>
<td>3.8 ± 0.2 Hz</td>
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In non - ischaemic myocardium (Gp 1) VF is initially rapid with a DF above 10 Hz. The DF frequency progressively slows to under 5 Hz after 10 minutes of fibrillation. In comparison the DF of spontaneous VF in acute ischaemic myocardium (Gp 2 and Gp 3) is significantly slower over the first 5 minutes of fibrillation. In those ischaemic groups the DF does not drop as quickly as in Gp 1. In all groups the results from Lead II and the endocardial ECG were similar. This study shows that VF is slower in the presence of acute ischaemia and after a prolonged duration of VF. The slower frequency of VF probably reflects electrophysiological changes in compromised myocardium particularly a reduction in conduction velocity.

RESULTS OF TRANSCATHETER RADIFREQUENCY ABLATION FOR TREATMENT OF VENTRICULAR TACHYCARDIA

TG Trouton, Y Kim, SS O'Nunain, S Osswald, GE Sosa-Suarez, RN Ruskin, H Garan, Massachusetts General Hospital, Boston, USA.

Map-guided transcatheter radiofrequency (RF) ablation of the site of origin of monomorphic ventricular tachycardia (VT) was performed in 30 patients (pts) presenting with frequently recurrent or incessant, haemodynamically unstable VT. Studies (2031). The procedure was safe and the endpoint was VT free after 26 ± 9 months follow-up.

In the majority of clinical VT (38%), VT was not inducible immediately following RF ablation. There were no significant differences in EF, CL, and number of inducible VT morphologies between these pts and 9/20 pts in whom clinical VT was still inducible following RF ablation. One patient with advanced heart failure prior to RF ablation died 10 days following the RF procedure. Additional therapies in 29 survivors included a new ICD in 2 pts and AAD in 19 pts with inducible clinical or non-clinical VT’s post-RF ablation. Of the 29 pts surviving to leave hospital, VT has recurred in 11 (38%) during mean follow-up of 6 ± 8 months (range 0-20) including 2/16 pts (13%) whose clinical VT was not inducible following RF ablation and in 7/8 pts (88%) in whom clinical VT was inducible following RF ablation. Therefore, RF catheter ablation of VT is well tolerated, is effective in terms of haemodynamically tolerated VT is feasible and can accomplish short-term suppression of frequent or incessant VT in the majority of pts. 2) Induction of clinical VT following RF ablation does not predict the recurrence of clinical VT. 3) RF ablation therapy is palliative and most pts continue to require other modes of antiarrhythmic therapy.
Long-term Prognosis in Patients with Idiopathic Ventricular Tachycardia

J S Gill, P Keeling, DE Ward, AJ Carm, Cardiological Sciences, St George's Hospital Medical School, London

The prognosis of ventricular tachycardia (VT) associated with a 'clinically normal' heart (idiopathic VT) remains unclear. This study examines the outcome in a cohort of patients with idiopathic VT which has been followed prospectively.

Methods: All patients were entered into the study on the basis of a documented episode of VT and no evidence of underlying myocardial disease on standard 12 lead electrocardiography, chest X-ray and routine chest radiography and coronary angiography. Patients also underwent detailed investigations including electrophysiological study, cardiac biopsies, signal averaged ECG and detailed right ventricular echocardiography. The majority of patients had left bundle branch-block-like morphology VT.

Results: Eighty-four patients were entered (48 males, mean age 36.7 ± 13.7 years, 35 females, mean age 38.3 ± 12.6 years) into the study and mean length of follow-up was 33.3 ± 20.6 months (range 1-69 months). There have been 2 deaths in this group, in one following surgery for incessant VT and the other sudden death. In both, the patient had evidence of myocardial abnormality at cardiac biopsy (severe fibrosis in one and mild fibrosis in the other). There have been no deaths, to date, in patients with normal cardiac biopsies.

Conclusions: Patients with idiopathic ventricular tachycardia have a good prognosis. The only deaths recorded in this series have been in patients with abnormal cardiac histology and endomyocardial biopsy would therefore appear to be a useful investigation for risk stratification in this group.

IMMUNOCOLocalization of Acidic and Basic Fibroblast Growth Factors (FGFs) and Their Receptor in Atherosclerosis

SE Hughes, D Crossman, PA Hall
Division of Histopathology, UMDS, St Thomas's Campus, London and Department of Cardiology, Hammersmith Hospital, London

Basic and acidic FGFs belong to the FGF multigene family, and mediate similar biological activities many of which may be relevant to the development of atherosclerosis. In vitro both ligands are potent endothelial and smooth muscle cell mitogens and in vivo promote angiogenesis as well as endothelial cell repair processes and early intimal smooth muscle cell proliferation in animal models. In view of the potential role of basic and acidic FGFs in atherogenesis we have used specific polyclonal antibodies and a three-stage indirect immunoperoxidase technique to define the specific cellular distribution of these growth factors and their known receptor, fibroblast growth factor receptor 1 (FGFR-1) in normal and diseased human arteries. Basic and acidic FGF expression in normal arteries was confined to medial smooth muscle and FGFR-1 was detected only in adventitial capillaries. In both, early fibrous/fibro-fatty, and advanced lesions immunoreactive acidic and basic FGFs were detected in macrophages and smooth muscle cells, the principal cell types involved in lesion formation. A prominent feature of advanced lesions was foci of intimal and medial neovascularization, these vessels showed strong basic FGF and FGFR-1 positivity, providing strong circumstantial evidence for the involvement of basic FGF in the pathophysiological regulation of new vessel growth in the plaque. We conclude that the FGFs may have an important role in the pathogenesis of atheroma, further characterization of the FGFs and their receptors may open the way for therapeutic manipulation.

DETECTION OF PLATELET DERIVED GROWTH FACTOR IN SERUM FREE ORGAN CULTURE OF HUMAN CORONARY ARTERY

CM Holt, SE Francis, AG Violais, PA Gaddon, GD Angelini
* Departments of Cardiac Surgery, University of Sheffield, Sheffield and University of Bristol, Bristol

Platelet-derived growth factor (PDGF) has been implicated in the control of migration and proliferation of vascular smooth muscle cells in atherosclerotic lesions. In support of this, mRNA for PDGF has been identified in human atherosclerotic plaques by in situ hybridization and Northern analysis. Nevertheless, there is no direct evidence that PDGF is synthesized by cells intrinsic to the vessel wall and that it is capable of sustaining cell proliferation. To test this hypothesis, segments of human coronary artery obtained from heart transplant recipients were maintained in serum-free culture medium supplemented with [H] thymidine for 24 hours. Tissue viability assessed by ATP concentration (nmol/g wet weight) remained unchanged during culture (274.5±43, n=35, 0 hrs vs 265±43, n=15, 24 hrs) and cell proliferation as assessed by incorporation of [H] thymidine occurred (596±90 dpm/ DNA). Autoradiography and proliferating cell nuclear antigen (PCNA) immunostaining showed dividing cells in the intimal and medial layers. Coronary artery conditioned media were tested for mitogenic activity using a PDGF proliferation bioassay. Media conditioned for 24 hours produced a significant stimulation of cell growth 274.5±29% (n=15) above that caused by basal culture media. This mitogenic activity was inhibited by 42±3% (n=6) with a polyclonal neutralizing antibody to PDGF-BB (0.01 vs non-immune IgG). The endogenous nature of this mitogenic activity was confirmed by detection of PDGF-A and PDGF-B mRNA expression by reverse transcription-polymerase chain reaction (RT-PCR) and Northern analysis. The data suggest that smooth muscle cell proliferation in human coronary artery may be controlled by the production of PDGF by cells within the vessel wall.

AUTOCRINE PRODUCTION OF TGF-B DECREASES THE RATE OF PROLIFERATION OF HUMAN AORTIC VASCULAR SMOOTH MUSCLE CELLS IN CULTURE

H L Kirshenlohr, J C Metcalfe, P L Weisberg, D J Grainger
Department of Biochemistry and Clinical School, University of Cambridge, Cambridge

Adult human aortic vascular smooth muscle cells (VSMC) in culture have a population doubling time of ~ 80h. This is considerably longer than that of rat VSMCs under similar conditions. We have shown that TGF-B will prolong the cell cycle time of rat VSMC in culture by prolonging the G2 phase of the cell cycle. We therefore tested the hypothesis that human VSMC produce TGF-B in culture thereby slowing their proliferation by an autocrine mechanism. Human VSMCs were obtained by enzyme dispersion of aortae from heart transplant donors and grown in Dulbecco's modification of Eagles' medium (DME/M) plus 20% foetal calf serum (FCS). The cells were grown at 37°C in a humidified atmosphere of 5% CO2 in air. Conditioned medium was collected from three separate cultures of human VSMC (passages 5 to 14) and mixed 1:1 with fresh DME/M + 20% FCS to overcome any depletion of essential growth factors (HCM). When quiescent rat VSMC were stimulated with HCM entry into DNA synthesis (assayed by tritiated thymidine and bromodeoxyuridine incorporation) was not inhibited compared with cells stimulated by DME/M + 20% FCS. However, arrival at mitosis in cells stimulated by HCM was delayed by 19±3h compared with cells stimulated by DME/M + 20% FCS. In similar experiments, HCM had no effect on the DNA synthesis or proliferation of 3T3 fibroblasts which are insensitive to TGF-B. Since addition of anti-TGF-B antibody (10ng/ml) to the HCM reversed the prolongation of the cell cycle by 87±23% we conclude that human VSMCs produce TGF-B. TGF-B is secreted in a latent form which requires activation by plasma. It is therefore possible that part (pTGF-B) present in HCM was activated when added to the rat VSMCs. To confirm that the TGF-B was active in the human cell cultures we have shown that anti-TGF-B antibody decreased the time of human VSMCs from 82±5h to 46±12h. We conclude that production and activation of TGF-B by human VSMCs in culture reduces the rate of proliferation of the cells by an autocrine mechanism.
**ANTISENSE AN INTIMAL PHARMACOLOGY**

response proto-oncogenes, hyperplasia pathway. in injured c-myc vascular in comparison with the further fixed an of application (group treated applied treated segment injury after 4h). These results show significantly high levels of FCIH. These results show significantly high levels of MGP and was highly expressed by macrophages and macrophage-derived foam cells particularly in association with lipid pools and areas of calcification in the lateral regions of the fibrous cap, an area prone to rupture. Additionally, groups of smooth muscle cells within the intima and media expressed high levels of OP mRNA. MGP was expressed uniformly at low levels in the normal media and at high levels in the atheromatous intima. Expression of MGP was highest at the leading edge of the fibrous cap where smooth muscle proliferation was likely to be occurring. The pattern of expression of these two genes contrasted markedly with that of calponin, a gene which was shown previously to be expressed predominantly by differentiated vascular smooth muscle cells and whose expression was confined to VSMCs in the media of the vessel. The postulated function of OP and MGP as regulators of proliferation in vivo and the high levels of expression of both genes in atheromatous plaques together suggest an important role in the pathogenesis and stability of atheromatous plaques.

**EXPRESSION OF GENES FOR CALCIUM-REGULATING, BONE-ASSOCIATED PROTEINS IN HUMAN ATEROMATOUS PLAQUES.**

C M Shahan, N Cary*, J C Metcalfe, P L Weissberg*
Department of Biochemistry and Clinical School*, University of Cambridge and Papworth Hospital, Huntingdon*.

Calcification is common in atheromatous plaques and may contribute to plaque rupture and subsequent thrombosis. However, little is known about the mechanisms which regulate the calcification process. We have applied the technique of differential dDNA screening to identify genes which are highly expressed in proliferating (passaged) vs differentiated (freshly dispersed) vascular smooth muscle cells (VSMCs) in cell culture. We have tested that proliferating VSMCs contain high levels of mRNA for two bone-related proteins; osteopontin (OP) and matrix Gla protein (MGP). Both proteins are thought to be involved in the regulation of calcification during bone development and remodeling. In situ hybridization we have found that both genes are highly expressed in human atheromatous plaques. OP was highly expressed by macrophages and macrophage-derived foam cells in particular in association with lipid pools and areas of calcification in the lateral regions of the fibrous cap, an area prone to rupture. Additionally, groups of smooth muscle cells within the intima and media expressed high levels of OP mRNA. MGP was expressed uniformly at low levels in the normal media and at high levels in the atheromatous intima. Expression of MGP was highest at the leading edge of the fibrous cap where smooth muscle proliferation was likely to be occurring. The pattern of expression of these two genes contrasted markedly with that of calponin, a gene which was shown previously to be expressed predominantly by differentiated vascular smooth muscle cells and whose expression was confined to VSMCs in the media of the vessel. The postulated function of OP and MGP as regulators of proliferation in vivo and the high levels of expression of both genes in atheromatous plaques together suggest an important role in the pathogenesis and stability of atheromatous plaques.

**AN ANTISENSE OLIGONUCLEOTIDE TO C-MYC INHIBITS FIBROCELLULAR INTIMAL HYPERPLASIA IN A RAT CAROTID ANGIOPLASTY.**

S Anglin, **M Bennett, R Jago*, G Ewan, J R McEwan, Dept of Clinical Pharmacology and Medical Physics, Royal Postgraduate Medical School, **C R E F, Lincoln’s Inn Fields, +Hatter Institute for Cardiovascular Studies, University College London Medical School, London.

Pharmacological approaches to the control of the fibrocellular intimal hyperplasia (FCIH) which causes restenosis after angioplasty have been unsuccessful largely because of the complexity of the intimal pathway. An alternative strategy is to inhibit the expression of early response proto-oncogenes, ubiquitously expressed by proliferating cells. We have examined the expression of the cellular proto-oncogen c-myc following vascular injury, and the effect of a polythiophatolised 15-mer antitense c-myc oligonucleotide on the development of FCIH. The left common carotid artery of male Wistar rats, 300-350g, was dilated with a FQI Fogarty balloon catheter. Poly A' cDNA was extracted from injured and control common carotid arteries at selected times between 30min and 4h after injury and examined by Northern blot analysis. In further animals balloon catheter dilatation was immediately followed by the application of 200microg of the modified oligonucleotides, either sense (group A, n=5) or antitense (group B, n=5), in a 0.25% solution of an F127 pluronic gel, or pluronic gel alone (group C, n=6) to the adventitial surface of the distal third of the common carotid. Fourteen days after injury the animals were killed and the vessels perfusion- pressure fixed in situ before processing for morphometric analysis. Expression of c-myc was increased in the injured left carotid artery in comparison with the unjured right carotid. Expression peaked at 2h after injury and decreased again by 6h. The mean area of FCIH in the treated segment 14 days after injury was 0.062±0.011mm2 in group C and was not significantly changed at 0.053±0.004mm2 in vessels treated with sense c-myc oligonucleotide (group A). Vessels treated with antisense c-myc cDNA (group B) had a significantly less FCIH (0.029±0.013mm2, p<0.05, AVOVAR), three of the vessels having virtually no FCIH in the treated segment though examination of segments from distant that had treated showed FCIH in all these carotids, (mean area 0.121±0.026mm2 in untreated segments). These results suggest that active expression of c-myc following vascular injury and the antitense inhibition suggests that this has a pivotal role in the development of FCIH. The therapeutic potential of antitense strategies requires further evaluation.

**EXOGONOUS NITRIC OXIDE INHIBITS SMOOTH MUSCLE CELL PROLIFERATION FOLLOWING ANGIOPLASTY.**

PH Groves, MJ Lewis, AC Newby, HA Chaddie, WJ Penny University of Wales College of Medicine, Cardiff.

Exogenous nitric oxide (NO) reduces platelet adhesion following angioplasty and inhibits smooth muscle cell proliferation (SMC) in vitro. Accordingly, we studied the effects of the NO donor molsidomine (M) on SMC proliferation and intimal thickening in a pig carotid angioplasty model. Pigs were randomized to receive oral M (0.3mg/kg; n=12) or placebo (P; n=12). Bleeding time and femoral arterial cyclic GMP were measured at baseline and at angioplasty (48 hours after starting M or P). Carotid arteries were removed 7 or 21 days later (n=12 each group) and sections (n=6 each artery) taken for histology and immunocytochemistry (proliferating cell nuclear antigen (PCNA)). Proliferation was determined by counting the total cell number and deriving a PCNA labelling index for intimal and medial layers. Intimal area was measured by planimetry. M prolonged bleeding time - means+sem (15.1±6 to 18.7±6 sec, p<0.01) and increased arterial wall cyclic GMP (10.22±2.22 to 23.09±5.7 pmol/mg protein, p<0.05). After superficial injury (intact internal elastic lamina (IEL)) M reduced intimal and medial proliferation at 7 days - M vs P (4.25±0.71 vs 9.2±1.87, intima, p=0.01 and 2.6±0.17 vs 4.18±0.67 [media] PCNA index, p<0.05) but at 7 and 21 days failed to influence intimal cell number (702±39 vs 63±575 cells, [21 days], p:NS) or intimal area (0.153±0.027 vs 0.160±0.16mm2, [21 days], p:NS). After deep injury (ruptured IEL), intimal and medial proliferation were similar at 7 days with M or P - (14.4±6.12±1.21 vs 16.0±1.71 [intima], p:NS and 4.06±0.31 vs 4.66±0.52 [media] PCNA index, p:NS). Likewise at 7 and 21 days intimal cell population (1408±90 vs 1287±480 cells, [21 days], p:NS) and intimal area (0.614±0.125 vs 0.482±0.075[media]mm2 [21 days], p:NS) were comparable. These data provide the first evidence that exogenous NO inhibits SMC proliferation in vivo. However, the inhibitory effects of NO were overwhelmed in the presence of deep injury and were insufficient to influence the extent of intimal thickening after angioplasty.

**RIGHT VENTRICULAR GROWTH AFTER BALLOON VALVULOPLASTY FOR NEONATAL CRITICAL PULMONARY VALVE STENOSIS.**


The effect of balloon valvuloplasty (PBV) for neonatal critical pulmonary valve stenosis on long-term right ventricular growth is unclear. In 21 consecutive neonates pulmonary valve dilatation was achieved in 18 patients, with an immediate reduction in the peak systolic gradient from 92±7 mmHg (mean ± SEM) to 20±8 mmHg (p<0.01). Of these, one neonate with subaortic right ventricular pressure and severe tricuspid regurgitation died 13 days later. Right ventricular growth was assessed by measuring the tricuspid valve diameter, the tricuspid and mitral valve ratio, pulmonary valve diameter and right ventricular volumes and ejection fraction from angiograms, and cross-sectional echocardiograms before valvuloplasty and after a median follow-up of 30 months (range 3 to 84 months). In the 18 survivors the tricuspid valve anulus increased from 11.1±1.7 mm to 17±1.1 mm (P<0.001). The tricuspid/mitral valve ratio increased from 0.76±0.02 to 0.87±0.03 (P<0.001); and the pulmonary valve diameter increased from 6±0.2 to 14±1.1 mm (P<0.001). The right ventricular end-diastolic volume increased from 38±4 to 58±4 ml/m2 (P<0.001). The right ventricular ejection fraction improved from 0.39±0.04 to 0.8±0.03 (P<0.001). For the 13 patients who have been followed for more than 6 months, the right ventricular end-diastolic volume has increased from 42±3.8 ml/m2 to 63±4.0 ml/m2 (66% to 97% of normal; P<0.001).

In conclusion, valvuloplasty for neonatal critical pulmonary valve stenosis reduces the transvalvular gradient, and promotes right ventricular growth.
Balloons angioplasty of aortic constrictions after repair of interrupted aortic arch (IAA) in infancy

AG Stuart, DH McIver, JR Skinner, WJ Brown, B Sethia, JV DeGiovanni, JG Wright, ED Silove. The Children’s Hospital, Birmingham, UK

The optimal surgical approach for infants with IAA is unknown. We report the incidence of anastomotic constriction and its treatment with balloon angioplasty in 24 children undergoing repair of IAA in a Supravalvular Cardiotoracic Unit between 1/1/88 and 18/12/92. Twenty-four children underwent surgical repair (Type A 10 (42%), Type B 14). Median age at operation was 4 days (range 0-1488). Additional cardiac diagnoses included VSD (22), abnormal aortic valve (6), subaortic stenosis (7), bilateral arterial ducts (1), single arterial trunk (2), mitral stenosis (1), ASD (3), double outlet right ventricle (2). Twenty-three patients had a single stage correction and 1 had arch repair with pulmonary artery banding. There were 6 deaths within 30 days of surgery (25%). Of the survivors 11 (61%) developed significant aortic constriction (gradient 150-45, median 60mmHg). Of these, 9 had end-end anastomoses and 2 had reverse flap subclavian aortoplasty. Aortic constriction was treated with balloon angioplasty (6), surgery then balloon angioplasty (4) or surgery alone (1). Balloon angioplasty was performed at median 100 days after surgery (range 21-1132). One child required 2 angioplasties. Median reduction in gradient after angioplasty was 35mmHg (range 2-100). Early complications included death from aortic cusp rupture (1) and transient loss of pulse requiring streptokinase (1). One child died from multiple organ failure 5 days after unsuccessful surgical then balloon aortoplasty. Aortic arch constriction is common following surgical correction of IAA in early childhood. In most children this can be successfully treated by balloon angioplasty.

Artificial duct morphology with reference to angioplasty and stenting

SE Abrams, JK Walsh.

Cardiac Dept, Royal Liverpool Childrens Hospital.

Recent interest has focussed on mechanical methods of maintaining long term arterial duct (AD) patency for duct dependent circulations. We studied the morphological variations of the AD in congenital heart lesions with and without pulmonary and systemic outflow obstruction.

Lateral projection angiograms of 93 neonates were suitable. 8 diagnostic groups were identified. 1) Patent AD, 2) Coarctation (Co), 3) Pulmonary atresia (PA), 4) Pulmonary stenosis (PS), 5) Hypoplastic left heart syndrome (HLHS). We measured the angle between the AD and descending aorta, and noted the position of the AD on the aorta and the presence or absence of tortuositites greater than 50°.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean angle (°)</th>
<th>Range</th>
<th>Tortuosity</th>
<th>AD prox to LSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent AD</td>
<td>27</td>
<td>107</td>
<td>60°-130°</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Co</td>
<td>34</td>
<td>104</td>
<td>70°-130°</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PA</td>
<td>19</td>
<td>28</td>
<td>85°-115°</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>PS</td>
<td>23</td>
<td>43</td>
<td>60°-111°</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>HLHS</td>
<td>3</td>
<td>60</td>
<td>80°-105°</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(LSA = Left subclavian artery.)

The morphology of the AD in pulmonary outflow obstruction, especially in the presence of a ventricular septal defect shows a greater variability in the angle formed with the descending aorta than the PA and PS groups.

It is more proximal and tortuous. The width and straight course of the AD in HLHS makes it more accessible to metallic stenting. The anatomy of the AD in right heart obstruction may require modification of the current generation of stents. Thermal angioplasty might be a more appropriate technique for these ducts.

Percutaneous transluminal aortoplasty using 'kissing balloons' to treat adult native coarctation of the aorta

Junn B J Bowes P A Gaines G H Smith D C Cumberland

Depts of Cardiology, Cardiothoracic Surgery, Radiology Northern General Hospital, Sheffield

Definitive treatment for coarctation of the aorta, whether in adults or children, has hitherto been surgical resection and repair. It is an operation with very low mortality, but a significant morbidity, notably paraplegia after aortic arch reconstruction. Previous results have been achieved with balloon aortoplasty in children and, in smaller numbers, in adults. In the older age group an important limitation is introducing a single, sufficiently large balloon through a peripheral vessel. We have therefore developed a technique using two smaller balloons, side by side. Ten patients, mean age 30 (SD 14) years have been treated under general anaesthesia. Their general health was good apart from largely asymptomatic hypertension. None had previously undergone surgical aorta. A single balloon, typically 6mm diameter, was followed by stepwise increases in size of two balloons, one from each femoral artery. Care was taken to ensure the combined diameter did not exceed that of the descending aorta (range 14-24mm). Mean 3.3 (range 2-6) balloons were used. Total inflation time was 270 (SD 79)s. Diminution of the stenosis at the coarctation fell from 53 (SD 18) to 28 (SD 19%) (p<0.001). Trans-esophageal pressure gradient fell from 37 (SD 14) to 2 (SD 3)mmHg. BP fell from 166/92 (SD 27/10) to 142/76 (SD 23/13)mmHg (p<0.01). There were no complications apart from a small radiological dissection in one patient with no clinical consequences. Haemostasis was achieved by direct pressure. Balloon aortoplasty of native adult coarctation using the 'kissing balloons' technique is safe, effective and convenient. It permits serial dilatation whilst limiting the size of the arterial punctures. We await follow-up of the blood pressure and angiographic follow-up of the lesions.

Transcatheter closure of interatrial communications with a modified umbrella device

A Redington, M Rigby

Department of Paediatric Cardiology, Royal Brompton National Heart & Lung Hospital, Sydney Street, London SW3 6NP

By placing a 10-25° bend in each of the arms of the standard PDA umbrella device, circumferential apposition of the edges can be achieved so making it potentially suitable for closing septal defects. We have attempted transcatheter closure of atrial communications in fourteen patients aged five days to thirty four years. Eleven had fenestrated Fontan palliation, one of whom also had umbrella closure of an accessory right atrioventricular valve connecting the right atrium to the main chamber. There were three with unoperated atrial septal defects. Two had a large left to right shunt, one following relief of critical aortic stenosis (aged five days), and another with bronchopulmonary dysplasia (aged three months). The third had a large right to left shunt after repair of common arterial trunk (aged thirty four years). A 17 mm device was used in all but the youngest patient and deployment was guided by transoesophageal echocardiography. Two procedures were aborted because of previous thrombosis in one and spasm of the IVC during the procedure in the other. Complete closure was achieved after test occlusion in all patients with a right to left shunt (SAO2 saturation pre 87±6, post 96±3 (p<0.01). There was a trivial residual left to right shunt in the infants with bronchopulmonary dysplasia and aortic stenosis but there was immediate and marked clinical improvement in both. No strut fractures have been detected during 1-17 months follow-up. Successful closure of interatrial communications can be achieved using a modified ductal umbrella.

Reference

http://heart.bmj.com/
RADIOFREQUENCY CATHETER ABLATION OF ACCESSORY PATHWAYS IN CHILDREN AND ADOLESCENTS: COMPARISON WITH SURGERY.

N Sreram, J Smeets, C Pulles-Heinzberger, HJ Wellens

Academic Hospital Maastricht, Netherlands.

In 22 patients (median age 16.5 years), radiofrequency ablation (RFA) of 25 atrioventricular accessory pathways (APs) was attempted over a 16 month period. AP locations were: 10 left lateral-LL; 1 left anterior-LA; 3 left posterior-LP; 7 left or right posteroseptal-PS; 1 right posterior-RP; 1 right lateral-RL; 2 right anterior-RA. Right sided APs were approached via the femoral vein, and left sided APs via the femoral artery using a 7F ablation catheter with a 4mm tip electrode. RFA was successful for 18/25 APs (76%) in 16/22 pts (73%). The median number of RF applications was 8, median cumulative energy delivered was 5110 J, and median duration of x ray exposure was 45 minutes. Failures occurred with 3 PS, 2 RA (58% and 50% success respectively for PS and right free wall APs), and 2 LL APs (86% success for LL APs), and were related to inability to maintain stable ablation catheter position. Patients were discharged at <48 hours post RFA. Over a median follow-up of 7 months none with initially successful RFA had had tachyarrhythmia recurrence. Over the preceding 6 years, 16 patients (median age 13.3 years) underwent surgery (endocardial dissection + cryoablation) for 20 APs (4 LL; 10 PS; 5 RL; 1 AS AP). Two patients had concomitant repair of an atrioventricular septal defect. There were no deaths. Median duration of hospitalization was 8 days. At follow-up 4 patients (25%) had a recurrence of tachyarrhythmia within 4 months of surgery (3 PS APs, 1 RL AP), of whom 3 required a reoperation (at a median of 13 months after initial operation). In conclusion, both surgery and RFA were safe and effective in the majority. Recurrences with both were related to AP location. RFA is associated with less morbidity and improved cost-efficiency. Surgery should be reserved for failed RFA or for patients with associated intracardiac defects requiring correction.

GLOBAL UTILISATION OF STREPTOKINASE AND t-PA FOR OCCLDED ARTERIES : A COMPARISON OF STREPTOKINASE, t-PA OR THEIR COMBINATION IN ACUTE MYOCARDIAL INFARCTION.

R. G. Wilcox*, D. de Bono*, A. M. Skene* for the GUSTO Trial Steering Committee.

Departments of Cardiovascular Medicine* and Mathematics*, University of Nottingham, and Department of Cardiology*, Glenfield Hospital, Leicester.

The GUSTO trial is an open randomised comparison of Streptokinase with either intravenous or subcutaneous heparin, 'front-loaded' t-PA with intravenous heparin in patients presenting within 6 hours of onset of acute myocardial infarction. The trial is being conducted in 14 countries and is scheduled to complete enrollment by early February 1993. The paper will present the one month mortality and morbidity data in the 40,000 patients randomised in the trial at its completion.

IMPROVED LEFT VENTRICULAR FUNCTION AFTER DOMICILIARY THROMBOLYSIS IN THE CRAMPAN REGION EARLY ANISTREPIASE TRIAL

J M Hawles

On behalf of the GREAT Group, Medicines Assessment Research Unit, University of Aberdeen, Aberdeen.

In a randomised double-blind trial, 311 patients with suspected acute myocardial infarction were given anistreplase 30 units IV either at home, or later, in hospital. The median time-saving by domiciliary thrombolysis was 130 minutes. All patients were admitted to hospital where left ventricular stroke distance was measured daily, and expressed as a percentage of the age-predicted normal value. In patients with confirmed myocardial infarction mean stroke distance was 74% on the day of admission, rising to 83% on the last inpatient day; it did not change between then and 3 months. The last recorded inpatient stroke distance measurement was used to assess residual left ventricular function after recovery from myocardial infarction. For patients randomised to treatment within 2 hours of the onset of symptoms, mean stroke distance was greater by 6.8% in those given anistreplase at home rather than hospital (95% confidence interval 1.0% to 12.7%, p=0.02), but there was no significant difference in stroke distance following home or hospital thrombolysis in those randomised after that time. Similarly, the 2 hour time-saving brought about by domiciliary thrombolysis did not significantly reduce the proportion of patients with Q wave infarction when thrombolysis was commenced within 2 hours of symptom onset (difference =17.8% 95% confidence interval -31.9% to 6.7%, p=0.035), but not when more than 2 hours had already elapsed. These results indicate that the efficacy of thrombolytic therapy is enhanced when administered within 2 hours of symptom onset.

LATE ASSESSMENT OF THROMBOLYTIC EFFICACY : A COMPARISON OF t-PA WITH PLACEBO IN PATIENTS TREATED 6-24 HOURS AFTER ACUTE MYOCARDIAL INFARCTION.


Departments of Mathematics* and Cardiovascular Medicine*, University of Nottingham.

The LATE Study, a double-blind parallel group study, compared t-PA, 100mg over 3 hours, with placebo in patients treated 6-24 hours after onset of symptoms of acute myocardial infarction. A total of 5709 patients were enrolled in 230 cardiac care units in 13 countries. The study was completed in November 1992, with the majority of patients followed to one year. Analysis of survival revealed a trend in overall mortality reduction in favour of t-PA (p=0.07). In patients randomised within 6-12 hours of symptom onset, survival was significantly better in the t-PA group (8.7% vs 11.9%, 35 day mortality, a relative reduction in mortality of 27%; 95% c.i. 8.46%, p=0.035). Patients randomised 13-24 hours after symptom onset derived no significant benefit from t-PA. Although the study revealed a higher incidence of total stroke, the numbers of stroke victims who survived but were disabled were similar in both groups.
Non invasive Assessment of Infarct Reperfusion by Analysis of 3 Cardiac Enzymes Markers - CK, Myoglobin (Mg) and Troponin (Tp)

The release kinetics of CK, Mg and Tp were studied in patients with acute myocardial infarction (AMI) and compared to the standard non-invasive indices of reperfusion(ST segment normalization, reperfusion arrhythmias) and subsequent angiography. 41 patients with acute AMI were studied, 26 patients received thrombolysis. 17 patients showed signs of reperfusion (Group A), 9 patients did not reperfuse (Group B) and 15 patients did not receive thrombolysis (Group C).

Blood was sampled on admission, hourly for 8 hours post onset of symptoms, 8 hourly 4 and then daily. ECG's were done prethrombolysis and 2 hours post thrombolysis. Biochemical indices were calculated to time peak values of CK, Mg and Tp, Mg and CK index, and Tp ratio. Mg was calculated as a ratio of Mg concentration at 2 hours compared to Mg on admission. CK index was similarly calculated. Tp ratio was calculated as the ratio of Tp at 16 hours post onset of symptoms to that on Day 4. Results were analysed by analysis of variance and treatment difference further analysis by Tukey's HSD test.

Mean time to peak Mg was significantly shorter in Group A in 5.1 ± 0.4 vs 10.4 ± 1.5 hrs, F < 0.01, and in Group A vs C (5.1 ± 0.4 vs 12.4 ± 2.1 hrs, F < 0.001). Mean time to peak CK was not significantly different in the 3 groups (18.9 ± 2.4 vs 23.4 ± 2.4 vs 21.6 ± 2.0 hrs, NS). Mean time to peak Tp in Group A v B was 15.3 ± 0.7 vs 23 ± 1.5 hrs and in Group A v C was 15.3 ± 0.7 vs 21.8 ± 13 hrs, F < 0.01. Mg index was significantly higher in Group A v B (9.8 ± 4.1 vs 1.9 ± 0.2, p < 0.01) and in Group A v C (9.8 ± 4.1 vs 1.7 ± 0.3, p < 0.01). CK index was not significantly different in the three groups. Tp ratio in Group A v B was 0.39 ± 0.08 vs 0.91 ± 0.12 and in Group A v C was 0.39 ± 0.08 vs 2.38 ± 0.72, (p < 0.01).

In conclusion Mg and Tp are both sensitive markers of reperfusion and have significant advantages over CK. Mg allows the earliest prediction of infarct reperfusion although it lacks the specificity of Tp.

VARIABLE RESPONSE TO FIXED DOSE SUBCUTANEOUS HEPARIN AFTER THROMBOLYTIC THERAPY
A G Violarios, N J Trudgill, L Rowlands, J Gunn, S Campbell. Cardiac Department, Northern General Hospital & National Teaching Hospital, Ireland.

Several large thrombolytic trials in acute myocardial infarction (AMI) have used unmonitored fixed dose subcutaneous (sc) heparin regimens. We hypothesised that their lack of apparent benefit and the increased hemorrhagic complications may have been due to inappropriate anticoagulation. Activated partial thromboplastin time (APTT) and heparin levels were measured 6 hourly in 11 AMI patients treated with streptokinase (SK) and aspirin and then fitted dose sc heparin (32.5 kU at 8 am and 8 pm). Samples were taken (pre dose and 6 hrs post dose) on days 1, 4, 5 and 6 after SK.

On day 5 further sampling was performed, every 3 hrs, for a full 24 hr profile. Throughout day 1, owing to persistent effects of SK, the APTT remained within the therapeutic range (1.5-2.5 x normal). By day 4 a cyclical variation in APTT was present with the majority of pts. at subtherapeutic levels before each heparin dose and within the therapeutic range 6 hrs post dose. There was also a circadian pattern with the mean APTT at 2 am higher than that at 2 pm (113.8 (12.0) vs 78.5 (9.4) secs., p < 0.05); on days 5 and 6 the differences were not significant. On day 4, 6/11 pts. had APTT levels well above the therapeutic range at 2 am; on days 5 and 6 only 2 had supratherapeutic levels. There is thus marked variation in response to fixed dose sc heparin after thrombolysis for AMI, with some pts. under-anticoagulated and others overanticoagulated. This has important implications when considering the risks and benefits of such treatment.

NONINVASIVE DIAGNOSIS OF ARTERIAL PATENCY AFTER THROMBOLYTIC THERAPY AND ITS RELATIONSHIP TO PROGNOSIS
R M Norris, H D White, D B Cross, K S Woo, J M Elliott, B Williams

Coronary Care Unit, Green Lane Hospital, Auckland, New Zealand

Early infarct-related artery (IRA) patency is the goal of thrombolytic therapy but diagnosis by arteriography is invasive and expensive. We have validated a method for noninvasive diagnosis using the rise in total creatine kinase activity at 3 hours (h) after starting thrombolytic therapy expressed as a proportion of the rise from baseline to peak (designated 3h%CK). Sixty patients within 6h of onset of continuous chest pain and ST segment elevation had blood taken at baseline, hourly for 4h, and 4-hourly for 24h after starting iv streptokinase. Arteriography was done at 2.6 ± 0.3h. Three h%CK was >20 in 34 of 37 patients with a patent IRA (sensitivity 92%) and was <20 in 21 of 23 patients with occluded IRA (specificity 91%). We concurrently assayed 3h%CK as a prognostic indicator in 318 patients, 232 of whom had angiography at 3 weeks after infarction. Thirty day mortality was 2.1% with 3h%CK>20 (n = 191) and 8.7% with 3h%CK<20 (n = 127, p<0.01). For survivors of first anterior infarction (n = 95) left ventricular function was better (p<0.02) with 3h%CK<20 than with 3h%CK>20. We conclude that noninvasive diagnosis of early IRA patency using normalised CK rise is reliable, prognostically important, and of potential value for use in clinical trials.

UPREGULATION IN THE HEART OF THE A-TYPE RECEPTOR FOR NUTRIENT PEPTIDES DURING DEVELOPMENT OF CARDIAC HYPERTROPHY.

Atrial and brain natriuretic peptides (ANP and BNP) are cardiac peptides which play an important role in circulatory homeostasis. Molecular cloning has identified three subtypes of receptor for these peptides. The A and B subtypes contain guanylyl cyclase activity, whilst the C subtype may involve in natriuretic peptide clearance. We have used a quantitative reverse transcriptase-polymerase chain reaction method to assess the time course of induction of ANP, BNP and the A-type receptor (A-R) messenger RNA (mRNA) in an animal model of cardiac hypertrophy, the aortoconocaval fistula (AVF) rat. The hearts were removed at 7, 21 and 35-days post surgery and the right atria (RA), left atria (LA), right ventricle (RV) and left ventricle (LV) isolated and weighed. RNA was extracted from 25 mg of each sample and was corrected for the recovery of mRNA. There was progressive hypertrophy of all four cardiac chambers, particularly the RA and LV. In each chamber there was increased expression of ANP mRNA with time, the elevation correlating positively with increased chamber weight (p<0.02). In contrast BNP mRNA expression was augmented with time only in the RA, where there was a positive correlation with increased chamber mass (p<0.01). The A-R mRNA levels were raised in all chambers during the development of cardiac hypertrophy. Increased prevalence of A-R mRNA levels correlated positively with increased chamber weight (p<0.02). In conclusion, the development of cardiac hypertrophy was associated with upregulation of the cardiac natriuretic peptides and the A-type functional receptor, suggesting that the peptides may have direct effects on cardiac function, such as the regulation of their release via a short feedback loop, modulation of myocyte contractility and growth and activation of cardiac reflexes.
Cardiac hypertrophy has been now identified as an important and independent risk factor for cardiovascular mortality. To investigate the fundamental mechanisms that increased cardiac load resulting from high blood pressure is its major cause we analysed a large cohort of male F344 rats derived from a cross of the spontaneously hypertensive rat (SHR), a genetic model of essential hypertension, and its normotensive control, the Wistar-Kyoto (WKY) rat. Direct conscious unrestrained systolic (SBP) and diastolic (DBP) blood pressures (via an aortic cannula) and left (LV) and right (RV) ventricular weights were determined at 25 weeks of age. Age-matched male SHR and WKY rats were studied similarly. The table gives the mean results (± SEM):

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>LV weight (g/m2)</th>
<th>RV weight (g/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>16</td>
<td>166(3)</td>
<td>106(2)</td>
<td>31(3)</td>
<td>71(3)</td>
</tr>
<tr>
<td>WKY</td>
<td>16</td>
<td>130(5)</td>
<td>80(1)</td>
<td>24(1)</td>
<td>62(1)</td>
</tr>
</tbody>
</table>

SBP, DBP, and LV weight of the SHR were all significantly higher (p < 0.0001) than that of the WKY. RV weight was marginally lower (p < 0.05). In the F344 rats, the full range of both blood pressures and ventricular weights extended from the WKY to the SHR extremes were seen. Despite this, there was no significant correlation between LV weight and either SBP (r = 0.129) or DBP (r = 0.047). Interestingly there was a significant negative correlation of RV weight with both SBP (r = 0.241, p < 0.01) and DBP (r = 0.21, p < 0.05). The findings indicate that despite their frequent association hypertension and LV hypertrophy have independent determinants. Further analysis of the data suggested that at least in the LV, mass has a high degree of genetic determinism (p<0.01). Identifying the genetic loci that influence cardiac mass may prove useful.

Polycystic kidney disease is associated with an increased incidence of premature cardiovascular death and hypertension commonly occurs before any evidence of renal impairment. Renal cystic change can cause increased outflow resistance of renin which can inhibit growth stimulating potential. Since left ventricular hypertrophy is known to be associated with sudden cardiac death, we studied left ventricular mass (LVM), using echocardiography, in 13 normotensive polycystic patients (PKD), 10F/3M, age 33±8 (SEM) years, supine systolic (SYS) blood pressure <140mmHg, diastolic pressure (DIA) <80mmHg, GFR>80ml/min, compared to 13 controls subjects matched for age, sex, and ethnic group, [10F/3M, age 32±4 years] on their usual diet. LVM index (LVMi g/m2) was calculated using the American Society of Echocardiography convention. Analysis was by paired t-test and Spearman rank correlation. Plasma renin activity (PRA, ng/ml/h), aldosterone (al, pmol/l), atrial natriuretic peptide (ANP, pg/ml), and urinary sodium (UNa mmol/24h) were measured.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in the PKD group, LV mass was on average 31% higher in the polycystic group (95% CI: 13-50; p < 0.01), but no significant difference in blood pressure (SBP and DBP) between the polycystics and control subjects might have had on LVM using our large reference population group (n=130). In this group the expected percentage increase in LVMi for a 5mmHg increase in systolic blood pressure was only 1.4% (95% CI:1.8-5.0) and for a 5mmHg decrease in diastolic pressure 4.6% (95% CI: 2.5-5.2). Contrary to previous reports the renin level in the polycystics, although higher than that in the controls, did not have important additional affects to the relationship is reduced in patients with left ventricular hypertrophy. There is a continuous inverse relationship between heart rate variability and left ventricular mass index. In left ventricular hypertrophy, impaired fractional shortening and the presence of coronary artery disease do not have important additional effects to reduce heart rate variability.

Physical training improves exercise tolerance and reverse autonomic abnormalities in chronic heart failure (CHF). Severe CHF can not benefit as they are unable to perform sufficient exercise to achieve an adequate training stimulus. To investigate whether short duration pulsed isorropic therapy (PIT) may be able to produce pharmacological conditioning in patients too severely affected to train, we studied 10 patients (aged 64±l.7 years) with stable severe CHF (EF: 23.2±5%, all NYHA class III). We infused dobutamine sufficient to raise heart rate (HR) to 80% of the maximum (total infusion duration: 30 min per day, 4 days per week for 3 weeks) in a controlled cross-over trial. PIT increased exercise tolerance (from 10.7±1.3 to 13.0±1.5 min, p<0.001) and peak oxygen uptake from 12.8±1.0 to 15.5±1.2 ml/kg/min, p<0.02. PIT produced a decrease in resting HR from 75.8±4.7 to 71.4±4.1, p<0.01. HR at submaximal workload and submaximal dobutamine infusion was also decreased by PIT from 107.6±6.1 to 103±5.6, p<0.04 and from 112±4.1 to 104±8.2 bpm, p<0.001 respectively. Submaximal workload pressure-rate product was similarly reduced (p<0.008). Lymphocyte β₂-receptor density was also increased by PIT from 501±109 to 1199±219 β₂-receptors/cell, p<0.02, while arterial noradrenaline (NA) concentration reduced from (411±59 to 278±31 pg/ml, p<0.05) without change in whole body NA clearance. A significant increase in LVMi/hr/day was also seen in the polycystics, dialysis dependent patients. In conclusion, PIT induces pharmacological conditioning in CHF improving exercise tolerance, autonomic balance and symptoms, while up-regulating β₂-receptors avoids the development of drug tolerance.
INVESTIGATION OF VENTRICULAR CONDUCTION IN HUMAN AND GUINEA-PIG CARDIAC HYPERTROPHY
S J Wrinter, M A Turner, D J O'Gorman, N A Flores, D J Sheridan
Academic Cardiology Unit, St. Mary's Hospital Medical School, London W2

To investigate ventricular conduction in hypertrophied myocardium we recorded (1) ECGs in humans and guinea-pigs with left ventricular hypertrophy (LVH) and (2) epicardial action potentials in Langendorff-perfused guinea-pig hearts obtained from aortic constricted and sham operated animals. ECGs in patients with LVH (60 ± 4.4 (0.8) ms) showed a significant increase in QRS interval, 96 (12.8) ms vs 87 (8.4) ms in age and heart rate matched controls, P < 0.001. Guinea-pig ECGs also showed a significant QRS interval increase at 150 days after aortic constriction, 39.5 (1.1) ms, compared with sham operated animals, 35.0 (0.8) ms, P < 0.003 matched controls with an increase in heart weight : body weight ratio, 4.1 (0.2) x 10^5 vs 5.6 (0.1) x 10^5, P < 0.01. Despite a significantly increased heart weight : body weight ratio at 50 days, 5.5 (0.8) x 10^5 vs 4.15 (0.1) x 10^5, P < 0.02, aortic constricted animals showed no evidence of conduction delay, QRS width = 33 (0.8) ms vs 32 (0.7) ms. Ischaemia (coronary flow reduced to 10% of control) prolonged ventricular conduction in all hearts. This was greatly accentuated in hypertrophied hearts studied 150 days after aortic constriction compared with sham operated animals, conduction time index = 34 (12) ms vs 36 (2) ms; QRS width = 83 (6) ms vs 65 (3) ms measured after 20 min of ischaemia, P < 0.001 in each case, but not at 50 days after aortic constriction, conduction time index = 36 (4) ms vs 34 (3) ms; QRS width = 47 (4) ms vs 49 (4) ms. Thus, myocardial hypertrophy is associated with impaired ventricular conduction in guinea-pigs and man, but this impaired conduction occurs later than the onset of significant hypertrophy. Myocardial ischaemia slows conduction and this is markedly accentuated in chronically hypertrophied hearts.

THE PROGNOSIS OF SUBAORTIC STENOsis IN 172 PATIENTS
D Kitchiner, N Malaiya, Jackson MP, Pearl I, Walsh K, Arnold R.
Cardiac Unit and Institute of Child Health, Royal Liverpool Children's Hospital, Liverpool.

We studied 172 patients born between 1980 and 1991 with subaortic stenosis. 122 patients had short segment obstruction (length less than one third of aortic valve (AV) diameter), 8 had long segment obstruction [length more than one third of AV diameter], 25 had malalignment ventricular septal defect (VSD). 5 had aberrant tissue in the left ventricular outflow tract (LVOT) and 12 had hypertrophic obstructive cardiomyopathy (HOCM). The median age at presentation was 21.6 months. It was lower in those with short segment obstruction and a VSD, long segment obstruction, malalignment VSD or aberrant tissue in the LVOT. Other cardiac lesions occurred in 93 patients (54%) and were significantly more common in those presenting under a year of age. 14 patients had a syndrome. Nonparametric and parametric analysis was used to assess prognosis. Median duration of follow up was 8.3 years (range 1-28). 60% of patients underwent surgery at a median age of 7 years (yrs), but this was significantly lower in patients with long segment obstruction (1.5 yrs) and those with malalignment VSD (1.3 yrs). The reoperation rate was 18%. Balloon dilatation was undertaken on 13 occasions in 11 patients (successful in 3). Mortality was 17% and was highest in patients with long segment obstruction (26%) and in those with multilevel obstruction (36%). Suicide death occurred in 1%

CONCLUSIONS Subaortic stenosis a heterogeneous group of conditions with a wide spectrum of severity and in those with multilevel obstruction was reported. Prognosis is related to the type of obstruction, the presence of other cardiac lesions and multilevel obstruction. Balloon valvuloplasty does not appear to be a successful treatment, probably because of the anatomical substrate.

CARDIAC AND AEROBIC ADAPTATIONS TO ENDURANCE RUNNING TRAINING IN PRE-PUBERTAL CHILDREN
A Brydie, V Uthman, A Houston
Department of Cardiology, Royal Hospital for Sick Children, Yorkhill, Glasgow, G3 8SJ

The existence of the 'Athlete's Heart' phenomenon and aerobic adaptations in pre-pubertal boys in response to endurance running is controversial. This was investigated and the reliability of post-exercise M-mode echocardiography assessed. Nine control and eight trained subjects completed two maximal treadmill runs. Peak VO2 was measured and M-mode echocardiography performed before and after maximal exercise to assess left ventricular characteristics. The following differences between the groups reached statistical significance: posterior wall thickness (p=0.014); peak VO2 (ml/kg/min), p=0.008; peak VO2 (ml/min), p=0.015; exercise duration (p=0.016). Post-exercise echocardiography revealed no differences between the two groups. Reliability of echocardiography was poor, especially post-exercise, but was good (>90%) for the peak VO2 test parameters. It is concluded that trained pre-pubertal male endurance runners do exhibit limited evidence of the 'Athlete's Heart' and have greater aerobic capacity than controls, and that the echocardiographic techniques used have low reliability, especially post-exercise.

CHRONOTROPIC INCOMPETENCE IN HYPERTROPHIC CARDIOMYOPATHY AND ITS ASSOCIATION WITH IMPAIRED EXERCISE CAPACITY
A K B Slade, P J Keeling, C F Shakespeare, P J Counihan, W J McKenna, Turner, D J
Department of Cardiological Sciences, St George's Hospital Medical School, London, UK.

The major determinants of exercise intolerance in hypertrophic cardiomyopathy (HCM) remain uncertain. Recent reports on the association of chronotropic incompetence (CI) and exercise capacity in systolic disease and systolic heart failure have provoked interest in the use of rate-adaptive pacing as a means of restoring chronotropic competence and improving symptoms. To determine the prevalence of CI in HCM and its relationship to exercise capacity we analysed the chronotropic response at maximal and during submaximal exercise using Wilkoff's method in 131 consecutive patients with HCM. All patients underwent simultaneous respiratory gas analysis and all achieved anaerobic threshold (mean respiratory quotient 1.07). All patients were in sinus rhythm and no patient was taking beta blockers, calcium antagonists or digoxin. No patient had evidence of exercise induced ischaemia. CI was observed in 49/131 (37%) patients during exercise. CI at submaximal exercise strongly correlated with CI at maximal exercise (R=0.82, p=0.0001). CI was associated with impaired exercise capacity [6.7 vs 8.6 peak Mels (p=0.001)], 63% vs 75% percentage predicted maximal O2 consumption (p=0.002)]. Patients with CI had reduced maximal left ventricular hypertrophy (22.7 vs 25.7 ммм (p=0.025). Other echocardiographic variables (left atrial size, fractional shortening, end-diastolic and end-systolic dimensions and presence of total or partial obstruction) did not show any significant differences when compared between the two groups. Conclusion: CI is common in patients with HCM and its presence is associated with significant impairment of exercise capacity. Further studies are warranted to determine the mechanisms of CI in HCM and whether correction of chronotropic response with rate-adaptive pacing might improve exercise tolerance.
The interaction between hypertensive stress and alcohol on cardiac protein synthesis

Siddiqi T1, Richard P J1, and Freedy V R2
Departments of Cardiology and *Biochemistry, King’s College School of Medicine & Dentistry, Bessemer Road, London, SE5 9PJ

Excessive alcohol induces specific myocardial lesions that contribute to the entity of alcoholic heart muscle disease. The pathogenic mechanisms include defects in protein turnover. We tested the hypothesis that the deleterious effects of ethanol on cardiac protein synthesis were exacerbated in hypertensive heart disease.

Male Wistar rats were subjected to aortic constriction or sham operations, and after 30 days rats were injected with ethanol (75 mmol/kg, i.p. 2.5 hrs) or identically treated with NaCl (0.15 mol/l). Fractional rates of protein synthesis (i.e., k2, %/day) were measured with labelled phenylalanine, 2.5 hrs after the injection of saline (controls) or ethanol. Hypertension induced marked cardiac hypertrophy and caused a small decreases in k2, i.e. 8.8 ± 0.6%/day and 7.5 ± 0.4%/day in sham-operated and hypertensive rats, respectively (P<0.05, all data are mean ± SEM, n= 5-7). In sham-operated and hypertensive rats treated with ethanol, k2 values were 7.1 ± 0.4 and 5.4 ± 0.5%/day, respectively (P<0.05 and P<0.01, respectively, compared to saline-treated sham-operated rats). There was a significant additive effect, because k2 values in ethanol-treated sham-operated rats were significantly higher than k2 values in ethanol-treated hypertensive rats (P<0.05).

We conclude that the deleterious effects of ethanol on the left ventricle were significantly augmented in the presence of chronic hypertension. Identical conclusions were obtained when data were expressed relative to RNA (i.e., kRNA or RNA activity, mg proteins synthesised/day/mg RNA), signifying that the ethanol induced defects were primarily a consequence of translational deficiencies. These results have important implications for cardiac abnormalities where there is also concomitant ethanol exposure.

(154) MODERATED POSTER

Relative Effects of Ventricular Mass and Conduction Disturbance on Activation in Left Ventricular Hypertrophy

HB Xiao, SJ Brecker, DG Gibson, Royal Brompton National Heart and Lung Hospital, London.

Activation is an important determinant on left ventricular (LV) systolic and diastolic function. To study its effect in LV hypertrophy (LVH), we investigated 46 patients (pts) (aged 16 to 81 years) with LVH due to aortic stenosis, hypertrophic cardiomyopathy and hypertension, using computerised electrocardiogram (ECCO) and echocardiogram. By normal distribution analysis, values of QRS duration (QRSD) were segregated into two normally distributed populations, with a cut off point at 135 ms. Comparing pts (n=36) with QRSD <135 ms to those (n=10) with QRSD ≥ 135 ms, there were no differences in age, heart rate, LV size, LV mass (by Penn convention) and QRS amplitude. In pts with QRSD <135 ms, QRSD correlated negatively with QRS axis (r = 0.40, p = 0.05) and positively with LV mass (r = 0.81, p = 0.01); LV contraction was synchronous with a greater peak rate of dimension shortening (9±2 cm/sec vs 7±2, p = 0.01) over the range of QRSD. By contrast, in pts with QRSD >135 ms, QRS axis rotated rightwards as QRSD increased (p=0.61, p=0.05); the onset of LV free wall motion was delayed by 45±20 ms, its extent correlating with QRSD (r = 0.65, p < 0.05) and QRS axis (r = 0.62, p < 0.05). LV mass was no longer a significant determinant.

Thus, in pts with LVH, the main determinant of QRS duration is LV mass for values below 135 ms. Values of QRSD greater than this are due to an associated conduction disturbance which has the statistical, electrical, and mechanical properties of an associated discrete posterior hemiblock.

(155) MODERATED POSTER

Load Dependent Electrophysiological Changes and Arrhythmogenesis in Experimental Left Ventricular Hypertrophy

W Jauch, MN Hicks, SM Cobbe.
Medical Cardiology, Royal Infirmary, Glasgow.

The influence of loading conditions on electrophysiology and arrhythmia susceptibility was studied in an animal model of left ventricular hypertrophy (LVH). LVH was induced in NZW rabbits by perinatal hypertension. Isolated perfused hearts were studied in Langendorff and working heart mode, thus allowing manipulation of afterload and preload. Left ventricular monophasic action potential duration (APD), local effective refractory period (ERP), inducibility of ventricular tachycardia (VT), and ventricular fibrillation (VF) threshold were determined under different loading conditions. The LV dry weight to body weight ratio was 3.88 ± 0.16 g/g in the hypertensive animals (n=8) and 2.86±0.18 g/g in the controls (n=7), p=0.0001 representing a 31% increase in LV mass. The APD and ERP data under unloaded, baseline loaded, and changes under the different loading conditions are tabulated below (mean ± SE).

<table>
<thead>
<tr>
<th>L</th>
<th>L</th>
<th>L</th>
<th>BIV</th>
<th>+P</th>
<th>+P</th>
<th>+A</th>
<th>+A</th>
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<tr>
<td>147</td>
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<td>138</td>
<td>137</td>
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<td>3 (3)</td>
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</table>

L = Langendorff (unloaded), BIV = Baseline loaded heart, +P = increased preload, +A = increased afterload, vs baseline (P<0.05 vs controls, +A = P<0.05 vs BIV). When unloaded, VT was not inducible in any preparation. Under different loading conditions 44% of hypertrophied hearts became inducible while control hearts remained non-inducible. The two groups did not differ with respect to VF threshold when unloaded. Hypertrophied hearts were more susceptible to VF under increased loading conditions than controls, median threshold current 35 mA and >100 mA respectively, P<0.05.

In conclusion hypertrophied hearts demonstrated prolonged repolarization under basal conditions and an increased susceptibility to arrhythmias under increased loading conditions.

(156) MODERATED POSTER

Altered Calcium Handling in Heart Failure - A Sub-Cellular Mechanism for Arrhythmogenesis

Department of Medical Cardiology, Glasgow Royal Infirmary, and *Institute of Physiology, Glasgow University, Scotland.

Heart failure is associated with increased sympathetic tone which results in an increase in intracellular calcium via several mechanisms. The resulting "calcium overload" has been implicated as a possible cause of contractile dysfunction and may also be involved in the development of arrhythmias. We have investigated alterations in myofilament Ca-sensitivity and sarcoplasmic reticulum (SR) Ca-handling properties in a rabbit coronary artery ligated model (LJG, n=7) using Saponin- and Triton-treated right ventricular trabeculae. Heart failure was assessed by echocardiography and invasive measurements of cardiac output (CO). Sham-operated rabbits (SH, n=7) were used as controls.

LJG animals had increased end diastolic diameters (LVEDD) compared with SH (1.66±0.21cm vs 1.46±0.15cm, mean±SD, p=0.05) and lower ejection fraction (47.15±9.1% vs 69.4±6.8%, p<0.01). The LJG group had a lower resting CO (274.15±8.56 vs 313.6±36.8 l/min) and a diminished response to a fluid challenge (16.8±16.76% vs 26.4±2.3%, p<0.01). Isolated trabecular force per unit cross sectional area was similar in LJG vs SH (4.5±3.03 vs 4.5±3.03mg, g/cm², p>0.5). Myofilament Ca-sensitivity was not different between groups (p=0.05 being approximately 5%). Loading the SR for a constant period of time and at a controlled [Ca2+] on resulted in a greater tension response to application of 20mM caffeine (which releases Ca from the SR) in the LJG group, e.g. 2 minute loading at 250mM Ca produced 63.0±22.0%max at 3.1±3.1μM Ca, p<0.01. The LV of SJLJG rats had reduced loading times compared with SH, e.g. At 150mM [Ca2+] tension responses were produced after 30secs in 71% of LJG vs 53% of SH (p<0.01). This enhanced Ca-uptake was a good predictor to spontaneous Ca release from the SR (tension oscillations). For arbitrary loading conditions of [Ca2+] and time the probability (p) of oscillations was over 4 times greater in the LJG group.

The enhanced Ca-uptake by the SR may represent an adaptive response to increased diastolic [Ca2+] which occurs in heart failure. This alteration in SR loading was, however, associated with spontaneous Ca releases. These Ca releases might initiate after-depolarisations and subsequently act as an arrhythmogenic mechanism.
(158) MODERATED POSTER

CREATINE (CK) MB ISOFORMS AND TROPONIN-T RELEASE IN HYPERTROPHIC CARDIOMYOPATHY
M Hossain-Nia, P Brown, C MacRae, A O' Donoghue, D W Holt, W J McKenna
Department of Cardiological Sciences, St George's Hospital Medical School, London, SW17 ORE

Hypertrophic cardiomyopathy (HCM) is characterised by left ventricular hypertrophy and hyperdynamic systolic performance. Approximately 10-20% of patients develop wall thinning with LV cavity dilatation and overt cardiac failure. The pathogenesis of this process, and the identification of susceptible patients, remains unknown. Analysis of CK-MB isoforms (cytoplasmic enzyme) and cardiac-specific Tropinin-T (TN-T) (structural protein) has been shown to improve the sensitivity for the detection of acute myocardial damage. The aim of this study was to assess CK-MB isoform measurement and TN-T as markers of myocardial damage in patients with HCM, and in unaffected first degree relatives. Blood samples were collected from 139 patients (78M/61F, median range age 39 (14-75) years) with a diagnosis of HCM, and 70 unaffected relatives (40M/30F, age 38 (12-83) years). The median (range) total CK, CK-MB and CK-MB2 activities (U/L) were significantly higher in the HCM patients compared to the unaffected relatives- 104 (39-987) vs 81 (28-377), 5.2 (0.3-32.5) vs 3.2 (0.6-9.4), 2.6 (<0.4-18.3) vs 1.1 (<0.4-5.2), p<0.001, respectively. MB2/MB1 ratio was above 1.0 (range 1.1-4.8) in 82 HCM patients, but in only 13 unaffected relatives (range 1.1-1.9), p<0.001 2x2 test. TN-T concentration was within the normal range in all samples (median 0.02ng/ml).

Conclusions: The finding of a significantly higher proportion of cardiac-specific Tropinin-T (TN-T) isoform, within and unaffected of normal levels of CK release from the myocardium in the absence of definitive evidence of myocardial damage in this condition. The mechanism of this increased CK-MB2 release and its prognostic significance in HCM patients merit further investigation.

(159) POSTER

THROMBUS IN UNSTABLE ANGINA: BIOLOGICAL AND HISTOLOGICAL FINDINGS WITH IMPLICATIONS FOR THE NATURAL HISTORY OF THE SYNDROME
Javier Escaned, Marcel de Jong, Victor A Umani, Donald C MacLeod, Robert J van der Meer, Fred T Bosman, Pim J de Feyter, Patrick W Serruys. Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

In the present study we have investigated the histopathological and biological characteristics of coronary specimens obtained in 98 consecutive directional atherectomy (DA) procedures, performed in 50 (52%) and 48 (50%) male and female patients respectively. Smooth muscle cells (SMC) were cultured from DA specimens using an explant technique. Successful primary SMC outgrowth was chosen as a surrogate for the migratory and proliferative potential of the SMC present in the explant. In this way the influence of other histological constituents present in the plaque on SMC biology was maintained while the modifications in cell phenotype associated to prolonged culture, multiple cell divisions and cell passage were minimised. Information on plaque histology was obtained in a representative sample of each specimen. The presence of different histological constituents, media and adventitia were recorded. Clinical variables including age, sex, previous MI, previous intervention, and coronary risk factors were also recorded. Chi-square and unpaired Student's t test were used as required in the analysis of data. Results: Coronary thrombus or plaque haemorrhage was found in 10/47 (21%) UAP specimens (9 primary and 1 restenosis lesion) and in 1 (2%) SAP patient (primary lesion) (p<0.01). All thrombotic samples show foci of organisation which, on the grounds of experimental evidence, bore no relation to the time interval between the onset of chest pain at rest and DCA. Once in culture explants from coronary specimens containing organising thrombus showed more frequent smooth muscle cell outgrowth (810, 80%) than explants with other histological constituents (3568, 40%) (p<0.05). Outgrowth was not significantly influenced by any other clinical or histological variable. Conclusions: In DA specimens from UAP lesions we have found 1/ low prevalence of thrombus or intraplaquie haemorrhage; 2/ foci of organisation in all thrombotic samples; 3/ major discrepancies between the degree of thrombus organisation and the duration of the syndrome. In the overall study population thrombus appeared as the only determinant of initial SMC outgrowth in vitro. These observations may be relevant to the understanding of the pathobiology of UAP plaques and the natural history of the syndrome.

(160) POSTER

TEMPORAL CHANGES IN CARDIOPARASYMPATHETIC ACTIVITY DURING UNSTABLE ANGINA: A COMPARISON WITH NORMAL SUBJECTS AND UNCOMPLICATED ACUTE MYOCARDIAL INFARCTION
W Jong, V Nolan, JMB Neilson**, KAA Fox*
*Department of Cardiology and **Medical Physics, Royal Infirmary, Edinburgh, UK

Reduced heart rate variability post myocardial infarction (MI) is associated with a poor prognosis and a high incidence of sudden death. Unstable angina (UA) has a similar 12 months mortality to MI but information relating to the autonomic dysregulation of such patients is limited. We studied: (1) 16 patients with UA, admitted within 8 hours from the onset of symptoms, (2) 18 patients with UA, admitted 12-48 hours after the onset of symptoms, (3) 19 patients with uncomplicated acute MI and (4) 12 age matched normal subjects. Heart rate variability was measured from continuous electrocardiograms commenced immediately after counting the number of times successive RR intervals exceeded the preceding RR interval by > 50 ms over a 24 hour period. This is a previously validated sensitive and specific index of cardiac parasympathetic activity.

RESULTS

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEART RATE</th>
<th>24 HOUR COUNTS</th>
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<td></td>
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<tr>
<td>&lt;60 years</td>
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<tr>
<td>&gt;60 years</td>
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</table>

Individual comparisons were significant (p<0.05) for 24 hour counts in early vs late UA, early UA vs normals, MI vs normals and for heart rate in late vs early UA MI, by t-test. CONCLUSIONS: Patients with early unstable angina have reduced cardiac parasympathetic activity of a comparable magnitude to patients with uncomplicated acute myocardial infarction. This autonomic dysfunction resolves within approximately 48 hours with intensive medical treatment. Unstable angina is associated with significant parasympathetic impairment which may be relevant to the poor prognosis of this syndrome. Further studies to relate the heart rate variability and prognosis in unstable angina are indicated.

(161) POSTER

CORONARY OCCLUSION AND QT DISPERSION: THE IMPORTANCE OF SEVERE ISCHAEMIA AND MULTI-VESSEL DISEASE
P. D. Higham, R. Stevenson, S. S. Furniss.
London Chest Hospital, London and Academic Cardiology Department, University of Newcastle upon Tyne, U.K.

Regional ischaemia rapidly alters action potential durations leading to regional variation in ventricular electrical recovery. QT dispersion defined as QT maximum minus QT minimum measured from the 12 lead ECG reflects regional changes in ventricular recovery and is increased during the early hours after myocardial infarction. To study the spatial variation, the degree and time course of ischaemia-induced dispersion of ventricular recovery in man we analysed changes in QT dispersion in 49 patients undergoing coronary angioplasty (PTCA). ECGs were recorded at 50 ms/s prior to inflation, at 60s inflation and post inflation. Analysis was blind and all values rate corrected. PTCA was performed to 21 left anterior descending (LAD), 16 right (RCA), and 12 circumflex vessels (CX). Mean QT dispersion (QTD) to PTCA was 47 ± 3 ms increasing to 55 ± 4 ms at 60s inflation [p<0.05] and showing some recovery post inflation (mean QT dispersion = 49 ± 4 ms). In the 25 patients with x = 1mm ST elevation the mean increase in QT dispersion at 60s inflation was greater at 18 ± 6 ms compared to no overall change in mean QT dispersion in the remainder (2 ± 4 ms) [p<0.01]. ST elevation occurred in only 25% of CX infarctions compared to 50% for RCA and 62% for LAD (p<0.05) and was commoner in patients with triple (80%) compared to double (53%) or single vessel disease (44%) (p<0.001). Conclusion: Increased QT dispersion occurs rapidly following coronary artery occlusion in man reflecting underlying alterations in ventricular recovery due to ischaemia. Increased QT dispersion is generated by severe ischaemia occurring more commonly in patients with ST elevation and associated multi-vessel disease.
(162) POSTER

ASSESSMENT OF VENTRICULAR FUNCTION IN THE VERY ACUTE AND CONVALESCENT STAGE OF MYOCARDIAL INFARCTION BY THE FIRST-PASS TECHNIQUE

SR Vallath, NPS Campbell, JL Laird, W McNair
Royal Victoria Hospital, Belfast, United Kingdom

Assessment of ventricular function by nuclear techniques in the very acute stages of myocardial infarction has traditionally been hindered by the static nature of conventional gamma cameras. The multiwire camera is a mobile, self-contained unit which facilitates measurement of parameters of cardiac function in the catheterisation laboratory or by the patients' bedside.

Supine radionuclide angiography (RNA) was performed on twenty-four patients with a diagnosis of acute myocardial infarction after institution of thrombolytic therapy using the multiwire camera and Tandem-178 at a mean of 68 (acute) minutes (range 30-120 minutes). Convalescent rest and stress RNA studies were performed at a mean of 8.6 (intermediate) days (range 6-22 days) and 192 (late) days (range 141-258 days) post-infarction. Exercise was performed only in those patients where it was not excluded for clinical reasons. Mean global ejection fractions at each stage were

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean LVEF% (SD)</th>
<th>Mean RVEF% (SD)</th>
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<tbody>
<tr>
<td>Acute</td>
<td>43.2 (14.3)</td>
<td>42.2 (7.2)</td>
</tr>
<tr>
<td>Intermediate rest</td>
<td>48.9 (15.4) NS</td>
<td>46.7 (9.2)**</td>
</tr>
<tr>
<td>Intermediate exercise</td>
<td>49.0 (11.8) NS</td>
<td>45.0 (6.8) NS</td>
</tr>
<tr>
<td>Late rest</td>
<td>52.2 (16.1)*</td>
<td>46.7 (8.2)</td>
</tr>
<tr>
<td>Late exercise</td>
<td>50.3 (15.1)**</td>
<td>42.3 (5.4) NS</td>
</tr>
</tbody>
</table>

* differs from acute LVEF p = 0.007; ** differs from acute LVEF p = 0.036; *** differs from acute RVEF p = 0.030; NS not significantly different from acute value

Whilst the global right ventricular data suggests that this chamber may behave differently from the left with recovery detectable at an earlier stage, the observed changes in global left ventricular function at rest support the theory that myocardial stunning following acute infarction may persist for a period of weeks with recovery occurring at a later stage.

(163) POSTER

PREDICTION OF VENTRICULAR ENLARGEMENT FOLLOWING MYOCARDIAL INFARCTION: A NEW ROLE FOR HIGH-RESOLUTION ELECTROCARDIOGRAPHY?

AG Zaman
Department of Cardiology, The General Infirmary at Leeds

Ventricular dilatation is an important determinant of prognosis following myocardial infarction. The role of ventricular dilatation in the pathogenesis of slow conduction is unclear.

A prospective study assessed the relation between ventricular dilatation and late potentials following myocardial infarction. Echocardiograms and signal-averaged electrocardiograms were recorded on days 1, 3, 7 and 42 in 68 patients with a first anterior myocardial infarction.

Late potentials were detected on the first day. Their incidence rose throughout the first week, declining thereafter. Late potential development preceded ventricular dilatation. Early late potentials were associated with significant increases in end-diastolic volume to 6 weeks. Day 3 late potentials were the strongest predictor of subsequent ventricular dilatation: positive patients showed an increase in end-diastolic volume of 26.1±7.7%, negative patients a fall of 5.2±3.3% (p<0.001). There was no relation between 6 week late potentials and ventricular dilatation.

The dependence of late potentials on infarct size and reperfusion was assessed. Day 3 late potentials were associated with larger infarcts and with failed reperfusion. Late potentials, were, however, an independent predictor of ventricular dilatation.

Late potentials during the first week post-infarction are associated with ventricular dilatation. They may be a manifestation of myocyte slippage and loss of gap junctions. These findings suggest a possible role for high-resolution electrocardiography, following myocardial infarction, in identifying patients susceptible to ventricular dilatation.

(164) POSTER

ACUTE IMPAIRMENT OF CORONARY RESISTIVE VESSEL FUNCTION IN REMOTE MYOCARDIUM AFTER MYOCARDIAL INFARCTION


Recovery of myocardial blood flow (MBF) after thrombolysis for transmural myocardial infarction has been associated with improved ejection fractions on echocardiography (PET). We investigated MBF in remote myocardium in 13 patients aged 62±11 years (mean±SD). Patients received intravenous (IV) streptokinase (1.5 MU) 4.2±2.3 h after the onset of chest pain. Mean peak creatine kinase (CK) was 773±194 IU. The infarct-related artery was the left anterior descending in 8 patients, the right coronary artery in 4, and left circumflex artery in 1; the remaining arteries in all patients were angiographically normal. At coronary angiography 25±36 days post-MI, 2/13 infarct-related arteries were occluded. Basal and maximal MBF were measured by PET using H215O before and after IV dipyridamole (Dip), 0.5 mg/kg over 4 min, 8±1 days (PET1) and 6±1 months (PET2) after MI. The regional coronary vasodilator response (CVR; maximal/basal MBF) was determined in the infarct region and in a remote region subtended by an angiographically normal artery. At PET1, in the infarct region, basal and maximal MBF were 0.81±0.22 and 0.91±0.51 ml/min/g respectively, giving a CVR of 1.12±0.51; in a remote region, basal and maximal MBF were 1.09±0.32 and 1.70±0.72 ml/min/g (p<0.01 vs. infarct region) respectively, giving a CVR of 1.53±0.36 (p<0.05 vs. infarct region). At PET2, in the infarct region, basal and maximal MBF were 0.82±0.21 and 1.20±0.45 ml/min/g respectively, giving a CVR of 1.42±0.37 (p<0.05 vs. PET1); in a remote region, basal and maximal MBF were 1.09±0.18 (p<0.05 vs. infarct region) and 2.38±0.89 ml/min/g (p<0.01 vs. infarct region, p<0.05 vs. PET1), giving a CVR of 2.19±0.69 (p<0.05 vs. infarct region, p<0.05 vs. PET1). The CVR in remote myocardium at PET2 was still significantly less than that of remote regions, subtended by a normal artery, in 10 stable patients with a single vessel coronary disease without MI, 5.17±0.72 (p<0.05). There was no correlation between CVR in the infarct region and residual stenosis diameter. Thus, there is a recovery in CVR several months after MI in infarct regions. In addition, the CVR is markedly decreased in regions remote from the site of infarction shortly after MI, but improves over several months, and may be due to an acute alteration in resistive vessel function in remote myocardium after MI.

(165) POSTER

CARDIOPROTECTIVE EFFECT OF INTERMITTENT CLOSURE OF CORONARY ARTERIES DURING MYOCARDIAL INFARCTION: PRECONDITIONING OR REPERFUSION?

A W Haider, F Andreotti, D Hackett, A Maseri, D Tousoulis, G J Davies, Department of Medicine (Cardiology), Royal Postgraduate Medical School, Hammersmith Hospital, London.

Spontaneous, intermittent occlusion of infarct-related coronary arteries (IRCA) is known to occur in patients with acute myocardial infarction (AMI). However, it is not known whether intermittency influences the angiographic response to thrombolytic therapy or the extent of myocardial damage. In 102 patients with WHO criteria of AMI receiving intravenous (IV) or intra coronary (IC) thrombolysis within 6 hrs of the onset of symptoms (IC streptokinase 0.5-0.6 mega units (MU) in 45 patients, IV t-PA 0.30-0.60 MU/kg in 57), intermittency was studied by angiography and Holter recording and was defined as angiographic intermittent occlusion and or 22 episodes of 1.5 mm ST elevation lasting 2 min on Holter monitoring, or both. Myocardial damage was assessed indirectly by daily measurements of plasma C-reactive protein (CRP) concentrations up to 72hrs. Intermittency in the first 24hrs was seen in 26.5% (Group 1) and was absent in 73.5% (Group 2) of patients. The two groups were similar regarding age and delay in treatment from the onset of symptoms. The IRCA patency rate (TIMI grade 2 or 3) in Group 1 and 2 was 40.7% vs 28% (p=0.001), before thrombolytic therapy, 92.6% vs 76% (p=0.001) at 90 min and 86.4% vs 72.5% (p=0.002) at 24hrs, respectively. Plasma CRP was similar before treatment, but significantly lower in Group 1 compared with Group 2 at 24hrs (16±12 vs 28±15, p=0.05), 48hrs (26±17 vs 62±49, p<0.04) and 72hrs (20±12 vs 4±19, p<0.02), respectively. In conclusion, in patients with AMI receiving thrombolytic therapy, intermittent occlusion is associated with higher IRCA patency rates up to 24hrs and reduced markers of myocardial damage. Intermittency may, either by providing nutrient flow or by preconditioning the myocardium, favourably influence the prognosis of patients with AMI.
LATE POTENTIALS FOLLOWING MYOCARDIAL INFARCTION ARE RELATED TO VENTRICULAR DILATATION

AG Zaman, JL Morris, JH Smyllie, JC Cowan
Department of Cardiology, The General Infirmary at Leeds

Late potentials in a healed infarct are thought to arise from viable myocytes trapped in areas of fibrosis. However, the pathogenesis and significance of late potentials (LP) in the early phase following myocardial infarction (MI) is uncertain. Ventricular dilatation may lead to disruption of myocyte function, thereby creating a substrate for slow conduction. We examined the relation between early phase LP and ventricular dilatation.

68 consecutive patients with a first acute anterior MI were prospectively studied. LP (40-250 Hz bidirectional filter) were recorded within 24 hrs of admission and at 3.7 and 42 days. LP positivity was taken as 2 of 3 standard criteria; QRS > 114 ms, RMS < 20μV, LAS > 38 ms. Apical 2 and 4 chamber views were recorded by echocardiography within 12 hours of admission and at 42 days. The % change in end diastolic volume (EDV) from day 1 to day 42 was calculated.

Day LP Change in EDV (%) (SEM)
1 pos +26.1 ± 9.2
neg -1.9 ± 3.7 p = 0.004
3 pos -26.1 ± 7.7
neg -29.2 ± 7.3 p < 0.001
7 pos +18.2 ± 7.7
neg -3 ± 3.3 p = 0.02
42 pos +11.5 ± 9.8
neg +5.1 ± 4.4 p = 0.84

LP in the first week following MI are associated with ventricular dilatation. This relation is strongest for day 3 and may be indicative of increased LV wall stress leading to further myocyte slippage and stretch. LP at 6 weeks are independent of ventricular dilatation and may be due to late fibrosis.

THE CHANGING FACE OF CORONARY CARE—1982 to 1991

Quan Fang, Thomas P Gumbricht, J Colin Doig, John P Bourke, Stephen S Furniss, Ronald WF Campbell. Freeman Hospital, Newcastle upon Tyne.

To investigate the changing activities and outcomes in a modern Coronary Care Unit (CCU) we reviewed 14,171 patients (pts) admitted to our CCU in the ten year period between January 1982 and December 1991.

Methods and results
Pts were considered in two groups: Group A comprised of 5,479 pts admitted between January 1982 to December 1985 and Group B consisted of 8,692 pts admitted between January 1986 to December 1991. Counterpulsation therapy was used from 1986 and was available for Group B pts only.

The percentage of pts presenting with acute myocardial infarction (AMI) fell from 37.2% (2,037 of 5,479) in Group A to 27.0% in Group B (2,348 of 8,692) (p < 0.005). In contrast, those presenting with unstable angina (UAP) increased from 21.5% to 32.6% in a same time period (1,178 vs 2,832 - p < 0.005). The ratio of AMI to UAP pts was 1.7 in Group A and 0.8 in Group B. However, AMI and UAP combined constituted a similar proportion of pts in both groups (58.7% vs 59.6%).

Although pts presenting with heart failure increased from 3.1% in Group A to 4.3% in Group B (170 vs 370 - p < 0.005), the use of intra-aortic balloon counterpulsation concurrently dropped from 1.4% to 0.5% (77 vs 44 - p < 0.005), probably reflecting that fewer pts presenting with AMI developed severe heart failure.

The mortality rate for AMI decreased from 11.4% in Group A to 8.1% in Group B (p < 0.005). However, if AMI and UAP pts are excluded, the mortality rate for all other diagnoses was unchanged (5.2% vs 5.8%). There was no significant difference in mortality rates for AMI between the first and second two-year periods in Group A (11.4% vs 11.5%). In Group B, the AMI mortality rate for the last two year period was significantly higher than for the preceding four year period (10.1% vs 7.1% - p < 0.025). This may reflect the significant increase in tertiary referrals of critically ill pts (21% of total pts in the last two years vs 15.0% of those in the preceding four years in Group B).

Implications
Our review suggests that: 1) Although the mortality rate for AMI has fallen, the number of pts admitted to this hospital suffering from acute ischemic events (AMI + UAP) has not changed in the past ten years. 2) The diagnosis UAP has markedly increased - there are many possible but unproven reasons. 3) Thrombolytic therapy is likely to be the principal factor in reducing both mortality rate for AMI and the use of intra-aortic balloon pumps.

EARLY DISCHARGE AFTER ACUTE MYOCARDIAL INFARCTION: RISKS AND COST-BENEFIT ANALYSIS

P Wilkinson, K Ramajadhawan, K P Lai, R Stevenson, B Marchant, A D Timms. Department of Clinical Epidemiology London Chest Hospital, Department of Cardiology Newham General Hospital.

Many patients with uncomplicated myocardial infarction are discharged from hospital after 5 to 7 days. To assess the potential risks of early discharge we recorded the timing of first major adverse events (death, re-infarction, unstable angina and secondary ventricular fibrillation (VF)) in 533 patients with confirmed myocardial infarction. These were consecutive patients admitted to the coronary care unit of a district hospital between January 1988 and December 1991, 73% of whom received thrombolytic therapy. Complete information on outcome was obtained on 597 patients (439 men, 158 women) whose mean age was 62 years (range 26-94 years). During the study period the physicians at the hospital did not have a uniform policy on the length of hospital stay following uncomplicated infarction. Patients with left ventricular failure (LVF) had a high risk of major events (32% in the first 10 days) and their early discharge cannot be recommended. But the 404 patients without LVF or cardiogenic shock had relatively low risk. Fourteen patients in this group had a major event between 6 and 10 days, including 4 who died while still in hospital, 3 who developed unstable angina after discharge, 2 who had episodes of secondary VF (none of whom had been well enough for early discharge), and 5 who suffered re-infarction. A Poisson regression curve of event rates against time suggested that the incidence in this low risk group fell from 6.1 events/1000 persons/day to 0.2 events/1000 persons/day on day 1, to 0.4 events/1000 persons/day on day 6, to 3.4 events/1000 persons/day on day 10, to 1.2 events/1000 persons/day on day 21. The corresponding cumulative risk between days 6 and 10 was 2.9%. The financial cost of keeping a patient in hospital is around £270 per day. Thus, to keep 1000 patients without LVF or shock in hospital between 6 and 10 days would cost around £1,350,000, but the 23 patients expected to develop a major event in this time would receive more intensive treatment. This might be a relatively small clinical benefit and it seems justifiable to consider discharging a low risk patient after five days if the clinical course has been uncomplicated.
P38

(170) POSTER
Acute Impairment of Coronary Resorptive Vessel Function in Remote Myocardium After Myocardial Infarction


Recovery of myocardial blood flow (MBF) after thrombolysis for transmural myocardial infarction (MI) was investigated using positron emission tomography (PET) in 13 patients, age 62±11 years (mean±SD). Patients received intravenous (iv) streptokinase (1.5 MU) 4.2±2.3 h after the onset of chest pain. Mean peak creatine kinase (CK) was 273±1914 IU/L. The infarct-related artery was the left anterior descending in 8 patients, the right coronary artery in 4, and left circumflex artery in 1; the remaining arteries in all patients were angiographically normal. At coronary angiography 22±6 days post-MI, 2/13 infarct-related arteries were occluded. Basal and maximal regional MBF (PETI), MBF by iv heparin before and after continuous dipridamole (Dip), 0.5 mg/kg over 4 min, 853 days (PETI) and 6±1 months (PET2) after MI. The regional coronary vasodilator response (CVR; maximal basal MBF) was determined in the infarct region and in a remote region subtended by an angiographically normal artery. At PETI, in the infarct region, basal and maximal MBF were 0.8±10.22 and 0.9±10.51 ml/min/g respectively, giving a CVR of 1.1±0.51; in a remote region, basal and maximal MBF were 1.0±0.72 ml/min/g (p<0.05 vs. infarct region) and 1.7±0.22 ml/min/g (p<0.01 vs. infarct region), respectively, giving a CVR of 1.5±0.36 (p<0.05 vs. infarct region). At PET2, in the infarct region, basal and maximal MBF were 0.8±10.21 and 1.2±0.51 ml/min/g respectively, giving a CVR of 1.4±0.37 (p<0.05 vs. PETI), in a remote region, basal and maximal MBF were 0.9±0.16 (p<0.05 vs. infarct region) and 2.3±0.89 ml/min/g (p<0.01 vs. infarct region, p<0.05 vs. PETI), giving a CVR of 2.1±0.69 (p<0.01 vs. infarct region, p<0.05 vs. PETI). The CVR in remote myocardium was significantly less than the CVR in the infarct region, subtended by a normal artery, in 10 stable patients with single vessel coronary disease without MI, 3.1±0.72 (p<0.05). There was no correlation between CVR in the infarct region and residual stenosis diameter. Thus, there is a recovery of CVR in several months after MI in infarct regions. In addition, the CVR is markedly decreased in regions remote from the site of infarction shortly after MI, but improves over months, and may be due to an acute alteration in resistive vessel function in remote myocardium after MI.

(171) POSTER
AUTOREGULATORY ESCAPE OF CORONARY ARTERIOLES FROM DILATION BY NITROGLYCERIN

C J H Jones, L Kuo M J Davis and W M Chilian
Microcirculation Research Institute, Texas A&M University Health Science Center, TX, USA and Department of Cardiology, University of Wales College of Medicine, Cardiff

Under steady state conditions, nitroglycerin (NG) dilates small coronary arteries (>100 μm) but not arterioles (<100 μm). These findings do not explain the striking early increase in coronary blood flow after NG, which must be due to dilation of arterioles, since these vessels impose the majority of coronary resistance. We have hypothesized that coronary arterioles are initially dilated by NG, but that arteriolar dilation is not sustained in vivo, due to intrinsic autoregulatory escape mechanisms. We measured diameter changes during continuous NG administration by either intracoronary infusion (1, 3 and 10 μg/kg/min) or epicardial infusion (10-3 M) in canine coronary microvessels in vivo by intravital microscopy during fluorescein microangiography (n = 17 animals), and during extraluminal exposure in vitro by video microscopy (6 vessels).

After 1 - 3 minutes of intracoronary NG in vivo coronary arterioles dilated by 4 ± 1%, 7 ± 2% and 13 ± 2% (diameter change from baseline, mean ± SEM, all p<0.05) while small arterioles had dilated by 1 ± 2%, 3 ± 1% and 4 ± 1% (p<0.05 for the higher doses). After 15 - 20 minutes of intracoronary NG (3 μg/kg/min), the arteriolar dilatation had reduced to 3 ± 2% (p<0.05 vs initial change) whereas small artery dilatation remained significant at 4 ± 1% (p<0.05). Coronary blood velocity increased initially by 45% (p<0.05), but returned to normal by 15 - 20 minutes, consistent with autoregulation. NG administered by epicardial infusion also initially dilated arterioles by 17 ± 5% (p<0.05), although not small arteries. Arteriolar dilation by NG was preserved to 3 ± 2% (p<0.05, vs earlier change) by 15 - 20 minutes, whereas the small artery dilatation became significant at 5 ± 2% (p<0.05). In vitro NG (10-9 to 10-4 M) caused dose-dependent dilation of coronary arterioles to maximal diameter (81 ± 4 μm). Arteriolar dilatation by NG in vitro was sustained for 20 minutes. Thus, NG initially dilates coronary arterioles in vivo and in vitro. NG dilatation of arterioles, but not small arteries, diminishes in vivo, but is sustained in vitro. These data suggest strongly that intrinsic autoregulatory mechanisms enable coronary arterioles to escape from dilation by NG in vivo, and that this accounts for heterogeneous coronary microvascular dilation by NG under steady state conditions.

(172) POSTER
EFFECTS OF SEROTONIN ON EPICARDIAL VESSELS IN NORMALS AND IN PATIENTS WITH MICROVASCULAR ANGINA (SYNDROME X)

E MCdFadden, LA Corr, J Kooner, ME Bertrand, GJ Davies, A Maseri. Hammersmith Hospital, London; University of Lille, France, and Catholic University, Rome.

Patients with microvascular angina may have a regulatory defect in prearteriolar vessels. Since serotonin, an endogenous endothelium-dependent dilator, can cause ischaemia due to intense distal coronary constriction in patients with stable angina, we investigated the effects of serotonin in 11 consecutive women referred for further evaluation of microvascular angina (stable angina, exercise-induced ST depression ≥1 mm, negative ergonovine tests and previously documented normal coronary arteriograms) compared to 6 control women without chest pain referred for investigation of mitral valve disease. The effects of intracoronary infusion of graded doses of serotonin (10-6 to 10-4M) were compared to those of the direct acting vasodilator isosorbide dinitrate (2mg). Vessel diameter in normal controls did not change significantly at infused concentrations of 10-6 or 10-5M. The vessels tended to constrict at 10-4M with maximal reductions (± SEM) of 10.4±7.3% in segments (p=0.08) and 18.4±7.5% in distal segments (p=0.06) compared to baseline. There was no pain or ST shift. Vessels from patients with Syndrome X developed diffuse dose-dependent constriction with maximal reductions of 3.5±0.7% (p=0.03), and 42.0±3.7% (p=0.001) of 10-4M compared to baseline in proximal and distal segments. Five developed angi, with ECG changes in 2. Proximal (p=0.005) and distal constriction to serotonin (p=0.05) was markedly greater in syndrome X vessels than in control vessels, whereas the vasodilator response to isosorbide dinitrate was similar. Thus while serotonin infusion does not cause significant constriction in normal vessels, it causes dose-dependent constriction in smooth vessels in patients with syndrome X.

Abnormal epicardial vasomotor reactivity may play a role in the pathophysiology of chest pain in patients with microvascular angina.

(173) POSTER
STRUCTURE AND FUNCTION OF SMALL PERIPHERAL ARTERIES IN MICROVASCULAR ANGINA

A.C. Tweddel*, S.J. Bund, I. Hutton*, A.M. Haegerty, Department of Medical Cardiology*, Royal Infirmary, Glasgow and Department of Medicine, Manchester University

In patients with microvascular angina, there is increasing evidence of widespread vascular involvement, of peripheral vessels, the pulmonary circulation and the gastrointestinal tract. 9 patients with exertional angina and abnormal gated thallium scans, with no overt evidence of diabetes or hypertension, were identified and matched with controls for age, sex, height, weight and blood pressure. Biopsies were taken of skin and subcutaneous fat and the small arteries were dissected free and mounted as ring preparations in a myograph. Morphological measurements were made at 37°C (using water immersion microscopy). Two arteries were studied from each patient and controls. There was a small increase in medial thickness with an associated minor reduction in luminal diameter, resulting in a significant increase in medial thickness: luminal diameter ratio in the patients with microvascular angina, compared to control (5.6 ± 0.45 vs 4.0 ± 0.22% p<0.01). Contractile function was also enhanced in microvascular angina. Vasodilator responses were tested having pre-constricted the vessels with the thromboxane mimetic U46619. Endothelium independent relaxation (tested with sodium nitroprusside and forskolin) did not differ. In patients with microvascular angina, there was an enhanced relaxation with endothelium dependent agents - (acetylcholine, p<0.05, and bradykinin, p<0.05). These data suggest that small vessels function differently in patients with microvascular angina compared to control patients.
HYPERINSULINAEMIA OF SYNDROME X
A Chauhan, J Foote, P A Mullins, S Thurlaisinghm, M C Petch, P M Schofield
Regional Cardiac Unit, Papworth Hospital, Cambridge

The aim of this study was to compare insulin responses to an oral glucose load (75 g) in patients with coronary artery disease (CAD), patients with chest pain and normal coronary arteries on angiography (Syndrome X), and healthy volunteers (controls). All subjects were matched for age, sex and body weight. Patients with overt diabetes mellitus or hypertension were excluded. Venous blood samples were taken during fasting and at 30, 60, 90, and 120 minutes after the glucose load. Samples were analysed for immunoreactive insulin (IRI).

<table>
<thead>
<tr>
<th>CAD</th>
<th>SYNDROME X</th>
<th>CONTROLS</th>
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<td>n</td>
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IRI Levels (µU/L)

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<tr>
<td>Fasting</td>
<td>10.5±6.20</td>
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<tr>
<td>30-min</td>
<td>70.1±12.19</td>
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<tr>
<td>60-min</td>
<td>85.9±19.69</td>
<td>73.6±30.12</td>
</tr>
<tr>
<td>90-min</td>
<td>83.1±14.19</td>
<td>68.5±31.21</td>
</tr>
<tr>
<td>120-min</td>
<td>67.8±26.15</td>
<td>68.4±24.15</td>
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*p<0.05 compared to control group.

The results are given as mean (range). The IRI levels were compared using the Wilcoxon paired rank sum tests. A p value < 0.05 was considered significant.

There was no significant difference in the IRI levels at fasting, and at 30 minutes between the controls and other groups. However, the CAD group had significantly higher IRI levels at 60, 90 and 120 minutes as compared to the controls. The Syndrome X group had significantly higher levels at 120 minutes compared to the control group. Although the CAD group tended to have higher insulin responses there was no significant difference in IRI levels at all sampling points between the Syndrome X group and CAD group.

Conclusion: Both Syndrome X and CAD group have stimulated hyperinsulinaemia. Patients with coronary artery disease are known to have microvascular dysfunction. This study suggests that hyperinsulinaemia of Syndrome X may contribute to the pathophysiology of Syndrome X.

ALTERNED CATECHOLAMINE RESPONSE TO EXERCISE IN SYNDROME X: A POSSIBLE PATHOPHYSIOLOGICAL MECHANISM
J Marcomichelakis, P Taggart, S Gallivan, R Mattin, P S Sever, R H Swanton
Department of Cardiology, The Middlesex Hospital and Department of Clinical Pharmacology, St Mary's Hospital, London

Functional abnormalities of the small coronary arteries have been implicated in the pathogenesis of Syndrome X (SX). The purpose of this study was to compare plasma catecholamine concentrations between subjects with SX and a normal control group during exercise testing.

Fifty subjects were studied during maximal treadmill exercise testing. SX comprised 24 subjects with anginal pain, a positive exercise test, a normal coronary arteriogram and a normal left ventricular angiogram; together with 26 matched asymptomatic controls. Maximal treadmill exercise testing was carried out in all subjects. Two venous blood samples were taken and analysed for catecholamines; the first pre-exercise and the second immediately after exercise.

Total plasma catecholamine concentration, noradrenaline and adrenaline increased between resting values and immediately post-exercise in both groups. The increase in total catecholamines and noradrenaline was significantly greater in the SX group compared to the control group. Median total plasma catecholamines increased from 851 to 2123 pg/ml in the SX group compared to an increase from 832 to 1403 pg/ml in the control group; median noradrenaline concentrations increased from 652 to 1469 pg/ml in SX compared to an increase from 684 to 990 pg/ml in the control group. The median percent increase in total plasma catecholamine concentration for the control group was 61% and for SX group was 186% (p<0.0001).

This study has shown that there is a different neurohumoral behaviour in response to exercise in SX subjects compared to a control group. We suggest that in SX, catecholamines and other neurotransmitters may induce functional alteration of the small coronary arteries and result in a vasoconstrictor-vasodilator imbalance and consequent inappropriate vasodilatation.

EFFECTS OF KETANSERIN ON PROXIMAL AND DISTAL SEGMENTS AND CORONARY SYSTENES AFTER ANGIPLASTY IN PATIENTS WITH STABLE ANGINA PECTORIS
D Toussulis, C Tsentoloulou, D Tagall, J M Stylios, T Apostolopoulos, P Toutouzis. Cardiology Units, Athens University Medical School and *Hammersmith Hospital, RPMS, London

Previous studies have demonstrated the development of vasoconstrictor dilation to a distal stenosis immediately after PTCA, presumably as a result of endothelial injury, although the precise mechanism remains unknown. The effects of the 5-hydroxytryptamine receptor antagonist ketanserin on proximal, stenotic and distal segments immediately after successful percutaneous coronary angioplasty (PTCA) were studied in 12 patients (10 male, 2 female; mean age 54 years). Ketanserin 1 mg was infused intracoronary immediately after PTCA. Proximal, distal and coronary stenosis luminal diameters were measured by quantitative coronary angiography (CAAS system) immediately before and after PTCA and after ketanserin. Angiographically normal proximal and distal segments of coronary arteries subjected to PTCA were compared to those of arteries not subjected to PTCA. Immediately after PTCA vasoconstriction was observed distal to the PTCA site (1.44±0.05 mm before vs 1.32±0.05 mm after PTCA; p<0.05), but no change occurred in the control arteries (proximal segments 2.84±0.19 and 2.87±0.17 mm; distal segments 1.44±0.05 and 1.42±0.05 mm (p>NS) before and after PTCA respectively).

Intracoronary ketanserin administration induced distal to the PTCA site dilatation from 1.32±0.08 to 1.56±0.11 mm (mean dilatation 18.4±7.8%; p<0.001). No change occurred in residual coronary stenoses diameter 1.80±0.08 and 1.93±0.15 mm (p>NS) before and after ketanserin respectively. No significant dilatation occurred in control arteries (proximal segments 2.87±0.19 and 2.94±0.16 mm; distal segments 1.44±0.05 and 1.53±0.06 mm (p>NS) before and after ketanserin respectively). These findings suggest that 5-hydroxytryptamine receptor stimulation underlies at least part of the distal segment coronary vasoconstriction which commonly follows coronary angioplasty.

PLASMA FIBRINOGEN AND FIBRIN D-DIMER LEVELS IN PATIENTS WITH CORONARY ARTERY DISEASE AND LEFT VENTRICULAR ANEURYSMS
G Y H Lip, M J Metcalfe, A A Rumley, K J Hoog, P A Ye, F G Dunn,*G D O Lowe
Department of Cardiology, Stobhill General Hospital; and *University Department of Medicine, Royal Infirmary, Glasgow

Plasma fibrinogen (PF) levels are associated with an increased incidence of cardiovascular events and stroke. In addition, plasma fibrin D-dimer (DD) levels reflect intravascular clotting levels and are a marker of fibrin turnover. We, therefore, performed a prospective population-controlled study to determine PF (CLAUS) and DD levels (ELISA) in 51 patients with angiographic coronary artery disease. Seventeen patients had normal left ventricular function (Group 1), 21 had left ventricular dysfunction (Group 2) and 13 had left ventricular aneurysms (Group 3). These groups were compared to 157 controls of similar sex and age from a random population sample. Group 1 had higher median levels of PF than population controls (2.89 vs 2.60 g/l; p<0.05). Group 2 also had increased median PF when compared to population controls (3.13 vs 2.60 g/l; p<0.01) but this was not significantly different from Group 1 (2.66 vs 2.60 g/l; p<0.001). Group 3, however, had increased median PF when compared to both population controls (3.37 vs 2.60 g/l; p<0.001) and Group 1 (3.37 vs 2.89 g/l; p<0.05). In addition, Group 3 had increased median plasma DD levels when compared to Group 2 (163.0 vs 82.0ng/ml; p<0.05) and population controls (183ng/ml vs 76.0ng/ml; p<0.05). This study demonstrates increased PF levels in patients with coronary artery disease and normal left ventricular function when compared to population controls. There is a further increase of PF in patients with left ventricular aneurysms, who also have higher DD levels, suggesting increased intravascular thrombus formation and fibrin turnover. These findings may contribute to the increased rate of thromboembolism in patients with left ventricular aneurysms.
IS THE LIMITATION OF CORONARY PERFUSION RESERVE IN MICROVASCULAR ANGINA REGIONALLY INVARIANT?
Department of Cardiology, Department of Nuclear Medicine*, University Hospital of Wales, Cardiff.

Angina with a positive exercise test despite normal coronary angiograms and in the absence of overt cardiac disease implies abnormal control of coronary blood flow. If there were generalised dysfunction throughout the coronary microcirculation, the site of inducible microvascular perfusion defects may vary.

To test this hypothesis, paired symptom-limited standard Bruce protocol exercise thallium perfusion scans were performed 4-6 weeks apart in 12 microvascular angina patients (aged 48-72, 5 males). Therapy remained constant throughout except that vasodilators were stopped for 48 hours before each test. Images were analysed blind by 2 observers using standard techniques with reference to a total of 15 regionally defined myocardial segments in 3 standard views.

Exercise time (384±37 & 387±35 sec, mean±SEM), peak systolic blood pressure (166±10 & 161±8 mmHg) and maximum heart rate (140±7 & 145±8 b.min⁻¹) were similar in the 2 tests.

All patients developed a reversible thallium defect on exercise on both tests, anterior in 5, posterior in 3 and inferior in 4 on the first test; anterior in 3, posterior in 4 and inferior in 5 on the second. The perfusion defect was always localised to one of these 3 regions. The site of the perfusion defect differed from the first test to the second in 8 of 12 patients (p<0.001).

These results suggest that the site of induced and reversible myocardial perfusion defect in patients with microvascular angina is not fixed. They imply that the underlying defect may indeed be a generalised functional abnormality of the coronary microvasculature.

AMBULATORY ISCHEMIA IN NEW PATIENTS WITH ANGINA PECTORIS IN THE GENERAL POPULATION
M M Gandhi, F C Lampe, D A Wood
Department of Medicine (Cardiology), University of Southampton, Southampton, UK

Characteristics of ischaemia during daily living activities in patients presenting for the first time with exertional angina (AP) in the general population are not known. To investigate these, referrals ≤ 70 years age from a randomly selected general practice population with no previous CHD were assessed prospectively, and 96 of 110 patients, with a history AP (mean±SD) age 57.5 (9.9) years, and 95 age, sex and practice matched asymptomatic healthy controls (CON) underwent technically suitable 24 hour ambulatory electrocardiographic recordings. All were prior to anti-anginal therapy and analysed blind. Ischaemic ST segment depression (AI), defined as ≥ 1mm horizontal/down sloping shift from baseline at J+80 msecs and lasting > 1 min, was prevalent in 52% (50 of 96) AP patients and in 9% (9 of 95) of CON. AI was present in 34 of 64 (53%) men with AP compared to 7 of 59 (12%) male CON, and in 16 of 52 (30%) women with AP compared to 2 of 36 (6%) CON. Of 225 episodes of AI recorded in AP patients with a range of 1 to 15 episodes per patient [mean (SD) 4.5 (3.6), median 3.5, 71% (159 of 225) were silent. Mean duration of ischaemia was 117 minutes (range 1 to 782, median 66 minutes), with mean (SD) ST depression of 2.4 (1.1)mm. Only 8.4% of AI episodes occurred between midnight and 6 am, the rest were evenly distributed with a small peak in both sexes between 12 and 6 pm. In logistic regression analysis including all clinical characteristics, serum cholesterol (p = 0.02) and exercise ischaemia (p = 0.003) were independently associated with the presence of AI in men with AP; but only the latter was significant in women; this may reflect a different pathophysiological basis for AI in women. Characteristics and prevalence of AI in new unselected patients with AP in the general population differ compared with reported series of selected hospital patients, have a large interpatient variability, and the latter is five fold higher than in healthy individuals.

REPORTED MANAGEMENT OF ANGINA PECTORIS BY GENERAL PRACTITIONERS: THE NEED FOR GUIDELINES
M M Gandhi, F C Lampe, D A Wood
Department of Medicine (Cardiology), University of Southampton, Southampton, UK

To investigate General Practitioners (GPs) management of angina pectoris (AP), a postal questionnaire survey of a representative sample of 217 GPs was undertaken between April and August 1992. Response rate was 79% (171 of 217). Of 171 GPs, symptoms frequency and duration of AP were considered a reliable guide to severity of underlying coronary artery disease (CAD) by 49% and 46% respectively. Three quarters were usually (67%) or almost always (8%) confident about interpreting a resting electrocardiogram for signs of ischaemia or infarction although a quarter were only sometimes (19%) or almost never (6%) confident. By contrast, the majority were almost never (56%) or only sometimes (24%) confident of correctly interpreting an exercise test. The majority thought an exercise test was frequently (41%) or almost always (36%) useful for diagnosis of CAD. Almost half either didn’t know (12%) or thought it was only sometimes (29%) or almost never (7%) useful for prognosis. When asked whether there was scientific evidence for the benefits of revascularisation, the proportion of ‘yes’, ‘no’ and ‘don’t know’ responses respectively were as follows: PTCA relieves symptoms (79%, 3%, 18%) and/or prolongs survival (21%, 39%, 40%); CABG relieves symptoms (96%, 0%, 4%) and/or prolongs survival (62%, 20%, 18%). Of the 171 GPs, 80% referred a maximum of only 10% of their patients with AP to a cardiologist at a regional centre and 72% referred a maximum of only 25% of patients with AP to any other hospital physician for assessment.

GPs’ report that the majority of their patients with AP are not referred for hospital cardiological assessment, and their understanding of the scientific evidence about revascularisation shows considerable variation between practitioners. Guidelines for the clinical management of AP are required.

OUTCOME OF NEW PATIENTS WITH ANGINA PECTORIS ASSESSED AT AN OPEN ACCESS CHEST PAIN CLINIC
M M Gandhi, F C Lampe, D A Wood
Department of Medicine (Cardiology), University of Southampton, Southampton, UK

The majority of patients treated for angina pectoris (AP) in the general population are not referred for hospital assessment. To improve access to cardiological services, we investigated the feasibility of an open access (9am-1pm, Mon-Friday) Chest Pain Clinic (CPC) for patients ≤ 70 years presenting for the first time with suspected stable AP. The service was offered from a 238 acute-bed hospital, and 117 general practitioners from a random sample of 17 practices agreed to refer all patients with suspected stable AP. There were 467 referrals over 18 months or 193 patients/100,000 population ≤ 70 years/ year. Clinical classification of referrals, assessed by a cardiology registrar within 24 hours, was as follows: 24% (110 of 467) typical AP, 13% (63 of 467) possible angina, 13% (63 of 467) "atypical pain ?cause", 44% (204 of 467) non-cardiac pain, and 6% (27 of 467) admitted to CCU with unstable angina or myocardial infarction. Exercise tests (ET) carried out on 217 patients increased the department’s annual ET workload by 23%, and resting ECG workload by 4%. Outcome assessed in the 110 AP patients at one year was 97% complete and revealed the following events (median time to event since clinic visit in months): 3.6% deaths (26), 6.3% myocardial infarction (6), 14% coronary artery bypass graft (74), 11.8% PTCA (26), and in 7.2% CABG (75). Of the remainder, 37.3% (41 of 110) reported continuing symptoms despite medical therapy, in 8% medical therapy was adequate and in 1.8% symptoms resolved spontaneously. By the cardiological assessment of new patients with stable AP through an open access CPC is feasible. Short-term prognosis in the 110 patients with AP was not benign; 10% sustained a myocardial infarction or died and 19% underwent revascularisation within one year.
THE ROLE OF TRIGLYCERIDES AND OTHER RISK FACTORS IN CORONARY ARTERY STENOSIS PROGRESSION
Department of Cardiological Sciences, St. George's Hospital Medical School, London

Recent epidemiological studies have demonstrated a relationship between raised plasma triglycerides and acute coronary events. In order to evaluate the role of triglycerides and other risk factors for coronary disease in coronary artery disease, we analysed clinical, biochemical and angiographic data from 159 male patients with non-urgent coronary artery disease awaiting coronary intervention procedures (CAVES, n=63, PTCA n=90) who underwent a second angiogram after at least three months (11.2.5). Only patients presenting with chronic stable angina or unstable angina that had settled on medical therapy were included.

Results. Lesions were visualized in at least two orthogonal views and defined as complex (uneven or overlapping edges, ulceration or thrombus) or smooth (in the absence of any of these features). Stenosis was defined using an automatic edge detection system (CAAS). Lesion progression was defined as a >20% increase in severity in established lesions, a new lesion >30% in a previously normal area or the development of total coronary occlusion (TCO).

Results. There were 385 lesions >20% at first angiography. Forty-one lesions progressed to TCO or by >20% and 8 new lesions developed. Multiple regression analysis showed that lesion progression was associated with increased plasma triglycerides (trig) (p=0.01), complex lesion morphology (CL) (p=0.02), unstable angina (USA) (p=0.001) at presentation and time on waiting list (p=0.012). Age, F/M, HT, SM, HT, previous MI and DM were not associated with progression of stenosis. This study demonstrates that triglycerides, CL and USA are important independent factors for disease progression in patients awaiting coronary intervention procedures.

CORONARY STENOSIS SEVERITY AND MORPHOLOGY BEFORE ACUTE MYOCARDIAL INFARCTION
D Tousoulis, T Drake, N Uren, S Rosen, W Halder, G Davies
Cardiology Unit, RPMS, Hammersmith Hospital, London

To assess severity and morphology of coronary stenosis in both the infarct related artery (IRA) and the non-IRA, before spontaneous acute myocardial infarction (MI), we analysed computerized edge detection coronary angiograms obtained 16.32±1 range 1 to 6 months before MI in 32 consecutive untreated pts (27 male, 5 female, mean age 54±10), of whom 30 gave a history of angina. Progression in stenosis was defined as an increase of ≥20% diameter reduction and morphology was classified as complex (symmetrical stenosis), eccentric (asymmetrical stenosis) or irregular (asymmetrical and or irregular with a rough contour and overhanging edges). In the IRA before MI 16 stenoses were ≤50% and 16 were >50%. Of the 16 ≤50% 9 were smooth, 4 intermediate and 3 had no stenosis. After MI all stenoses in the IRA were >50% (p<0.001). Furthermore 14 of 32 (44%) pts had single vessel (IRA) disease and, in 11 pts of the remaining 18 (61%) with 2-3 vessel disease, the most severe stenosis was in the non-IRA. In the non-IRA before MI, 25 stenoses were ≤50% and 21>50% (p<0.05). After MI, 27 were ≤50% and 29>50% (p<0.05) (10 new stenoses had developed, 4 stenoses had progressed). In the IRA (n=26) the percentage of stenoses before MI which were concentric, eccentric and irregular were 12%, 15% and 75% respectively and in the non-IRA (n=46) 43%, 37% and 20% respectively. This difference in distribution of morphology between the groups was significant (p<0.01). In conclusion, in patients with angina history the pre-existing lesion dominating the coronary occlusion is usually of irregular morphology, but often not the site of greatest stenosis.

RAPID ANGIOGRAPHIC CORONARY ARTERY STENOSIS PROGRESSION IN PATIENTS WITH ISCHAEMIC HEART DISEASE
Cardiological Sciences Department, St. George's Hospital Medical School, London

In order to determine the incidence and clinical and angiographic features of rapid coronary stenosis progression we studied 92 consecutive patients (pts) (77 men, 15 women) with angina and documented coronary artery disease awaiting coronary intervention procedures. Sixty-one pts presented with chronic stable angina and 31 with unstable angina, that stabilised following conventional medical therapy. All pts underwent coronary angiography immediately (IRA) and at least three months (11.2.5) after first angiography. Progression was assessed in 196 stenoses by means of computerized angiographic analysis (CAAS). Stenoses were classified as either complex lesions (CL) (overlapping edges, irregular borders, ulceration or thrombus, n=72 (37%) or smooth lesions (SL) (the absence of complex features, n=124 (63%)). Of the 196 stenoses, 116 (59%) were ≤50% and 80 (41%) ≥50%. Stenosis progression was defined as >20% increase in severity of a previous stenosis or progression to total occlusion. On average, diameter (mm) of complex stenoses decreased from 1.5±0.65 to 1.23±0.69, whereas that of smooth stenoses decreased from 1.5±0.63 to 1.30±0.65 (p<0.001). Progression occurred in 20 of 78 (26%) complex lesions and 7 of 124 (6%) smooth lesions p<0.001). Total coronary occlusion developed in 23 complex and 2 smooth stenoses. Acute coronary events developed in 26 pts (28%), which were associated with progression of complex stenoses in 14 pts and of smooth stenoses in 4 pts. In 8 (31%) of the 26 pts the acute event developed in the absence of stenosis progression. Acute events were more frequent amongst pts who presented with unstable angina compared with those with stable angina (17/31 (58%) vs 9/61 (15%); p<0.001). The results of this study indicate that rapid stenosis progression is relatively common. It occurs more frequently in pts with complex lesions and with unstable angina, in spite of stabilisation with medical treatment. These findings may have clinical and pathogenetic implications.

THE EVOLUTION OF COMPLEX CORONARY STENOSES IN STABLE CORONARY ARTERY DISEASE
Department of Cardiological Sciences, St. George's Hospital Medical School, London

Several studies, originating outside the UK, have indicated that the morphological appearances of stable coronary artery stenoses is an important determinant of their subsequent behaviour. In order to determine the natural history of complex lesions (CL) and smooth lesions (SL) in patients with non-urgent coronary artery disease we determined the morphological appearances and severity of all coronary stenoses (>20%) in the initial diagnostic angiogram and smooth lesions (SL) in patients with non-urgent coronary artery disease we determined the morphological appearances and severity of all coronary stenoses (>20%) in the initial diagnostic angiogram and smooth lesions (SL) in patients with non-urgent coronary artery disease were assessed immediately after the angiogram (PTCA, n=96 or CAVG, n=34) after at least three months (11.2.5) in 130 male patients. Clinical and biochemical details were recorded. All pts had symptomatic angina that was stable at first presentation. Lesions were defined as complex (uneven or overlapping edges, ulceration or thrombus) or smooth (in the absence of any of these features). Stenosis was defined using an automatic edge detection system (CAAS). Lesion progression was defined as >20% increase in stenosis severity or total coronary occlusion (TCO) in established lesions. Lesions >30% in a previously normal area were defined as new lesions (NL).

Results. There were 201 SL and 112 CL identified at the first study. CL were more severe than SL at first angiogram (60% ±1.4 vs 49.21, p<0.001) and at the second angiogram (68% ±1.5 vs 52% ±2, p<0.001). Thirty lesions progressed and was more frequent in CL (n=16, 14.2%) compared to SL (n=14, 7%) (p=0.03, Chi-sq). Univariate analysis revealed no differences between CL and SL with respect to patient age, family history, previous diabetes, hypertension, myocardial infarction, or smoking. Plasma lipids were closely similar in both groups. Eight new lesions (NL) developed in angiographically normal segments 18.5 months ±2.6 after first angiogram (mean ± stenosis 54±7). One NL had progressed to TCO to 3 CL and 4 SL. This study shows that complex lesion evolution is associated with more rapid disease progression than smooth lesions in chronic stable angina and is consistent with similar observations after thrombolysis or PTCA. In addition, this study confirms that overall lesion progression complicates only a minority of lesions (<10%) over 11 months and that TCO rarely develops in angiographically normal segments.
EXERCISE CHARACTERISTICS OF NEW PATIENTS WITH ANGINA PECTORIS IN THE GENERAL POPULATION.

M M Gandhi, P C Lampe, D A Wood,
Department of Medicine (Cardiology), University of Southampton, Southampton, U.K.

Characteristics of inducible electrocardiographic (ECG) ischaemia in incident angina pectoris (AP) in the general population were prospectively investigated. Among consecutive referrals ≤ 70 years of age with a positive CHD from a randomised selected general practice population, 110 [mean (SD) age 57 (9.6) years, n=70 male] had typical AP. Prior to initiating medical therapy, 103 of 110 AP patients, and 180 asymptomatic age, sex and practice matched healthy controls (CON) underwent a symptom limited Bruce protocol treadmill exercise test. All records were analysed blinded. Ischaemic ST segment depression (STD), defined as ≥ 0.1mV horizontal/downsloping shift from baseline at J+80 msec was induced in 61% (63 of 103) AP patients; in 29% (30 of 103, 20 male) there was ≥ 3mm STD at a mean (SD) exercise duration of 5.9 (2.2) min. Silent ischaemia was prevalent in only 11% (11 of 103). Peak rate pressure product (x10³) in AP patients was equally and significantly reduced in those with (28.2 vs 30.9 in CON, p < 0.05) and without (28.1 vs 32.5 in CON, p < 0.001) ischaemia. Total exercise duration [mean (SD) in minutes] was also significantly reduced in those with [6.5 (2.6) vs 9.8 (2.5) in CON] and without [7.0 (2.7) vs 10.4 (2.9) in CON] ischaemia (all ischaemia vs no ischaemia, p=NS; all AP vs CON, p < 0.001); this difference was found in both men and women. Logistic regression analysis of age, sex and cardiac risk factors could not predict the presence of ≥ 3mm STD at low workloads; only systolic blood pressure was weakly associated (OR 1.03, 95% CI 1.00, 1.05). These results, representative of new AP in the general population, show that exercise capacity is significantly reduced in both sexes regardless of ischaemia, and severe ECG ischaemia at low workloads is frequent and cannot be predicted from symptom frequency or duration.

STABLE AND UNSTABLE ATHEROSCLEROTIC PLAQUES RELATE TO THE LOCAL IN SITU INFLAMMATORY PROCESSES.

A C van der Wel, A E Becker, C M van der Loos, A J Tigges, P K. Das
Department of Cardiovascular Pathology, Academic Medical Center, Amsterdam, The Netherlands

Background: Stable atherosclerotic plaques have a dense fibrous cap with a small atheroma. Unstable plaques show a large atheroma with a small cap and loosely arranged collagen. Atherosclerotic plaques also contain an inflammatory reaction (T-lymphocytes and macrophages). One may hypothesise that the inflammatory process affects plaque composition.

Objective: This study was designed to evaluate the relationship between stable and unstable plaque morphologies and the cellular component make-up.

Material and methods: Plaques were obtained at autopsy from the aorta, the carotid and coronary arteries; classified histologically as fibrous (n = 7), atheromatous (n = 13) and *intermediate* (n = 21). The distribution of smooth muscle cells (SMC), macrophages and lymphocytes were studied with immunohistochemical techniques.

Results: Stable (fibrous) plaques were dominated by SMC; unstable (atheromatous) plaques by macrophages and T-lymphocytes. The "intermediate" lesions had mixed patterns of SMC and inflammatory cells or localized areas dominated by inflammatory cells.

Conclusion and speculation: Stable and unstable plaques show an inverse relationship between SMC and inflammatory cells, which supports a concept of a modulating effect on plaque composition of the in situ inflammatory reaction.

FREE RADICAL RELEASE DURING REPERFUSION IS ATTENUATED BY PRIOR HEAT STRESS.

S E Steare, S M Mocanu, M C Evans, J H Nugent, D M Yellon.
The Hatter Institute for Cardiovascular Studies, Division of Cardiology, University College Hospital, London, UK.

Heat stress (HS) has previously been shown to enhance post ischemic functional recovery and reduce biochemical indices of injury after global ischemia-reperfusion. This protection is associated with an increase in endogenous cardiac catalase activity, which may play an important role in the protection against free radical injury of reperfusion. We have used an electron spin resonance (ESR) technique to examine whether HS affects free radical release during reperfusion in the isolated rat heart.

Twenty four hours after HS or sham treatment (Control,C), rat hearts were excised and retrogradely perfused with Krebs-Henseleit buffer. After a 10 min stabilization period, hearts were subjected to 10 min of no-flow global ischemia, followed by 10 min reperfusion. At specific time points, 4 ml of coronary effluent was collected in 1 ml of 30 mM phenyl-tert-butyl nitrate (PBN) for ESR measurement. Cardiac catalase activity was determined using an UV spectrophotometric assay. A PBN adduct was identified with characteristics consistent with a lipid alkoxyl radical of PBN-PBN=O. ESR signal intensities: Examples taken during the reperfusion period are expressed as a percentage of the stabilisation value.

In control hearts a burst of free radical release occurred in the first two minutes of reperfusion, with elevated levels continuing through the 10 minutes of reperfusion. Prior heat stress completely attenuated this release pattern. This protection was associated with a 50% decrease in cardiac catalase activity. These results suggest that HS leads to a reduction in free radical mediated injury during reperfusion.

DURING ACUTE REGIONAL MYOCARDIAL ISCHAEMIA MECHANO-ELECTRIC FEEDBACK IS INCREASED.


The mechanical activity of the heart is known to influence its electrical activity but this relationship has not been investigated before during acute regional myocardial ischaemia. We studied the changes in monophasic action potential duration following increases in venous loading during acute regional ischemia in the in situ porcine heart.

Pigs were anaesthetised with halothane (1-2%) in a 1:1 mixture of nitrous oxide and oxygen; the chest wall removed and a snare placed around the proximal aorta. Left ventricular pressure and aortic arch pressure were monitored using fluid filled catheters. The right atrium was paced. The left anterior descending, diagonal or obtuse marginal coronary artery were tied and ventricular loading increased by aortic occlusion. This was performed every 5 minutes for 30 minutes following coronary artery occlusion. The monophasic action potential (MAP) was continuously recorded from the ischaemic area. One hundred and thirty two occlusions in 10 pigs were measured. The Wilcoxon signed ranks test was used to compare the groups.
CONTRIBUTION OF INTRACELLULAR pH (pHi) TO CONTRACTILE RECOVERY FOLLOWING PERFUSION REPERFUSION OF ISCHAEMIC MYOCARDIUM

JI Vanderberg, PC Mellors, AA Grace
Departments of Biochemistry and Medicine, University of Cambridge.

During myocardial ischaemia acidosis is a significant contributor to ischaemic contractile failure. Following reperfusion there is a triphasic recovery of left ventricular developed pressure (LVDP) - an initial rapid recovery with LVDP almost reaching the pre-ischaemic LVDP, followed by a decline (often termed myocardial stunning) and finally full recovery which may take many hours. In this study we have investigated to what extent does recovery of pHi contribute to the initial recovery recovery of LVDP.

Isolated ferret hearts were perfused with HCO₃⁻-buffered phosphate-free solution at 5-6 ml.min⁻¹. pHi was monitored from the chemical shift of the 3¹P NMR resonance of intracellular phosphate and LVDP was monitored using an intraventricular balloon. Hearts were made globally ischaemic by switching off the perfusion pump and clamping the aortic inflow line.

The effect of changes in pHi on LVDP may be described by the equation LVDP = C·[H⁺]⁻¹/₄. C was calculated from the pre-ischaemic pHi (7.13) for an initial LVDP of 100%.

The recovery of LVDP during the first minute is more rapid than can be accounted for by the change in pHi. The subsequent recovery of LVDP, however, closely parallels the associated change in pHi.

The difference between pHi and LVDP recovery during the first minute may be explained by vascular refilling and changes in [P].

Subsequently, pHi makes a significant contribution to LVDP recovery. The secondary decline in LVDP occurs despite full recovery of pHi which suggests that any effects pHi has on LVDP during this phase must be indirect.

The EFFECT OF THROMBOLYSIS ON LIPOPROTEIN (a) CONCENTRATIONS

Academic Unit for Cardiovascular Medicine, Department of Medicine, Charing Cross and Westminster Medical School, London.

Introduction: Lipoprotein(a) (Lp(a)) is being increasingly recognised as an important independent risk factor for Ischaemic Heart Disease. Several small studies have given conflicting results of the changes in Lp(a) concentrations in patients suffering acute myocardial infarction (MI) and hence the appropriate time frame for measurement for risk assessment remains unclear. This study was undertaken to determine the effects of thrombolysis on Lp(a) concentrations in patients sustaining an MI.Methods: 49 patients, 40 males and 9 females, mean age 61 (range 42-78) who had sustained a definite MI confirmed by serial cardiac enzymes and Electrocardiographic changes were studied. 39 patients received Thrombolysis using 1.5million units of Streptokinase over 1 hour. Ten patients did not receive thrombolysis. Samples were taken at baseline and frequently throughout the hospital stay and up to 2 months post discharge, immediately centrifuged and stored in liquid nitrogen before transfer to a -80 freezer. Samples were measured in batches, in duplicate by Biopool ELISA (Porto).Results: There were no significant changes in either group in the first 24 hours. From the 3rd day, Lp(a) concentrations in the thrombolysed group began to rise significantly (p=0.0085),reaching a peak at a mean of 12 days (p=0.0001). Lp(a) concentrations were falling but still significantly different from the admission value (p=0.0005). The Non thrombolysed group did not show any significant change in Lp(a) concentrations throughout the entire study period. We confirmed that Streptokinase did not interfere with the Biopool Lp(a) assay. Conclusion: This study shows that Lp(a) concentrations significantly change in patients receiving thrombolysis with a time course that makes it unlikely to be due to an acute phase response. The mechanism for the change in this group when no change was observed in the non-thrombolysed group is not clear but does mean that if not measured in the first 24 hours of admission, measurement of Lp(a) for coronary risk factor assessment in thrombolysed patients should be deferred for at least two months post infarction.

r-PA TREATMENT AFTER FAILED REPERFUSION WITH STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

JP Mounsey, JS Skinner, TE Hawkins, A MacDermott, SS Furniss, PC Adams and DS Reid. Freeman Hospital, Newcastle on Tyne.

Failure of resolution of ST segment elevation shortly after treatment with streptokinase (SK) in acute myocardial infarction (AMI) is associated with failed coronary reperfusion and impaired left ventricular (LV) function. It may also be associated with failure to achieve a lytic state with SK, so further thrombolysis with t-PA may result in reperfusion and thus myocardial salvage. 21 patients (pts) with AMI who showed ECG evidence of failed reperfusion (<25% reduction of ST elevation in the lead of maximum ST shift) 30 min after SK (1.5 megaU/1hr) were recruited from 2 centres. They were randomized to receive either t-PA (100mg/3hrs, 13pts), or placebo (12pts), in a double blind fashion. 29 pts with ECG evidence of reperfusion after SK acted as controls. Fibrinogen (F) levels were measured before and after SK and a lytic state was defined as F <1g/l after SK. Outcome was assessed from the Selvester q wave score of a predischarge ECG and ejection fraction (LVEF) from a gated scan 4 weeks after discharge. The patients were well matched for age, sex, infarct size and ECG predicted infarct size. The outcome, mean (SD), is summarized in the table. p values are for t-PA vs placebo, assessed by t test.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SK only</th>
<th>SK+t-PA</th>
<th>SK+Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (g/l)</td>
<td>3.4(1.4)</td>
<td>3.7(0.6)</td>
<td>3.4(1.0)</td>
</tr>
<tr>
<td>t=60min</td>
<td>0.4(0.6)</td>
<td>0.9(0.8)</td>
<td>1.0(1.1)</td>
</tr>
<tr>
<td>q Wave Score</td>
<td>4.2(2.8)</td>
<td>4.5(2.7)</td>
<td>7.2(3.0)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49.1(12.3)</td>
<td>49.1(8.8)</td>
<td>35.4(17.8)</td>
</tr>
</tbody>
</table>

26/29 SK only pts and 12/25 randomized pts achieved a lytic state at 60mins. Failure to achieve a lytic state was not predictive of a response to t-PA. Patients who failed to show ECG evidence of reperfusion after SK and who received t-PA had significantly lower q wave scores and higher ejection fractions than who received placebo. Patients who received t-PA were indistinguishable from those who showed evidence of reperfusion with SK only.

Conclusion: Patients who fail to show ECG evidence of reperfusion after SK may benefit from further lytic therapy with t-PA.

ANGIOGRAPHIC ASSESSMENT OF EFFICACY OF DOUBLE BOLUS ALTEPLASE IN ACUTE MYOCARDIAL INFARCTION

Cardiac Department, Royal Victoria Hospital, Belfast.

Patency of the infarct-related coronary artery (IRA) is considered to be Thrombolysis In Myocardial Infarction (TIMI) 2 or 3 grade.However the in-hospital mortality of patients with TIMI 2 grade is similar to that of TIMI 0 or 1 (i.e. occluded IRA). It is therefore essential to assess the percentage of patients with TIMI 3 patency particularly in any new approach used to increase patency of the IRA. Accelerated dosage regimens of alteplase produce high coronary patency rates. We advanced the concept of accelerated dosing by administering two bolus injections of 50mg of alteplase separated by 30 minutes to 84 (55 male, 29 female, mean age 59 years, range 29 to 74) patients up to 6 hours from the onset of a first acute myocardial infarction (in that territory).

Mean delay from onset of symptoms to alteplase was 155 (range 35 to 360) minutes. Coronary angiography was performed 60 and 90 minutes after the first bolus injection and scored according to the TIMI scale. We scored TIMI 3 as a favourable outcome in our assessment of this novel approach to increase coronary patency. At 60 minutes, 55/64 (86%, 95%CI =75-93%) patients exhibited TIMI 3 patency. At 90 minutes, 74/84 (88%, 95% CI =70-94%) patients exhibited TIMI 3 patency. At follow-up angiography (19-48 hours), 66/69 (96%, 95% CI = 88-99%) patients had retained TIMI 3 patency. Eight (11%) patients with TIMI 3 patency at 90 minutes experienced late reocclusion (up to 30 days). Bleeding episodes were mostly minor. There were no cerebrovascular accidents. Thirty day mortality was 5/84 (6%), 2 of these patients had TIMI 3 patency at 90 minutes. Thus, double bolus therapy produces high (86, 88%) early coronary patency which is sustained at follow-up angiography. The incidence of complications and mortality are low.
(194) POSTER

Reduction of ST-segment Depression in the Early Post-Infarction Period by Thrombolytic Therapy as an Indicator of Improved Prognosis

A Cheng, D Shanit, RA Greenbaum
Cardiovascular Research Unit, Edgware General Hospital, Edgware

We prospectively studied the incidence and significance of transient, reversible ST-segment depression (TSTD) following acute myocardial infarction (AMI) and the results of thrombolytic therapy on these changes. 127 patients (pts) were studied. Seventy (70) pts with AMI underwent 24 hours of Holter monitoring immediately after admission to the Cardiac Care Unit. There were a total of 202 episodes of TSTD in 44 (35%) pts. Of these 44 pts, 34 (77%) had only painless TSTD (137 episodes); 5 (11%) had TSTD only accompanied by chest pain (21 episodes) and 5 pts had both painless (39 episodes) and painful (5 episodes) TSTD. Thirteen of the 23 (57%) patients who did not receive thrombolytic therapy developed TSTD whereas 31 of 104 (30%) patients receiving thrombolytic therapy developed TSTD (p<0.02). After 6 months follow up, further cardiac events occurred in 35 of 44 (80%) pts with TSTD compared with 35 of 83 (42%) of those without TSTD (Table) (p<0.0004). The sensitivity of TSTD as a predictor of further cardiac events in the six months after AMI was 49%; specificity was 81% with a predictive value of 75%. We conclude that silent TSTD is seven times more common than TSTD accompanied by chest pain immediately following AMI. Thrombolytic therapy almost halved the incidence of TSTD. TSTD detected in the first 24 hours following AMI is a useful predictor of an increased incidence in cardiac events over the following six months.

Table: 6 month clinical outcome of patients with and without ST-segment depression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No complications</th>
<th>Death or non-fatal reinfarction</th>
<th>Post-infarction or unstable angina</th>
<th>Ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment depression noted</td>
<td>9 (20%)</td>
<td>14 (32%)</td>
<td>20 (46%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>ST-segment depression not noted</td>
<td>48 (78%)</td>
<td>14 (17%)</td>
<td>21 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>p value</td>
<td>=0.0004</td>
<td>&lt;0.05</td>
<td>0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

(195) POSTER

HOLTER MONITORING FOR RISK STRATIFICATION AFTER ACUTE MYOCARDIAL INFARCTION TREATED BY THROMBOLYSIS


The natural history of myocardial infarction has changed with the introduction of thrombolytic therapy, there being a lower mortality but a higher incidence of recurrent thrombotic events. Preliminary evidence indicates that Holter ST monitoring may be of prognostic value in patients with acute myocardial infarction, but there have been no studies in patients treated by thrombolysis. We prospectively studied 256 consecutive patients who presented with acute myocardial infarction treated by thrombolysis, all of whom underwent early 48 hour Holter ST monitoring and were followed up for 8 (range: 3-13) months. Recurrent ischaemic events occurred in 45 patients (fatal infarction 17, non-fatal reinfarction 12, unstable angina 16), and a further 15 patients required revascularisation. Analysis of the Holter data showed that 32% of patients had at least 1 episode of isolated ST depression (≥0.1mV) (STD) and 41% either ST depression or elevation ≥0.2mV (STD/E). Ischaemic episodes were silent in 95% of cases. Event free survival analysis demonstrated a significant association between Holter findings and recurrent ischaemic events (STD: p=0.009; STD/E: p=0.002). Risk was greatest when the cumulative duration of ST shift was ≥1hr or when there were ≥23 episodes. This difference remained significant when the end-point was restricted to fatal or non-fatal reinfarction (STD: p=0.005; STD/E p=0.001), the period of greatest risk for patients with an abnormal recording occurring early after investigation. Thus, an abnormal Holter recording identified patients at risk of early (within 30 days) reinfarction with 79% sensitivity and 60% specificity. Although positive predictive accuracy was low (11%), a normal Holter recording was associated with 98% negative predictive accuracy. In conclusion, early after thrombolytic therapy for acute myocardial infarction, ST change on Holter monitoring identifies patients at increased risk of recurrent ischaemic events, and in particular early reinfarction.

(196) POSTER

SHOULD WE CATHETERIZE PATIENTS WHO ARE ASYMPTOMATIC FOLLOWING THROMBOLYSIS? DATA FROM THE LIFT STUDY REGISTRY.

R Roberts, Susan P Glenn, Babak Balafar
London Chest Hospital London E2 9JX

The Late Intervention Following Thrombolysis (LIFT) study was designed to test the hypothesis that delayed intervention, 1 to 2 months after myocardial infarction (MI) treated with thrombolysis, significantly reduces the incidence of recurrent cardiac events, being death, reinfarction, unstable angina and angina requiring intervention by coronary artery bypass surgery (CABG) or balloon angioplasty (PTCA). Between December 1989 and June 1992, 539 patients, free of cardiac symptoms, underwent catheterization at a mean time of 19 days (3-42) following MI. The MI was anterior in 275 (51.9%), inferior in 255 (48.1%) with Q-waves in 283 (52.5%), 89% were male, mean age 49 (29-70), 76% were smokers and 5.6% had a prior history of MI. At catheterization 92% were taking aspirin, 53% a beta-blocker and 9% diuretics. Angiography revealed single vessel coronary artery disease (CAD) in 289 patients (53.6%), double vessel CAD in 153 (28.3%) and triple vessel CAD in 75 (13.9%). In 13 patients (2.4%) the coronary arteries were angiographically normal despite unequivocal evidence of MI. 168 patients (31.1%) had an occluded infarct related artery (IRA) with TIMI 0 or 1 antegrade flow; 71 (13.2%) had less than 50% residual stenosis in the IRA in all angiographic views and 300 (55.7%) had a patent IRA with 50-99% residual stenosis. 36 patients (6.7%) declined randomization and 27 (5%) received medical treatment only due to poor LV function or isolated distal CAD. 33 patient (6.1%) required elective CABG, 19 (3.5%) for proximal triple vessel CAD and 14 (2.6%) for significant left mainstem disease. The remaining 204 patients (38%) were randomized, 99 to conservative treatment and 105 to interventional. Choice of intervention, based on angiographic findings, was CABG in 21 (20%) cases and PTCA in 83 (80%). These findings represent important data on patients who do not routinely undergo invasive investigation following MI. 45% have multivessel CAD of whom 6% require CABG on prognostic grounds.

(197) POSTER

RECURRENT THROMBOTIC EVENTS AFTER ACUTE MYOCARDIAL INFARCTION: EVENT-FREE SURVIVAL ANALYSIS IN THE THROMBOLYTIC ERA

R Stevenson, K Ranjadayalan, P Wilkinson, R Roberts, A D Timmis.
Departments of Cardiology and Clinical Epidemiology, Newham General and London Chest Hospitals.

Observational studies have reported progressive reductions in hospital mortality from acute myocardial infarction in the last 30 years but there has been no evidence for similar improvements in long-term prognosis. It is expected that thrombolytic therapy will further reduce the hospital mortality but it is not clear that this will be associated with long-term prognostic benefit. The aim of this prospective study was to record acute and long-term prognosis and determinants of outcome in 633 consecutive patients with AMI admitted to the coronary care unit of a district general hospital between 1/1/88 and 31/12/91. All cause mortality, non-fatal thrombotic events (myocardial infarction, unstable angina) and revascularisation were recorded. Hospital mortality was 14.2%, but in the 73% of patients who received thrombolysis it was only 9.7%. Follow-up was obtained in 97.5% of patients: mortality (95% CI) at 30 days, 1 year, and 3 years was 16.3% (13.6-19.5%), 21.9% (18.8-25.5%), and 29.6% (25.5-34.1%), respectively. Event-free survival (survival without a non-fatal thrombotic event) was 80.2% (76.7-83.2%) at 30 days, 68.7% (62.7-70.4%) at 1 year, and 55.9% (51.1-60.5%) at 3 years. Survival in patients treated with thrombolysis was considerably higher than in those treated without (3 year survival: 76.6 vs 53.5%), although the incidence of non-fatal thrombotic events was the same in the two groups. Multivariate determinants of 6 month survival were: vein closure, treatment with thrombolysis and aspirin, smoking history, bundle branch block, and age. For patients who survived 6 months, age was the only factor related to long term survival. We believe this to be the first long-term mortality study outside the context of a clinical trial since the use of thrombolytic therapy became widespread. Although patients treated by thrombolysis had a relatively good prognosis, long term mortality and the incidence of recurrent thrombotic events remained high. These data confirm that in the thrombolytic era there remains an important need for effective strategies for identification and treatment of these high risk patients.
(198) POSTER

CLINICAL AUDIT MAY REDUCE THE TIME TAKEN TO ADMINISTER THROMBOLYSIS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

P Currie, S M Gray, T R D Shaw, I R Starkey
Department of Cardiology, Western General Hospital, Edinburgh

The prognosis of patients with acute myocardial infarction is improved by coronary thrombolysis plus aspirin. The greatest benefit of thrombolysis is greatest when it is given as early as possible after the onset of symptoms but may be a disappointingly long time delay before some patients arriving in hospital receive this treatment. Therefore the success of clinical audit in reducing the "door-to-needle" time for thrombolysis and the delay in patients with myocardial infarction receiving aspirin. We made a retrospective analysis of the main time delays for giving thrombolysis (i.e. recording an ECG, transferring patients to the coronary care unit and beginning the infusion) and aspirin to 60 patients during a period of 5 consecutive months. The data were presented to medical and nursing staff and written information was circulated detailing a breakdown of the time delays at each stage. The retrospective data was then compared with a prospective time interval of 4 consecutive months (n=56) immediately following the presentation of the audit results. In patients (n=71) with unequivocal evidence of myocardial infarction at the time of arrival in hospital the measures above were associated with (i) a 31% reduction (P=0.013) in the "door-to-needle" time for thrombolysis (median 53 minutes [range 21-148] vs 38 [15-155]; (ii) a 57% fall (P<0.001) in the time taken to record an ECG (14 minutes [4-34] v 6 [1-19]); (iii) a 33% decrease (P=0.047) in the time taken to begin thrombolysis in the coronary care unit (15 minutes [0-110] v 10 [5-70]). The median time taken to give aspirin was also reduced (P=0.001) from 58 minutes (15-600) to 17 (3-1640). These results demonstrate that the time required to administer thrombolysis and aspirin in patients with acute myocardial infarction can be reduced by the presentation of results obtained during clinical audit.

(199) POSTER

INTIMAL SMOOTH MUSCLE CELL PROLIFERATION IN ORGAN CULTURE OF HUMAN CORONARY ARTERY SUBJECTED TO BALLOON ANGIOPLASTY

AG Violaris, SE Francis, CM Holt, C Clelland, PA Gadsdon, GD Angelini.* Departments of Cardiac Surgery, University of Sheffield, Sheffield and "University of Bristol, Bristol, U.K.

Intimal smooth muscle cell proliferation, the primary cause of restenosis following balloon angioplasty, is difficult to investigate in man and studies have to rely on limited amounts of post-mortem material. To overcome this we investigated whether intimal proliferation occurred in organ culture of human coronary artery subjected to balloon angioplasty.

Fresh coronary arteries (from the cardiac transplant program) were subjected to balloon angioplasty (3mm balloon, 10 atmospheres, 60 seconds), opened out, pinned intimal side uppermost and maintained at 37°C in RPMI 1640 medium containing 30% fetal bovine serum for 14 days. Cultures were supplemented with [3H]-thymidine for the last 24 hours.

Balloon angioplasty resulted in substantial medial injury as assessed by a fall in adenosine triphosphate (ATP) concentration (nmol/gm wet weight) (103±25 [SEM], vs freshly isolated vessel 240±34, P<0.05). Left ventricular ejection fraction 14 days in culture (210±38, P=ns vs. freshly isolated vessel). No intimal thickening was observed in histological sections of cultured vessels, with a mean thickness of 47±12 μm, P<0.001 vs freshly isolated vessel.

 Autoradiography showed proliferating cells in this neointimal layer with few dividing cells in the media. Immunostaining revealed that the neointimal cells were positive for alpha actin, suggesting a differentiation towards smooth muscle cells.

Thus intimal smooth muscle proliferation occurs in human coronary artery subjected to balloon angioplasty. The model promises to be useful for studying the in vitro progression of restenosis in man.

(200) POSTER

CORONARY ANGIOPLASTY IMPROVES SYMPTOMS AND LEFT VENTRICULAR PERFORMANCE IN PATIENTS WITH IMPAIRED LEFT VENTRICULAR FUNCTION

R M Oliver, C E Handler, E Firmin, R H Swanton
Department of Cardiology, Middlesex Hospital, London

Coronary angioplasty (PTCA) improves angina but its effects on dyspnoea and radiodensity of left ventricular failure are less clear, particularly in patients with impaired left ventricular function. The serial effects of successful PTCA on symptoms and resting left ventricular ejection fraction (LVEF) were assessed prior to PTCA and at 1 and 6 months in 38 consecutive patients (mean age 58y, 29M). 16 of 31 patients with I- and 4 of 7 patients with 2-vessel disease had a history of previous myocardial infarction (MI). 23 showed a grade II or III (NYHA) dyspnoea which improved by at least one grade in 17 (74%) patients at 1 month and this improvement persisted in 15 (65%) at 6 months. Among the 20 patients with previous MI, dyspnoea improved in 10 (50%), remained the same in 9 (45%) (8 with grade 1 symptoms) and worsened in 1 after MI 4 months following PTCA. In 18 patients without previous MI, there was no significant improvement in left ventricular function (resting LVEF pre-PTCA, at 1 and 6 months were 50%, 53% and 53% respectively). Similarly, in the 18 patients with previous MI, PTCA resulted in no unusual changes in LVEF (43%, 45% and 46% respectively). However, in 16 patients with impaired left ventricular function prior to PTCA (LVEF < 45%), LVEF was 38% pre-PTCA, 42% at 1 month (p<0.02) and 46% at 6 months (p<0.05). In this group there was 12% (55%) MI. 23 showed 1 improvement in symptomatic grade. We conclude that, after successful PTCA, dyspnoea improves in most patients and left ventricular performance improves significantly in patients with reduced LVEF, results similar to those demonstrated after coronary artery surgical revascularisation.

(201) POSTER

CHANGES IN BLOOD FLOW OF THE CONTRALATERAL CORONARY ARTERY AND RECRUITABLE COLLATERAL VESSELS DURING BALLOON CORONARY OCCLUSION

M Kyliakidis, P Petropoulos, C Tentolouris, S Marakas, C Koukoudis, P Toutouzas
Department of Cardiology, Hippokrnatish Hospital, University of Athens, Athens, Greece

To investigate changes in blood flow of the contralateral coronary artery and their relation to the acute development of recruitable collaterals (RC) arising from this artery during balloon coronary occlusion (BCO) we studied 24 patients with single left anterior descending (LAD) coronary artery stenosis and normal left ventricle. Four successive LAD BCOs of 96±14 sec were performed. Before and during each BCO blood flow was measured in the proximal right coronary artery (RCA) by intracoronary Doppler velocimetry and quantitative RCA angiography. Chest pain was graded arbitrarily from 0 to 10. During BCO1 14 patients developed angiographically visible RC, 6 with (group A) and 8 without (group B) epicardial filling of the occluded LAD while 10 patients did not (group C). During the four successive BCOs, while there were no significant changes in systemic hemodynamics, the RCA flow showed transient, reproducible increases in group A (BCO1: 66±15%, BCO2: 60±11.5%, BCO3: 65±12.1%, BCO4: 64±9.8% , a=0.036) progressive increases in group B (BCO2: 17±9.4%, BCO3: 21±9.8% both p<0.06, BCO4: 48±9.8%, BCO5: 60±12.7% both p<0.014) and a significant change in group C (BCO1: 0±8.4%, BCO2: 1.8±8.0%, BCO3: 1.4±3.6%, BCO4: 0.9±3.6% NS). Changes (mean±SEM) are % from before to during each BCO. The angiographic RC extent did not change from BCO1 to BCO4 in any group. Chest pain during BCO4 was significantly less in group A (1±0.8) than in group B (8±1.2) or C (8±1.0), p=0.0003. From BCO3 to BCO4 chest pain declined significantly in group B (6±1.2 to 4±1.8, p=0.001) while remained unchanged in groups A and C. These findings suggest that the transient appearance of RC from the contralateral coronary artery during BCO is associated with a transient increase in flow of the collateral donor artery which appears to reflect collateral function better than the angiographic visualization of RC.
Major adverse cardiac events following PTCA - predictability from clinical parameters and quantitative and qualitative angiographic analysis. DP Foley, WH Herrmans, PW Serryns.
Thoraxcentre, Erasmus University, Rotterdam, Netherlands.

Major procedural and in-hospital adverse cardiac events (MACE) (death, non-fatal myocardial infarction, necessity for coronary artery bypass grafting or intervention) occur in 2-10% of all patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Although several risk factors have been identified, no study has yet used quantitative coronary angiography (QCA) to this end. This study examines the predictability of these events from clinical parameters and quantitative and qualitative angiographic assessment in 1452 patients treated by PTCA in two European multicentre clinical trials. All cinefilms were reviewed for comprehensive quantitative analysis in a core laboratory using an automated edge detection technique (CAAS), as well as extended qualitative review by 2 "blinded" experienced observers. For statistical comparisons, patients who suffered MACE (N=695) were randomly matched 1:3 with those who did not. Odds ratios (OR) for predictability of MACE were calculated for all variables. In stepwise logistic regression analysis (LR) the following variables, with OR >2 and lower 95% confidence interval >1, were retained: Variables: MACE/no.pats. MACE/no.pats. Odds Retained with variable without variable Ratio Dissection 46/111 18/153 3.53±2.90±10.0 Unstable angina 29/69 39/206 3.11±(1.72±5.61) Type C lesions 19/48 47/220 2.53±(1.86±6.01) Bend >45° 31/86 36/180 1.31± (1.2±1.51) Comprehensive QCA assessment failed to identify patients at risk of MACE after PTCA. Dissection was, not surprisingly, the strongest predictor of MACE. The only baseline variables associated with a greater likelihood of MACE were unstable angina "Type C" lesions and location in a bend >45°. Conclusion: Major adverse cardiac events after PTCA remain unpredictable from clinical knowledge and despite current angiographic technology.


Reoperation in patients with recurrent symptoms after previous coronary artery bypass grafting (CABG) is associated with an increased mortality and morbidity. Coronary angioplasty (PTCA) provides an alternative method of revascularisation in these patients. We studied 140 consecutive patients (mean age 58 years, 94% men) with previous CABG who underwent a first PTCA of the saphenous vein grafts (SVG) and/or native coronary arteries (NA) between 1981 and 1991. The majority had three vessel disease (86%) and a previous myocardial infarction (MI) (62%), and 49% had an ejection fraction <45%. Before intervention, 114 patients (81%) suffered grade III/IV angina, 23 (16%) had previous multiple CABG procedure and the mean number of patent grafts was 1.6 per patient. The median duration between CABG and PTCA was 50 months (range 1-168). In total, 104 patients (74%) had single vessel PTCA and 36 (26%) underwent multivessel PTCA. Angiographic success rate per vessel was 85% for non-occluded NA and 86% for SVG. A major complication (MI, emergency CABG or death) occurred in 5 patients (3.6%). Overall, clinical success occurred in 115 patients (82%). Complete follow-up was available on all 140 patients after a median of 24.5 months (ranging up to 108 months). At census, 117 patients were alive, of whom 11 sustained a non-fatal MI, 21 had elective CABG, and 31 had repeat PTCA during follow-up. The cumulative probability of survival was 91.5% (SE 2.6%) and 74.5% (SE 7.5%) at 1 and 5 years, respectively. The 1 and 5 year cumulative event free survival rates (freedom from death, MI, CABG) were 77.3% (SE 4%) and 53.9% (SE 7.8%). At census, of the 117 survivors, 36 patients (31%) were asymptomatic and 55 (39%) improved by at least two angina grades. Conclusion: PTCA in patients receiving an "unsuccessful" method of revascularisation in patients with prior CABG. This treatment strategy potentially avoids reoperation with its attendant risk.
(206) POSTER

DETERMINANTS OF CORONARY ANGIOPLASTY SUCCESS OF CHRONIC TOTAL OCCLUSIONS: A MULTIPLE LOGISTIC REGRESSION MODEL TO IMPROVE PATIENT SELECTION

Coronary angioplasty (PTCA) of chronic total occlusion (CTO) is associated with relatively low success rates. We evaluated 312 consecutive patients who underwent a first PTCA of CTO (TIMI grade 0 or 1 antegrade flow) between 1981 and 1992. The median duration of occlusion was six months (range from two weeks to 156 months). Angiographic success was achieved in 61.2% and clinical success in 60.9%. A major complication occurred in six patients (1.9%) with one death (0.3%) and five emergency coronary artery bypass grafting (1.6%). Analysis of 27 clinical and angiographic variables showed that procedural success rates were lower in patients with multivessel disease than with single vessel disease (53% versus vs 75%, p < 0.001), in lesions occluded for > 3 months than those <3 months (59% vs 74%, p = 0.02), in vessels <3 mm than those ≥3 mm (48% vs 73%, p < 0.001), in occlusions without a tapered entry configuration (43% vs 69%, p < 0.001), in lesions with side branches (53% vs 69%, p = 0.01), and in lesions with bridging collaterals (20% vs 70%, p < 0.001). Multiple logistic regression analysis identified duration of occlusion (p = 0.001), vessel diameter (p = 0.003), presence of bridging collaterals (p < 0.001) and tapered configuration (p < 0.001) as independent predictors of procedural outcome. The estimated probability of procedural success (p) is: 

\[ p = \frac{e^{y(1+e^y)}}{1 + e^{y(1+e^y)}} \]

where \( e \) is 2.72, and \( y = (-2.56 \times e^{y(1+e^y)}) + (1.29 \times \text{tapered configuration}) + (-1.35 \times \text{duration of occlusion}) + (1.00 \times \text{vessel diameter}) + 0.82. Using the jackknife method, the predictive value for procedural success (probability ≥70%) was 91% vs predictive value for procedural failure (probability <30%) was 81%. The model identified two groups, accounting for 56% of the lesions, as having an usually high (≥70%) or low (<30%) likelihood of procedural success. Conclusion: Procedural outcome of PTCA of CTO can be predicted from easily identifiable clinical and angiographic variables and allow better patient selection.

(207) POSTER

WHAT IS THE IMPLICATION OF CONVERSION TO A NEGATIVE EXERCISE TEST FOLLOWING PTCA?

Following successful PTCA, conversion to negative exercise test maintained at 6 months is often taken to indicate the absence of restenosis. We examined the rate of restenosis and the minimal lumen diameter (MLD) pre- and post-PTCA and at follow-up angiography in 70 consecutive patients with single vessel disease and a positive standardised exercise test who had converted to a negative test off treatment 6 months after PTCA. Quantitative analysis of the coronary angiograms at 6 months following PTCA demonstrated restenosis ≥50% in 16 patients (22.9%). There were no differences in demographic data, symptoms, risk factors, site of stenosis, previous MI, ejection fraction, or LVEDV before PTCA between this group (REST) and those patients who did not restenose (NON). On exercise testing before PTCA, the maximum heart rate (150±4.4 vs 151±2.6/min), systolic BP (180±4.7 vs 173±3.4/mmHg), exercise duration (8.1±0.8 vs 8.85±0.44/min) and maximum ST shift (-2.34±0.2 vs -2.50±0.17mm) were the same in REST and NON, respectively. There were no differences in the mean proximal coronary diameter (3.18±0.25 vs 3.08±0.99mm), % stenosis (72.6±2.2 vs 71.1±1.7mm), or MLD (0.78±0.08 vs 0.85±0.00mm) between the two groups before PTCA and there was an equal reduction in stenosis following PTCA (to 59.0±12 vs 19.8±17mm). At six months follow up there were again no differences between the two groups on exercise testing in maximum heart rate, systolic BP, exercise duration or maximum ST shift (-0.64±0.16 vs -0.63±0.1 mm), despite a restenosis of 63.1±3.1% in REST compared to 36.1±1.21% in NON (p = 0.001). In REST, the MLD was lower at follow up angiography than in NON (1.1±0.08 vs 1.87±0.06mm; p = 0.001) but it remained significantly greater than before PTCA (p < 0.01). We conclude that over one fifth of patients develop significant restenosis despite conversion to a negative test following PTCA.

(208) POSTER

SAVAGE CORONARY ANGIOPLASTY IN ELDERLY PATIENTS WITH A HIGH PREDICTED SURGICAL MORTALITY.
RJ Wanegedara, O Kypridoulus, JPM Feneal, S Griffin, W McCrea, PP Shaboo. Brook Cardio Unit, London, SE19 4LW.

Ischaemic heart disease in the elderly is associated with increased surgical morbidity and mortality. We reviewed the outcome of coronary angioplasty (CA) in 40 consecutive patients (22 males, 18 females) over the age of seventy (median age 70.7±7.7 years) in whom the a priori risk for coronary surgical mortality was assessed using the Parsonnet scoring system. 23 patients (57.5%) were considered unsuitable for coronary artery bypass graft (CABG) surgery and form the salvage angioplasty coronary artery bypass graft (SCA) group. All these patients were either refused operation by a cardiac surgeon because of poor left ventricular function (EF <20%) and/or extremely diffuse coronary disease; or, despite operability, were considered unlikely to benefit from CABG surgery for similar reasons (n=10). One of these patients had cardiogenic shock needing intra-aortic balloon support and ventilation. The remaining 17 patients (42.5%) were considered equally suitable for either CABG surgery or CA (non-salvage group, NSCA). The predicted surgical mortality for all patients was not less than 17% (33.7%). There was no difference between the SCA and NSCA groups. All vessels suitable for angioplasty were treated (diseased vessels per patient 2.4±0.8, treated vessels per patient 1.4±0.6). Primary angiographic success was achieved in 81/86 (91.1%) vessels attempted (SCA=88.2%; NSCA=95.4%, p<NS). Myocardial infarction occurred in 4 patients (10%), primary emergency CABG surgery in one patient (2.5%) and emergency stent implantation in one patient (2.5%). One patient died as a result of CA (2.5%). Primary clinical success was achieved in 32/40 (80%) patients before hospital discharge (SCA=73.9%; NSCA=88.2%; p<NS). During follow-up, mean 7.1±3.9(range 2-15) months five patients (12.5%) required elective CABG surgery for recurrence or significant restenosis. A significant restenosis was defined by a lesion in functional class [Canadian Cardiovascular Society] or angioplasty, from 3.2±0.8 mm to 1.6±0.06 mm past CA (p<0.001) was observed. We have shown that coronary angioplasty is relatively safe and effective as a salvage procedure in elderly patients refused surgical revascularisation or who carry a high surgical risk for elective CABG surgery (predicted mortality 25% versus actual mortality 2.5%, p<0.001).

(209) POSTER

PRIMARY CORONARY ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION: DIRECT IDENTIFICATION AND TIME COURSE OF FREE RADICAL PRODUCTION DETERMINED BY ELECTRON PARAMAGNETIC RESONANCE SPECTROSCOPY

In animal models oxygen-derived free radicals have been found to be important mediators of reperfusion injury to ischemic myocardium. However in man there is no direct evidence of free radical production after restoration of coronary artery patency and there is uncertainty how animal models relate to human studies. We have used primary coronary angioplasty for acute MI as a model of acute reperfusion to assess direct free radical levels. Nine patients (mean age: 58.3 years, range 47-66) undergoing successful primary angioplasty for acute MI (3 LD; 1 Intermediate; 5 RCA) of less than 6 hours duration (mean: 3.19 hours, range 2.1-5.0) had various sampling using the spin trap a-phosphyl N-tert-butylnitro. Samples were taken from the base of the right atrium/coronary sinus before angioplasty, and at timed intervals up to 24 hours, with more frequent sampling in the early period following recanalisation. Each sample was analysed by electron paramagnetic resonance spectroscopy. The pre-intervention mean free radical signal level lay above our control range (p <0.01). This was followed by a marked increase soon after recanalisation reaching a peak at 2 hours post recanalisation. The rate of decrease was to 1.59±0.8% of the pre-angioplasty value over the next 6 hours. A late increase in free radicals up to 24 hours were also observed and may have their origin from accumulating myocardial leukocyte infiltration. Relative to the baseline a significant increase in the radical was seen at 16 hours (p<0.01) and was maintained throughout the study period. This study provides the first direct and quantitative evidence of free radical production during myocardial reperfusion in man, and supports present concepts of free radical mediated reperfusion injury. Further studies to correlate free radical release with clinical evidence of reperfusion injury are needed.
CONTRAST MEDIA INDUCED PLATELET DEGRANULATION IN PATIENTS UNDERGOING PTCA
N A F Chronos, D J Wilson, A F Rickards, U Sigwart, A H Goodall, N P Buller.
Department of Invasive Cardiology, The Royal Brompton National Heart and Lung Hospital and \*Royal Free Hospital School of Medicine, London.

Thromboembolic events complicate the use of non-ionic contrast media (CM). CM have anticoagulant properties, however the effect on platelets are less clear. During coronary angioplasty (PTCA) platelet activation may influence the development of acute occlusion and restenosis. In this study whole blood from heparinised patients (PTT>300seconds) undergoing PTCA who were taking Aspirin (300mg/day) was mixed with three different CM to investigate the effect on platelet activation. Non-ionic (Omipaque), ionic (Urografin) and low osmolar ionic (Hexabrix) CM were added to equal volumes of whole blood and incubated for 1 minute. Platelets were analysed for changes in the surface expression of two granule membrane antigens; namely P-selectin of the alpha granule and CD63 of the lysosome using fluorochrome labelled antibodies detected by a Coulter Epics II Flow Cytometer.

Platelet degranulation occurred with Omipaque, P-selectin was expressed on 76.2±5.8% (mean SEM) and CD63 on 66.4±5.9% of platelets. Urografin caused only 18.4±4.7% of platelets to express P-selectin and 29.9±9.7% to express CD63. Hexabrix caused no degranulation as compared to a normal saline control. These differences were statistically significant (p<0.001). Identical results were found in blood taken from non-ionic and saline controls and platelet degranulation was paralleled by β-Thromboglobulin and Platelet Factor 4 release. In conclusion despite routine anticoagulation and aspirin therapy non-ionic CM caused significant platelet degranulation. This does not occur with the low osmolar ionic CM (Hexabrix).

PLATELET ACTIVATION POST ANGIOPLASTY - WHEN AND WHY DOCUMENTED BY FLOW CYTOMETRY.
MR Cahill, MG Hacey, JR Dawson+, AC Newland, Department of Haematology and *Royal Free Hospital School of Medicine, London Whitechapel, London E1 1BB.

To understand the factors which trigger increased platelet activation in coronary artery disease (CAD) we have studied 15 patients (8 male; 7 female) before, during and after percutaneous transluminal coronary angioplasty (PTCA) and control patients with 35 normal controls.

Features of platelet activation are the expression of glycoprotein IIb/IIIa, and P-selectin (normally confined within platelet granules) and a change in the configuration of the platelet fibrinogen receptor, GPIIb/IIIa. A sensitive whole blood flow cytometric technique with commercially available fluorescent antibodies to P-selectin and GPIIb and PAC1 antibody to activated GPIIb/IIIa (a gift from Dr SJ Shatill) was employed. Activation antigens were measured in resting and thrombin stimulated unfixed samples and analysis commenced within 10 minutes of PTCA. Baseline platelet activation was measured a median of 4 days before PTCA. There was evidence of increased platelet activation in resting samples (mean antigens: P-selectin 1.6% (2-14%) p<0.05) and GPIIb/IIIa 6.1% (2-17% p<0.05).

Incorporation of heparin and Omipaque but prior to PTCA showed a small increase in P-selectin (6%, 1-14%) but no further increase in GPIIb/IIIa (5.3%, 2-16%) compared to baseline. A major finding was of a sharp increase in GP53 in the 1st minute after angioplasty (6.5%, 2-14%). Thrombin stimulated baseline GP53 correlated with this increase (r=0.4 p<0.05). P-selectin and GPIIb/IIIa were taken the following day 18-24 hours post PTCA and significant rises in P-selectin and GP53 expression were found. (7.8% (5-16%) and 9.1% (4-14%)) respectively. Thrombin stimulated expression was expressed in the intra-procedure samples and our in vitro studies suggest this may be due to heparin. In 8 patients studied pre and post Omipaque an increase in antigen expression was detected (p<ns).

PTCA related platelet activation which starts within minutes and increases further in the next 24 hours. Omipaque may contribute to early activation but sustained activation is caused by the angioplasty procedure.

Changes in Insulin-like Growth Factor-1 Levels During Angioplasty
Cardiological Sciences, St George's Hospital Medical School, London.

Insulin-like growth factor 1 (IGF-1) is an circulating promoter of cellular growth, the majority of which is bound to a carrier protein. We have studied whether IGF-1 levels change during angioplasty and could be involved in restenosis. In 10 patients (mean age 55.7 ± 3.9 years) angioplasty of the left anterior descending artery was performed with balloon inflations maintained at 8-10 atm for 30-90 s. Samples were taken from the coronary sinus 1) after insertion of the catheters, 2) after initial cineangiography, 3) immediately after the end of balloon deflation and 4) 5 minutes after the end of balloon deflation. Samples were assayed for total and free IGF-1.

Results: There was no significant change in the levels of total IGF-1 (pg/ml) after injection of radiological contrast or following the balloon inflation (Table). However, free IGF-1 (pg/ml) were increased following injection of radiological contrast (Urografin) but returned to baseline values in the samples following balloon inflation.

<table>
<thead>
<tr>
<th>Total IGF-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>124</td>
<td>104</td>
<td>117</td>
<td>120</td>
</tr>
<tr>
<td>SD</td>
<td>27</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Free IGF-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>15</td>
<td>20</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>SD</td>
<td>15</td>
<td>15</td>
<td>21</td>
<td>11</td>
</tr>
</tbody>
</table>

Conclusions: The results suggest that there is no acute alteration in total IGF-1 release during angioplasty. However, the binding of IGF-1 to its carrier protein is decreased by radiological contrast, leading to a rise in free IGF-1. This transient rise in IGF-1 prior to IGF-1 release could predispose to the development of restenosis at the angioplasty site.

HUMAN AND PORCINE MITRAL VALVES RELEASE NITRIC OXIDE
L Sinay, M.J.Lewis. Department of Pharmacology & Therapeutics, University of Wales College of Medicine, Cardiff.

Vascular endothelial cells generate nitric oxide (NO), from L-arginine. Cultured porcine endocardial cells have also been shown to release NO and to contain the NO synthase enzyme. The aim of the present study was to investigate whether porcine and human rheumatic mitral valves were capable of releasing NO. The mitral valves were perfused with gassed Holman’s solution at 37°C containing indomethacin (10μM), superoxide dismutase (30μU/ml) and calcium (120mM) in the absence of endothelial cells for 1 hour. Samples were collected every 5 minutes and analysed by chemiluminescence. The detector tissue for the bioassay system comprised an endothelium-denuded ring of porcine coronary artery pre-constricted with 5-hydroxytryptamine. To normalise data, at the end of each experiment the ring was relaxed by exposure to a known concentration of sodium nitroprusside (NaNP) and the surface area of the valve was measured. Under basal conditions the porcine valves released 12.9±0.85 nMNO/cm²/min (n=12) which resulted in 513±% relaxation of the detector rings (cf NaNP), this relaxation could be reversed with haemoglobin. ADP, bradykinin (BK), substance P, thrombin (TH) and A23187 each significantly (p<0.05) increased NO release to 27.63±3.7, 19.7±0.9, 16.7±1, 20.4±3.1 and 18.5±2.2 nMNO/cm²/min and this was associated with a corresponding increase in relaxation of the coronary ring, except for TH which caused no additional relaxation. Furthermore NO release and the associated relaxation could be prevented by incubation with the detergent Triton-X 100 and reduced by the NO syntheses inhibitors L-N-nomonomethylarginine, L-arginine methyl ester and L-arginine benzyl ester. Removal of calcium from the perfusate also inhibited NO release. Human rheumatic mitral valves released NO under basal conditions with large variation between valves (from 1.8±0.2 to 7.5±3.6 nMNO/min). In addition NO release occurred following stimulation with ADP and BK, although the release here was also very variable between valves (4±0.2). Incubation of the human valve with Triton X-100 prevented this release and removal of calcium from the perfusate also prevented NO release in most but not all the valves. The study shows that the endocardium of both porcine and human rheumatic mitral valves can release NO under basal and agonist-stimulated conditions, and that this release is endocardial- and calcium-dependent.
(214) POSTER

LOCAL DELIVERY OF AN ANTIBODY TARGETED ANTIPLATELET-FIBRINOLYTIC AGENT REDUCES THROMBUS FORMATION IN-VIVO: A BASIS FOR PREVENTING CLINICAL RESTENOSIS?

R S More, J Underwood, M J Brack, S Pringle, D de Bono, A H Gershlick. Academic Department of Cardiology, Glenfield General Hospital, Leicester.

The "ideal" agent to prevent interaction between blood factors and damaged vessel wall would have potent local action but no systemic side-effects. To achieve this we have produced a novel molecular conjugate ATC(3), comprising an anti-platelet glycoprotein IIb/IIIa (H(1)) with a triple conjugate (Mb), an anti-cardiovascular endothelial cell MAb (P14G11) and urokinase (Ur) with a specific U activity of 20,000 IU/mg protein. Succinimidyl 3-(2-pyridyldithio)propionate was used as the coupling reagent. Intact platelet and damaged endothelium preparations confirmed targeting of ATC(3) to platelets and damaged endothelium. Platelet aggregation (Ag) studies showed 20ug/ml of ATC(3), unlike M735 alone, completely inhibited Ag induced by ADP(20uM), collagen (4ug/ml) or thrombin (1U/ml). The antithrombotic action of locally delivered ATC(3) was compared to an unconjugated mixture of these components (Ur and urokinase alone (Ur) in an in-vivo model of vascular injury induced platelet-thrombus (rat vena cava).

Thrombus

<table>
<thead>
<tr>
<th>ATC(3)</th>
<th>UM</th>
<th>Ur</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</table>

This data shows that the triple conjugate ATC(3) significantly reduces platelet-thrombus formation in-vivo when delivered locally to the site of injury and can be targeted. Targeted thrombolytic and antiplatelet conjugates when delivered locally through leaky balloons may have a role in reducing thrombus formation following vascular injury after angioplasty and coronary stent insertion.

(216) POSTER

INHIBITION OF INTIMAL HYPERPLASIA BY HEPARIN AND AN ANGIOTENSIN II ANTAGONIST IN A RAT MODEL OF ANGIOPLASTY RESTENOSIS

S Anglin, R Jagoe, JM Polak, *JR McEwan. Dept. of Clinical Pharmacology, Medical Physics and Histopathology, Royal Postgraduate Medical School, and *the Hatter Institute for Cardiovascular Studies, University College London Medical School, London.

Fibrocellular intimal hyperplasia (FCIH), which leads to restenosis after angioplasty, is probably stimulated by a complex, interacting cascade of growth factors and cytokines. We have identified one such factor. The results of recent studies have suggested that bFGF may be identified as playing a pivotal role in the pathogenesis of the lesion. We have examined the effects of two different inhibitors of FCHI, administered simultaneously, on a rat carotid model of restenosis after angioplasty. Three days prior to injury of the left common carotid artery with a Fogarty FG2 embolectomy catheter, an osmotic minipump was implanted into the back of male Wistar rats, 300-350g and connected via cannula to the right external jugular vein. The angiotensin II (AT1) receptor antagonist, losartan, was administered at two doses, (10microg and 10mg/kg/day), both with and without heparin at a dose of 0.3mg/kg/day by the minipump. Fourteen days after injury the rats were killed by exsanguination, the blood being reserved for coagulation studies. The carotid arteries were perfusion-pressure fixed in situ and processed for sectioning and morphometric measurement using the Context Vision Image Analysis System. Results were analysed by ANOVAR and multiple comparisons made by a Fisher test.

Area of FCIH(mm²)

<table>
<thead>
<tr>
<th>Losartan dose</th>
<th>Heparin</th>
<th>Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0176±0.0187 (n=3)</td>
<td>0.0154±0.014 (n=3)</td>
</tr>
<tr>
<td>10mg/kg/day</td>
<td>0.112±0.006 (n=3)</td>
<td>0.066±0.034 (n=3)</td>
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</tbody>
</table>

These results demonstrate that very low doses of losartan as well as high doses inhibit the development FCHI after vascular injury. In these animals heparin may have effects additive to those of losartan, though variability of the lesion means that further rats need to be examined in this group. Control of restenosis after angioplasty in patients may also require simultaneous administration of more than one drug.

(215) POSTER

CAN NITRIC OXIDE MODIFY THE PATHOPHYSIOLOGY OF VASCULAR INJURY?

P H Groves. University of Wales College of Medicine, Cardiff.

Balloon angioplasty causes plaque rupture, mural dissection and local platelet-thrombus formation. The reparative response involves the proliferation and migration of smooth muscle cells (SMC) which, if excessive in the clinical context, may result in restenosis. Adherent platelets are an important source of growth factors which stimulate vascular SMC. Nitric oxide (NO) inhibits platelet adhesion and also SMC proliferation in vitro. The effects of exogenous NO on the vascular response to angioplasty were therefore investigated.

The NO donor SIN-1 was shown to increase platelet cyclic GMP (p<0.005) and reduce platelet adhesion (p<0.005) and platelet-thrombus formation (p<0.05) at the site of pig carotid angioplasty. The time course of subsequent intimal thickening and SMC proliferation was then characterized and both were shown to be closely related to internal elastic lamina (IEL) rupture. Molsidomine (whose active metabolite is SIN-1) was shown to increase arterial wall cyclic GMP (p<0.05). When the IEL remained intact ("superficial" injury) molsidomine reduced intimal (p=0.01) and medial (p<0.05) SMC proliferation, but when it was ruptured ("deep" injury) proliferation was uninfluenced by molsidomine. Molsidomine did not reduce intimal thickening. These results provide the first evidence that NO inhibits platelet adhesion and SMC proliferation in vivo at sites of vascular injury. They also showed that intimal SMC proliferation is maximal at sites of IEL rupture and that the anti-proliferative effects of NO are overwhelmed in the presence of deep injury.

(217) POSTER

PERSISTENCE OF GROWTH FACTOR EXPRESSION AFTER VASCULAR INJURY IN A MODEL OF ANGIOPLASTY: AN EXPLANATION FOR INCREASED RESTENOSIS RATE AFTER EARLY REPEAT ANGIOPLASTY?


Rates of restenosis after early repeat angioplasty are reported to be higher than the restenosis rate following the first procedure (approximately 30% v 38%). Autocrine growth factor production by stimulated smooth muscle cells (especially intimal cells) may be an important factor in this process, with persistence of elevated growth factor levels at the time of the repeat angioplasty. We therefore evaluated the persistence of bFGF (basic fibroblast growth factor) in a rabbit model of balloon induced vascular injury at 2 hours, 3 days, 7 days, 14 days, 1 month and 3 month (n=2 for each time period). bFGF was detected using a monoclonal antibody, F-3393 (Sigma).

<table>
<thead>
<tr>
<th>Time</th>
<th>% cells positive for bFGF</th>
<th>Intima/Media</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intima</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ratio</td>
</tr>
<tr>
<td>Control</td>
<td>2.9 (0.6)</td>
<td>-</td>
</tr>
<tr>
<td>2 hours</td>
<td>7.5 (3.9)</td>
<td>-</td>
</tr>
<tr>
<td>3 days</td>
<td>10.9 (0.2)</td>
<td>-</td>
</tr>
<tr>
<td>7 days</td>
<td>46.2 (2.1)</td>
<td>10.2 (8.8)</td>
</tr>
<tr>
<td>14 days</td>
<td>30.4 (12.4)</td>
<td>55.2 (7.3)</td>
</tr>
<tr>
<td>1 month</td>
<td>24 (0.2)</td>
<td>16.4 (1.8)</td>
</tr>
<tr>
<td>3 months</td>
<td>23 (7.0)</td>
<td>30.9 (9.0)</td>
</tr>
</tbody>
</table>

In this vascular injury model intracellular bFGF became elevated soon after injury and remained elevated (in intima and media) up to 3 months after the procedure. Thus smooth muscle cells are in an increased state of "readiness": if repeat injury is carried out potentially high levels of bFGF may be released locally. This may provide part of the explanation for the higher restenosis rates observed after early repeat angioplasty.
Delivered Contractile Recovery Following Intracellular Acidosis in Perfused Heart: A A Grace, P J Metcalfe, P L Weissberg and J J Vandenberg Departments of Biochemistry and Medicine, University of Cambridge

Reduction in both myofilament calcium sensitivity and maximal calcium-activated force contribute to the decline in contracture during intracellular acidosis resulting from myocardial ischemia and could also underlie stunning. To test the hypothesis that acidosis per se may contribute to stunning we investigated the relationship between recovery of contractile force and pH during reperfusion. Pressure (LVPD) following an isolated proton load in the in situ Langendorff-perfused ferret heart. Intracellular acidosis was induced by NH₄Cl preflush (10 mM, 10 min) pHi was estimated from a NP nuclear magnetic resonance (NMR) signal of deoxyglucose-6-PDQ. Recovery of pHi (ΔpHi) and LVPD (ΔpHi/Baseline) from hearts (n=6) perfused with normoxic HCO₃⁻-free (HEPES, 5 mM) solution paced at 1 Hz. A recovery (min): pHi = 4.3 ± 1.0; LVPD 12.2 ± 2.0 (p<0.05). Changes in LVPD closely followed those in pHi during NH₄Cl exposure but after washout of NH₄Cl recovery of LVPD was significantly delayed compared to pHi. ATP, [PCr] and [Pi] showed no significant changes throughout and an independent effect of pHi has been excluded by the absence of adverse effect on contracture at normal pH during continued exposure.

In conclusion, as intracellular acidosis results in a rise in intracellular calcium concentration and sodium influx occurs during pH recovery this study suggests that delayed contractile recovery is a result of reduced myofilament calcium sensitivity. Intracellular acidosis occurring during ischemia is therefore likely to contribute to early post-ischemic ventricular dysfunction (stunning). This may be mediated either directly or indirectly possibly as a result of the modification of the Ca²⁺ sensitive phosphorylation status of the contractile proteins.

Post-Ischaemic Contractile Dysfunction: Sub-Cellular Damage Due to Hypochlorous Acid and Superoxide.

N G MacFarlane, M A Denerv, D S Steele & D J Miller Institute of Cardiovascular Science, Glasgow University, and Departments of Biochemistry and Medicine, Glasgow Royal Infirmary, Scotland.

Generation of free radicals/reactive oxygen species and disruptions to excitation-contraction coupling are among the mechanisms which have been proposed for post-ischemic contractile dysfunction. Neutrophils play little role in the contractile dysfunction seen on reperfusion after short periods of ischemia, but may be of importance after late reperfusion. We investigated the actions of the superoxide anion (O₂⁻) and hypochlorous acid (HOCI), which are released upon neutrophil activation, on the function of the contractile proteins and the sarcoplasmic reticulum (SR) in Triton- or Saponin-treated rat ventricular muscle.

At physiologically relevant concentrations, and after short incubation periods, both O₂⁻ and HOCI depress maximum calcium-activated force (Cmax) in Triton-treated preparations e.g. a one minute exposure to 10μM HOCI reduced force by 18.85±5.8% (n=8). Myofilament calcium sensitivity was assessed by measuring isometric force at calcium concentrations which produced sub-maximal responses. O₂⁻ depressed peak force without altering calcium-sensitivity and also slowed rates of activation and relaxation. HOCI depressed Cmax and paradoxically increased the calcium sensitivity of the contractile proteins e.g. 50μM HOCI decreased the calcium concentration required for half-maximal activation by 0.24±0.07 log units (n=5). In addition rates of force and relaxation were slowed and resting tension increased with HOCI treatment. Using Saponin-treated preparations O₂⁻ does not affect the ability of the SR to load or release calcium while HOCI depresses Cmax and accelerates the decay of calcium in the sarcoplasmic reticulum (SR) measured by Indo-1 fluorescence.

In summary, while both of these oxidative species depress Cmax, HOCI additionally depresses both resting tension and calcium sensitivity. O₂⁻ has no effect on the latter two parameters. HOCI further contributes to excitation-contraction uncoupling by depleting calcium release from the SR. These results are consistent with the systolic and diastolic abnormalities observed clinically in post-ischaemic myocardium.


Current methods for detection of viable myocardium (VM) in dysfunctional segments are based on the release of markers of necrosis, but our data suggest that enhancement of regional systolic function predicted recovery of contractile function. The purpose of this study was to determine the accuracy of dobutamine echocardiography for prediction of VM in 19 pts (17M, 2F, age 52±11) with previous anterior wall Q waves, who underwent revascularization (RVD) with angioplasty (n=8) or bypass surgery (n=11). Dobutamine echocardiograms were acquired with on-line digitization before RVD, 1 month after RVD was performed before myocardial infarction and 0.24±0.04 mg/kg/min, with 3 minute dose increments to 10 mg/kg/min. Dobutamine was given to achieve a maximum dose, or development of severe ischemia, or severe side-effects. Images were interpreted by observers blinded to the clinical parameters of those in pHi and HOCI. We also determined the effect of NH₄Cl on ischemia.

In conclusion, the contractile dysfunction induced by HOCI further decreased pHi and HR was significantly decreased compared to pHi. ATP, [PCr] and [Pi] showed no significant changes throughout and an independent effect of pHi has been excluded by the absence of adverse effect on contracture at normal pH during continued exposure.

In conclusion, as intracellular acidosis results in a rise in intracellular calcium concentration and sodium influx occurs during pH recovery this study suggests that delayed contractile recovery is a result of reduced myofilament calcium sensitivity. Intracellular acidosis occurring during ischemia is therefore likely to contribute to early post-ischemic ventricular dysfunction (stunning). This may be mediated either directly or indirectly possibly as a result of the modification of the Ca²⁺ sensitive phosphorylation status of the contractile proteins.


To investigate the integrity of the beta adrenergic system in stunned myocardium, 8 open-chest dogs were subjected to 5 min LAD occlusions and 10 min reperfusion, with a final 90 min reperfusion. Stunned regions (S) were identified as asynergic segments on 2D-echocardiography (ECHO). Regions with normal wall motion were used as controls (C). In 4 animals, myocardial blood flow (MBF, ml/min/g) and oxygen consumption (MMRO₂, ml/min/g) were measured non-invasively by positron emission tomography using the previously validated H₂²¹O and O₂ inhalation techniques, respectively, both at rest and after infusion of isoproterenol (ISO, 0.1 μg/kg/min). No significant differences between C and S were observed for both resting MBF (0.85±0.21 vs 1.02±0.34, mean ± SD) and MMRO₂ (0.15±0.06 vs 0.15±0.01). After ISO, MBF (1.30±0.40 vs 1.30±0.26) and MMRO₂ (0.30±0.13 vs 0.33±0.12) increased similarly in both C and S, and were associated with similar levels of hypercontractility in C and S assessed by ECHO. Absence of tissue necrosis in S was confirmed by post-mortem TTC staining and by the perfusible tissue index (a previously validated measure of tissue viability calculated from the PET data) being close to normality (0.98±0.04). In the other 4 animals, the hearts were removed after the final reperfusion period and beta adrenoceptor density (Bmax, fmol/mg protein) and affinity (Kd, pM) were measured in C and S biopsies from remote and stunned myocardial membrane preparations. Both Bmax (114±32 vs 136±41) and Kd (117±58 vs 123±37) were similar in C and S, respectively. In conclusion: 1) both resting MBF and MMRO₂ were unchanged in stunned regions despite depressed contractile function; 2) beta adrenoceptor density and affinity were unchanged in stunned myocardium; 3) stunned myocardium had a normal metabolic and contractile reserve in response to the beta agonist isoproterenol, suggesting that the beta adrenergic signal transduction pathways were intact. These data provide an in vivo demonstration of the integrity of the beta adrenergic system in stunned myocardium.
(222) POSTER

PROPHYLAXIS AGAINST THROMBO-EMBOLIC EVENTS: RESULTS OF A SURVEY OF BRITISH CARDIOLOGISTS.
JGF Cleland, E Sharouni, CM Oakley, G Sutton, A Fletcher, C Bulpitt, P Poole-Wilson.
Departments of Cardiology, Hammersmith Hospital and Hillingdon Hospitals and the National Heart and Lung Institute, London.

Recommendations for the use of anticoagulant prophylaxis in patients with heart failure derive from reports suggesting a high incidence of thrombo-embolic events in such patients which may be reduced by coumarin anticoagulants, but no controlled trial has been published. Anti-coagulant therapy is an expensive treatment to administer and is attended by a significant hazard. The present survey sought to discover cardiologists' attitudes to the use of warfarin or anti-platelet therapy in patients with heart failure of various aetologies. 598 questionnaires were sent out to members of the British Cardiac Society and 345 (58%) replies received, 329 of which indicated, in response to a test question, that they would usually (95%) anti-coagulate patients with atrial fibrillation and mitral stenosis. Responders were equally divided as to whether systemic emboli were a common problem in patients with heart failure (47% yes; 49% no). Most cardiologists indicated that they would not usually anti-coagulate patients with heart failure due to dilated cardiomyopathy (24%) or ischaemic heart disease (3%) in sinus rhythm, but were more likely to use warfarin if atrial fibrillation was present (74% and 33% respectively). Reasons given for not prescribing anti-coagulants were fear of complications of therapy (54%), inconvenience for the patient (17%), lack of importance of emboli (13%) and lack of manpower resources (9%). 52% of respondents considered anti-platelet agents as ineffective in preventing embolic events and 86% considered them less effective than warfarin, while few considered them as (5%) or more effective than warfarin. This survey suggests that most cardiologists believe there is not enough evidence that anti-coagulant therapy is of sufficient benefit to outweigh the hazards and costs of its administration to the majority of patients with heart failure.

(224) POSTER

EARLY EXPERIENCE WITH A MOBILE CARDIAC CATHETERISATION LABORATORY IN THE UK
AW Nathan, LM Shapiro, D Eddy, PM Schofield, AR Cunningham.

In the UK, cardiac catheterisation is only available at 49 NHS hospitals (18 in London) and 12 private hospitals (6 in London). Many trained cardiologists, particularly in District General Hospitals (DGH), have little access to these facilities. A mobile catheterisation service has been initiated, to operate at hospitals in the UK. The laboratory is installed in a 12.8m articulated vehicle which can be parked on any suitable flat road. Connections are necessary for power, water, drainage and the hospital telephone system. It is air conditioned, and has a back-up generator. The operating area has expanding sides and the vehicle is ready for work in less than 30 minutes. Patients enter via a motorized lift in a chair or trolley. The x-ray equipment is a standard, state-of-the-art, mobile digital system, capable of working in any projection, recording onto video or onto an on-board x-ray laser printer. Full resuscitation equipment is carried. The unit is capable of cardiac, neurological and vascular procedures, and can be used for interventional work if appropriate back-up is available within the hospital. It is staffed by an experienced team of radiographer, nurse and technician.

A total of 62 patients (49 males), aged between 34 and 77 (mean 57), have been investigated in hospitals without a permanent laboratory, with up to 7 cases being studied in a half day session. Left heart catheterization were performed in all cases, with right heart catheterization in 3. A femoral approach was used in 54, and brachial in 8. Coronary disease was suspected in 59 (grafs in 5), with valve disease in 2 and cardiomyopathy in 1. Procedure times (time on vehicle) varied from 17 to 68 (mean 29.2) minutes, with fluoroscopy times of 0.9 to 8.1 (mean 2.5) minutes. There were no major complications: 2 patients were vasovagal requiring atropine, transient LBBB was seen in 1, and 1 had a small haematoma. Mobile catheter laboratories can operate safely and cost effectively, and can be used in the DGH, or for overflow in cardiac centres including during temporary shutdown of existing facilities.

(223) POSTER

SURVEY OF ACUTE MYOCARDIAL ISCHAEMIA AND INFARCTION (S.A.M.I.I): DELAYS TO TREATMENT
T J Bowker, R M Boyle, K M Fox, J M Murphy, D A Wood on behalf of the SAMI I Study Group.
Clinical Epidemiology, National Heart & Lung Institute, University of London.

The variation in delays to treatment in patients admitted to district general hospitals (DGH) with acute myocardial ischaemia and infarction is not known. A prospective survey of admissions to a random sample of 23 out of 202 DGHs in the UK was undertaken. The DGHs each agreed to identify 10 consecutive patients (<70 years) admitted with a first working diagnosis of acute myocardial ischaemia or infarction, for which management was to be given. The first 17 hospitals ascertainment 122 males and 52 females (mean age 58 years) in a median survey duration of 9 days. The median time lag (and 75th centile) from onset of patients' symptoms to seeking medical advice was 1 hour (3.75), to receiving advice 1.6 hours (4.67), to arrival at hospital 2.5 hours (7), to admission to hospital 3.25 hours (6.5) and to initiation of treatment 3.7 hours (7.75). 40% of patients were given thrombolysis, 37% as initial management plan and 3% subsequently. In thrombolysed patients, median delay from symptom onset (and 75th centile) to seeking medical advice was 0.75 hours (1.75), to receiving advice 1.25 hours (2.3), to arrival at hospital 2.3 hours (4.5), to initiation of treatment 3.75 hours (4.6) and as subsequent plan 9.9 hours (23.9). Overall, median delay from symptom onset to thrombolysis was 4.5 hours (8.25). After the patients seek medical advice there is considerable variation in delays to treatment which could be improved, particularly for patients eligible for thrombolytic therapy.

(225) POSTER

Routine Transtelephonic Electrocardiographic Monitoring And Cardiac Assessment In Primary Healthcare Environment
D Shaniit R Niran R.A Greenbaum
Cardiovascular Research Unit, Edgware General Hospital Edgware.

To assess the viability of an on-line transtelephonic cardiac diagnostic service for General Practitioners (GP) in terms of quality, efficacy, convenience and cost-effectiveness as well as its impact on referral patterns for specialist services - we have offered 20 general practices and health centres totalling 87 GPs and serving a population of about 250,000 in north London the use of a miniaturised hand-held transtelephonic standard 12 lead electrocardiograph (ECC) transmitter and direct access around the clock to cardiological and ECC interpreters for the routine assessment of patients in their daily practice. When required they were to transmit from their practice or from their patients' homes, over ordinary phone lines, an ECC coupled with details of the patient's history, symptoms, medication, activity prior to symptom onset and reason for consultation which were documented and an ECC registered. A brief consultation offered by a cardiologist or staff grade physician - followed and a full report including ECC strips was then sent to the GP. If required, appointments for further investigations could then be made on-line. The automatic small and light (400 gram) ECC transmitter equipped with a patient harness for simple, easily applied, lead placement by the GP or his nurse, offered quick frequency modulated transmissions over ordinary phones requiring no dedicated interface. A total number of 1272 consultations have been made over a period of 6 months. Of these, 165 patients (13%) had symptoms suggestive of acute ischaemia. Significant ST depression was found in 60 (4.7%), patients while significant ST elevation was found in 51(4.6%) patients. 16(1.2%) patients have been diagnosed as acute myocardial infarction. 58(4.6%) had symptoms suggestive of arrhythmia, presenting 44 (3.4%) with atrial fibrillation, 6(0.4%) supraventricular tachycardia and one accelerated junctional rhythm. 3 patients presented ventricular bigeminy. Consultations could be classified into 4 categories: normal ECC; mild disorders requiring no further investigation; referrals for further assessment indicated; urgent or immediate hospitalisation indicated. We conclude that the application of transtelephonic cardiac diagnosis and ECC interpretation service is simple effective and efficacious in routine primary care. It offers consultation and supports the decision making process of GPs. It results in early detection of heart disease, on-line assessment of suspected acute events, adequate filtering and priority grading of referrals for patients requiring further investigation while reducing the load of unnecessary referrals for primary diagnosis.
(226) POSTER

PTCA: CAN WE AFFORD THE EXPERIENCE?
Wessex Cardiac Unit, Southampton General Hospital.

For purchasers and providers of healthcare to agree contracts it is essential that services are accurately costed. To determine the average cost of equipment used during a coronary angioplasty (PTCA) procedure we have analysed our first 5000 cases (1983-1991) on an intention to treat basis, and divided them into three consecutive cohorts, giving a breakdown of PTCA hardware used and its mean cost based on average 1992 prices.

<table>
<thead>
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<th>Procedure no. 0-500</th>
<th>501-1000</th>
<th>1001-1500</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.26</td>
<td>1.54</td>
</tr>
<tr>
<td>Range</td>
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<tr>
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<td>693</td>
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<tr>
<td><strong>Guiding catheters</strong></td>
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<tr>
<td>Mean</td>
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<td>1.40</td>
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<tr>
<td><strong>Guide wires</strong></td>
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<td>Mean cost (£)</td>
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<td>97</td>
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<td><strong>TOTAL MEAN COST (£)</strong></td>
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<td>901</td>
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With increasing experience, more complex PTCA procedures have been undertaken, such that single lesion PTCA accounted for 70% of the first cohort of (1-500) but only 48% of the last (1001-1500). As a consequence more equipment has been used, with an increase in cost of 31%. Prospective audit of case mix and PTCA equipment used is essential if accurate costing of contracts is to be achieved.

(227) POSTER

AUDIT OF DEMAND FOR INTERVENTIONAL CARDIAC ASSESSMENT AND THERAPY WITHIN THE TOWN OF ROCHDALE
M.Coupe, C.Buresh, Department of Cardiology, Birch Hill Hospital, Rochdale.

Assessment of demand for interventional cardiac therapy is often blurred because of varying referral patterns within and between towns and cities. We report the experience from Rochdale over 30 months where it can be shown that nearly all (98%) of patients pass through the hands of a single cardiologist. The catchment population of Rochdale is 200,000 and between Mar 1990 and Oct 1992, 521 patients were referred for interventional assessment (excluding pacemakers). Patients were referred on the basis of uncontrolled symptoms or a positive exercise test before 5 minutes (Bruce protocol). In particular, patients with uncomplicated myocardial infarction or controlled angina with negative or late positive exercise tests were NOT referred.

Of the 521 referred, 73 were transferred on an urgent basis. 40 patients did not receive cardiac catheterisation for personal and logistic reasons. 66 patients are still waiting. Of the 415 patients receiving cardiac catheterisation, 220 (53%) required surgery, 117 (28%) were not suitable for surgery and 35 (8.4%) had normal coronary arteries. Of the 220 patients requiring surgery, 142 were for severe valve regurgitation, 12 severe valve stenosis, 17 for coronary stenosis and 15 miscellaneous conditions.

Thus, allowing for those people on the waiting list, the present requirement for cardiac investigations in Rochdale is 102 per year or 510 per million population per year.

This accords well with the Cardiac Society recommendation of 500/million per year and is greatly in excess of the present woeful funding of 300/million per year in the North West Region.

(228) POSTER

AN AUDIT OF ATRIAL FIBRILLATION IN A DISTRICT GENERAL HOSPITAL
G Y H Lip, K N Tean, F G Dunn.
Department of Cardiology, Sibbhill General Hospital, Glasgow.

Atrial fibrillation is a common presenting dysrythmia among acute medical admissions. However, we have observed wide variation in its management among general physicians. To explore this further we conducted a prospective audit of emergency medical admissions to a district general hospital who were found to be in atrial fibrillation. Over a six month period, there were 170 patients (100 female (59%), 70 male (41%); age range 38-95 years; mean 73.5 years, standard deviation (s.d.)10.6) admitted with atrial fibrillation. Cardiac failure was present on admission in 61 (36%), cerebrovascular events in 23 (14%) and myocardial infarction in 17 (10%). Of those previously noted to be in atrial fibrillation [102 (60%)] with pauses) therapy on admission included digoxin in 71 (70%), warfarin in 20 (20%) and aspirin in 17 (17%). Of those not previously noted to be in atrial fibrillation [88 patients, (40%)], digoxin was used in 51 patients (75%), whilst amiodarone was used in 23 cases (34%). Overall there was also a surprisingly low rate of introducing anticoagulation (7% of those not previously on warfarin) and attempted cardioversion [16 (9%), 14 pharmacological, 2 electrical]. Complete information on length of stay and investigations undertaken was available for 146 patients (86%). The mean inpatient stay was 16 days (s.d. 19.7, range 1-154 days) largely due to the patients with stroke. In these 146 patients, thyroid function tests and echocardiography were performed in 92 (63%) and 48 patients (33%) respectively. These results indicate a suboptimal application of standard investigations in patients with atrial fibrillation and a reluctance to perform cardioversion or commence anticoagulant therapy, both of which are playing an increasingly prominent role in the management of this group of patients.

(229) POSTER

LIMITED VALUE OF A COMMUNITY TRAINING PROGRAMME IN CARDIOPULMONARY RESUSCITATION
C F M Weston, M D I Donnelly, D W Hughes.
Department of Cardiology and Epidemiology, Institute for Health Promotion, University of Wales College of Medicine.

Cardiopulmonary resuscitation (CPR) initiated by bystanders who witness pre-hospital cardiac arrest increases the likelihood of a successful outcome. In order to estimate the impact of a thorough community CPR training programme upon overall cardiovascular mortality, we reviewed all adult deaths in Cardiff (pop 272,600) during 3 months (Dec 91 - Feb 92). We performed a retrospective survey of death certificates, coroner's, medical and ambulance report forms with telephone interview of general practitioners where appropriate.

In the 13 weeks there were 701 deaths, of which 158 were cardiac (ICD 401-429, la-lc). After excluding cases of congestive heart failure, cardiogenic shock, haemopericardium and in-hospital cardiac arrest there were 70 pre-hospital cardiac arrests (44% of all cardiac deaths). 34 of these deaths were witnessed. In 22 cases the CPR was performed by citizens; we label these as "potentially preventable deaths".

Excluding seasonal variations, this extrapolates to 68 (3/10,000 pop) "potentially preventable" cardiac deaths per year. Our (unpublished) ambulance paramedic resuscitation rate following citizen CPR is 7.1% survival. This corresponds to a possible annual saving of an extra 6 lives (0.2/10,000 pop) and 16 reduction in cardiac mortality.
(200) POSTER

DELAYED REFERRAL AS A POSSIBLE CAUSE OF CORONARY ARTERY DISEASE MORTALITY AND MORBIDITY AMONGST SOUTH ASIANS

N Shaukat, D P de Bono
Department of Cardiology, University of Leicester, Leicester

Despite the fact that coronary artery disease (CAD) is a striking cause of mortality and morbidity in South Asians, there is little information on either uptake or access of care for this high risk group. We compared a consecutive series of 80 South Asians who had undergone coronary angiography at out unit over a two year period, with white case controls studied in the same unit over the same period of time (matched for age, sex and severity of coronary artery disease). There were no significant differences in the two groups with respect to conventional risk factors such as smoking, obesity, hypertension, total cholesterol, HDL cholesterol, total triglycerides and insulin. "Typical" anginal symptoms (as assessed by a cardiologist) were significantly higher for both South Asians and whites with CAD compared to those with normal coronary arteries (p<0.001 for both ethnic groups). There were no significant differences in symptomatology and documented positive exercise test between South Asian and whites (with and without CAD). The mean interval between the onset of anginal symptoms and first consultation in cardiology outpatient clinic was much greater (mean 17.43 months vs 6.86 months, p=0.0002) in South Asian patients compared to whites. There is little evidence that symptoms or perception of CAD are different in SA patients. The striking difference in referral delay seen in South Asian patients in Leicester compared to whites, could significantly increase their morbidity and mortality from CAD and requires urgent investigation.

(230) POSTER

CARDIOVASCULAR RISK FACTORS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY (CABG)

G.W. Tait, G.W. Lindsay, C.J. Packard, J Shepherd, A.A. Lordieer
Departments of Pathological Biochemistry and Medical Cardiology, Royal Infirmary, Glasgow, Scotland

It is widely accepted that secondary prevention of coronary disease is more cost effective than primary prevention. Previous studies have shown that the attrition rate of venous bypass grafts is related to pre-operative risk factors, and that the rate of progression of atherosclerosis in both the native vessels and the bypass grafts can be altered by reduction of these factors. It is not clear however to what extent risk factors are being addressed in this high-risk group. We have examined the principal cardiovascular risk factors in 542 patients undergoing coronary artery bypass graft surgery during a period of 38 months. Data on past history, family history, medication, cigarette usage and alcohol consumption was collected by a structured questionnaire. Blood pressure, serum lipids, height and weight were assessed at the time of admission for surgery. 81% of our subjects were men, with a mean age of 56 years (SD 8.5). 55% had a history of prior myocardial infarction, and 77% had previously undergone either CABG or coronary angioplasty. 401 (74%) admitted to a history of smoking, although 95% of these were no longer smoking at the time of surgery. 5.7% had systolic hypertension (≥160 mmHg), and 5.5% a diastolic pressure in excess of 95 mmHg. Mean total cholesterol was 6.23 mmol/l (SD 1.13); 83% of subjects had total cholesterol above 5.2 mmol/l, 34% above 6.5, and 8% exceeded 7.8 mmol/l. Of the 203 patients with a history of hyperlipidaemia, 44% had HDL cholesterol and 5.1% total cholesterol above 6.5 mmol/l, but only 23% of these were taking hypolipidaemic treatment. Dyslipidaemia is the most common modifiable risk factor identified in this survey. Appropriate intervention is frequently not applied, and this omission is likely to result in increased recurrence of symptoms and the need for further revascularisation.

(232) POSTER

FAMILY HISTORY AS AN INDEPENDENT RISK FACTOR OF CORONARY ARTERY DISEASE

E D Grech, C L Bray, E B Faragher, D R Ramsdale
The Cardiothoracic Centre, Liverpool, and The Regional Cardiac Centre, Wythenshawe Hospital, Manchester

In coronary heart disease, family clustering is too strong to be ascribed wholly to chance, and the familial occurrence of coronary atherosclerosis has been well documented in both family and twin studies. The relationship between family history of ischaemic heart disease and the presence of coronary artery disease was studied prospectively in 387 patients undergoing routine coronary arteriography prior to valve surgery. 107 patients (27.6%) had a family history of ischaemic heart disease. Of these, 52 (48.6%) patients had significant (one or more coronary artery narrowing ≥ 50% of luminal diameter) coronary disease, compared with 60 of 280 (21.4%) patients with no family history (p<0.001). The presence (one or more stenosis ≥ 50%) and extent of significant coronary disease (number of affected vessels) was greater in those patients whose brothers (p<0.001), sisters (p<0.001), fathers (p<0.001) and mothers (p<0.001) had a family history of ischaemic heart disease. No such association was found in second degree relatives. Moreover, the incidence of significant coronary disease increases as the number of relatives with ischaemic heart disease increases (p<0.001). Multiple logistic regression analysis suggests that family history is an independent predictor of the presence of significant coronary heart disease. Other independent predictors are diastolic blood pressure, smoking status, severity of angina and total-HDL cholesterol ratio. Although the precise mechanisms underlying familial predisposition remain ill-defined, this study confirms an important correlation between a family history of ischaemic heart disease in first degree relatives and the presence of coronary disease, as previously suggested by others.

(233) POSTER

PERFORMANCE OF AN ESTABLISHED SYSTEM OF FIRST RESPONDER OUT-OF-HOSPITAL DEFIBRILLATION.

THE SECOND YEAR OF THE HEARTSTART SCOTLAND PROJECT

M. Sedgwick, K Dalziel, J Watson, D J Carrington*, S M Cobbe
Department of Medical Cardiology, Royal Infirmary and Scottish Ambulance Service, Glasgow

The Heartstart Scotland project for out of hospital defibrillation covers a population of approximately 5,102,400 (48.3% male, 14.9% >65yrs). All 395 ambulances in Scotland are equipped with an automated external defibrillator and all crews are trained in basic cardiopulmonary resuscitation (CPR) and defibrillator use (EMT-D). Between 1/5/90 and 30/4/91 a total of 1700 cardiac arrests were reported by the ambulance service. Of the 1676 arrests which we could trace, 63% were witnessed and 63% occurred at home. A total of 1383 (83%) of all patients were declared dead on arrival at hospital or in the emergency department, 119 (7%) died in hospital, 174 (10%) were discharged alive and 145 (9%) were alive at one year. Of the 174 survivors to hospital discharge, 87% were conscious and normal at discharge, 9% had moderate residual disability, 2% severe disability and we had no data on 2%. Defibrillation was undertaken in 71% of the reported cardiac arrests. Bystanders attempted CPR in 28 % of cases overall and 43% of bystander witnessed arrests. Survival of bystander witnessed arrests was increased from 7% to 15% with bystander CPR (p<0.005). If the cardiac arrest was witnessed by the ambulance crew and required defibrillation, survival to discharge was 39%. Of bystander witnessed defibrillated arrests (n=643), 11% were discharged alive. In the witnessed non shocked group (n=168), 5% survived to discharge. No patient presenting with an asystolic or bradycardic arrest survived. In the unwitnessed shocked group (n=269) 4% survived to discharge and in the unwitnessed non shocked group (n=205) there were no survivors. Patients who were defibrillated within 4 minutes of arrest had a 43% survival rate to hospital discharge. The median call response interval of our system was 7min with 50% of cases reached between 5 and 10 min. This study demonstrates the importance of early defibrillation and bystander CPR in the management of out-of-hospital cardiac arrest.
LIPOPROTEIN (A) IS NOT A PROGNOSTIC INDICATOR OF FUTURE CARDIAC EVENTS POST CORONARY ARTERY BYPASS GRAFTING.

Angela Brown, Melanie Davies, Richard Wray.

St.Helens Hospital, Frederick Road, Hastings, E.Sussex.

Lipoprotein (a) (Lp[a]) levels >30mg/dl may be a cardiovascular risk factor. Lp(a) was assessed for use as a predictor of future cardiac events post coronary artery bypass grafting (CABG). Fasting blood Lp(a) was measured, (Rocket electrophoresis, Immuno, Wein, with a CV of 6% and a lower detection limit of 5mg/dl) in 190 patients post CABG (0.4 to 17yrs earlier) and a control group of 101 age and sex matched normals (no family history of IHD, normal ECG’s).

Myocardial infarction, unstable angina, an angioplasty or re-operation were taken as further events post CABG. The Mann Whitney U test was used for comparison and the 75th percentile quoted. Lp(a) levels were significantly higher in the subjects post CABG compared with controls (61 vs 23 mg/dl, p=0.0001). A significantly greater number of patients had Lp(a) values >30mg/dl in the CABG group compared with controls (46% vs 21%, p=0.0001, Chi squared test). There was no significant difference in cholesterol (5.7 vs 6.2 mmol/l, p=0.077), LDL cholesterol (3.99 vs 3.67 mmol/l, p=0.39) or triglycerides (1.74 vs 1.58 mmol/l, p=0.078); HDL cholesterol was significantly lower in the CABG group (1.41 vs 1.81mmol/l p=0.001). There was no significant difference in Lp(a) levels in those subjects who sustained a further cardiac event post CABG and those who remained event free (46 vs 36 mg/dl p=0.155). This study confirms that Lp(a) is a risk factor for IHD, but contrary to previous studies, Lp(a) was not a predictor of future cardiac events post CABG.

DO PATIENTS WITH HEART DISEASE SUFFER FROM MEDICAL PATERNALISM?

C P M Weston, R Watura, P Reeves, A G Fraser
University of Wales College of Medicine, Cardiff

It is now accepted that patients should be fully informed and then involved in making major decisions about their medical treatment. Arguably, this is particularly appropriate in patients with life-threatening heart disease. In order to review this process, we studied 140 patients (101 male) before diagnostic cardiac catheterisation, and 24 hours later after their cardiologist had discussed the results and planned treatment. All patients completed a general questionnaire, a personality inventory, and a psychological assessment of decision-making behaviour. Independently, doctors coded the contents of the interview. Cardiac surgery was discussed as possible treatment with 90 patients, and recommended to 39. Only 45 patients understood that there were risks involved; 34 had been informed that there was a risk of death and 24 had been quoted a precise risk. Angioplasty had been discussed with 40 patients, and recommended to 17. 21 patients understood that emergency surgery might be required; 17 had been told of a risk of death. 37 patients had been advised to continue medication. Of the others, 8 patients reported that no treatment was required, and 34 recalled no specific recommendation. On direct questioning 10 patients felt that too little information had been given, and 99 had asked questions during the consultation. Only 29 patients thought they had influenced the decision, while their cardiologists reported that 45 had influenced the final decision. Only 5 patients disagreed with the statement that the right decision had been made. This study suggests that patients are not given sufficient information to allow them to make fully informed decisions about treatment. However, they are confident in their doctors’ decisions, suggesting that a degree of medical paternalism may be justified.
WHY SO FEW CORONARY REVASCULARISATION PROCEDURES IN THE U.K?
K A Priestley, N P Buller
Department of Invasive Cardiology, Royal Brompton National Heart and Lung Hospital, London

This study examined whether referral patterns by the primary health care physician (GP) might influence the rate of revascularisation procedures in the UK. A postal questionnaire was sent to 5000 randomly selected GPs in the UK. Fully completed replies were received from 1235 (25%). Fifty-four percent of GPs saw up to 5 patients per week with new or previously diagnosed angina, 33% of GPs saw between 6 and 10 such patients a week. Severity of angina, poor response to initial drug therapy and patient age were selected as the 3 most important criteria for referral (as ordered). Only 23% of GPs referred >25% of their patients for specialist advice, 44% referred between 11-25% and 32% of GPs referred ≤10%. Low referral rates were seen from: Wales and the S.West (p<0.01); GPs who qualified between 1961-1970 (p<0.02); and GPs who considered their patients to be asymptomatic on drug therapy. GPs had lower referral rates if their previous experience of referral had been that ≤5% of patients received surgery or angioplasty (p<0.01). Referral rates were not dependent on the distance to the specialist centre, nor the delay between referral and specialist consultation, nor exposure within the past 12 months to educational material on coronary revascularisation. In conclusion the referral patterns by the GP of patients with angina vary considerably with much lower referral rates in some cases. Since many patients with angina in the UK are never seen by a specialist, referral patterns by GPs unquestionably influence the rate of revascularisation procedures in the UK.