ANNUAL CONFERENCE OF THE BRITISH CARDIAC SOCIETY

G-MEX, Manchester
20-22 May 1997

PROGRAMME AND ABSTRACTS OF PAPERS

* The conference will be held in the Windsor Hall and Seminar Centre of the G-MEX centre and the Alexandra Suite of the Holiday Inn Crowne Plaza Midland Hotel.

* Registration will take place in the entrance foyer, G-MEX. Desks will be open at the following times:
  - Monday May 19: 16.30–18.00 hrs.
  - Tuesday May 20: 07.30–17.30 hrs.
  - Wednesday May 21: 07.30–18.45 hrs.
  - Thursday May 22: 07.30–14.00 hrs.

* A location plan of the meeting rooms and exhibition hall is printed on the inside back cover of the programme.

* Abstract numbers 7-29, 36-57, 70-91, 98-120, 127-149, 156-198 will be delivered as short communications, with related posters on display in the Exhibition Hall throughout the conference.

* The Slide Preview room is located in the Windsor restaurant.

* Catering facilities are situated in the Exhibition Hall.

* The contact telephone number for the duration of the conference is 0161 832 1066.

* The exhibitors are thanked for their support of the conference. All those attending are encouraged to visit the exhibition.

* The Society thanks Bayer UK for the provision of the conference bags, and Philips Medical Systems for providing tea and coffee during the intervals.

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**BRITISH CARDIAC SOCIETY**

<table>
<thead>
<tr>
<th>OFFICERS:</th>
<th>COUNCIL: 1996-97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr R Balcon</td>
<td>Prof A A J Adgey</td>
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<tr>
<td>Prof R W F Campbell</td>
<td>Dr N A Boon</td>
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<tr>
<td>Dr I Hutton</td>
<td>Prof A J Camm</td>
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<tr>
<td>Dr N Brooks</td>
<td>Dr P Cummins</td>
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<td>Dr H Gray</td>
<td>Prof H J Dargie</td>
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<td>Prof M J Davies</td>
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<td>Prof D de Bono</td>
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</tbody>
</table>

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Please remember to bring this supplement with you to the conference
(1) CLOPIDOGREL IS CLOPIDOGREL V ASPIRIN IN PATIENTS AT RISK OF ISCHEMIC EVENTS J R Hampton for the CAPRIE investigators

Clopigogrel is a derivative of ticlopidine, and prevents platelet aggregation by blocking the ADP receptor on the platelet surface. CAPRIE was a randomised double blind international trial comparing the relative efficacy of clopidoqrel and aspirin, for the prevention of death, myocardial infarction and stroke, in patients with established vascular disease. Of 19,95 patients were included, roughly equally divided into groups who had initially presented with recent myocardial infarction, ischaemic stroke, or peripheral vascular disease. The mean follow-up was 1.9 years. There were 950 validated first events in the primary outcome cluster of vascular deaths, ischaemic stroke or myocardial infarction. On intention-to-treat analysis this represented an annual risk of 5.12% in the clopidoqrel group and 5.53% in the group treated with aspirin, a relative reduction of 9.7% in favour of clopidogrel (95% CI 0.3% to 16.5%, p = 0.045). Clopidogrel was well tolerated, and was not associated either with the gastro-intestinal effects of aspirin or the haematological adverse effects of ticlopidine. Subgroup analysis, not planned in the protocol, raised the possibility that patients included because of myocardial infarction, stroke and peripheral vascular disease might have responded differently to the two treatments, but data will be presented suggesting that this was in fact a random effect.

(2) DELAY IN MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION: FURTHER APPRAISAL OF THE "GOLDEN HOUR" R M Norris, Royal Sussex County Hospital, Brighton, on behalf of the UK Heart Attack Study Investigators.

Results of thrombolytic trials suggest disproportionate benefit if treatment is started within 1 hour of the onset of symptoms. However not all patients are suitable for thrombolytic therapy, and it is not known how this applies to the "real world". Data on 2189 patients aged <75 years treated in hospitals in Brighton, Cardiff and York during 1994-95 allowed us to study this. Time from onset to coming under care was calculated as the time to coming under paramedical surveillance for the 82% of patients who came to hospital by ambulance. Thirty-one per cent of patients came under care within 1 hour and 21% between 1 and 2 hours. Thirty-day survivors from documented cardiac arrest comprised 11 (95% CI 8-14) % of patients seen within 1 hour, 8 (6-11) % for those seen between 1 and 2 hours but only 3 (2-5) % of those seen later than 2 hours. By contrast only 2% of the 53% of patients who received thrombolytic therapy were treated within 1 hour and 23% at 1-2 hours. Fatality by 30 days for those treated within 2 hours was 5% vs 12% for those treated after 2 hours (p<0.001). Overall, we estimated that 34 lives were saved by thrombolytic therapy vs 145 by resuscitation. We conclude (i) potential benefits from the "golden hour" relate mainly to resuscitation; (ii) maximum benefit from thrombolyis may be obtained within 2 hours rather than 1.

(3) OUTCOME AND MANAGEMENT OF DIABETIC PATIENTS DURING THE UK HEART ATTACK STUDY Kathryn Griffith, York District Hospital, Wigginton Rd, YORK. On behalf of the UK Heart Attack Study Investigators.

The UK Heart Attack Study recorded all myocardial infarction and out-of-hospital coronary deaths aged <76 years in Brighton, Cardiff and York (population 960,000 ), during 1994 and 1995. We recorded 3,766 cases, 15% with a past history of diabetes mellitus. Thirty-day case fatality was higher in diabetic than non-diabetic patients (57% vs 44%; p=0.0005). It was higher in patients with diabetes both before admission to hospital (35% vs 30%; p=0.036), and after admission (32% vs 18%; p=0.0065). Diabetic patients were admitted less frequently to coronary care (73% vs 79%; p=0.0093), and were less likely to be given thrombolytic therapy (38% vs 51%; p=0.0005). 61% of diabetic patients had an ECG qualifying for thrombolysis, with ST elevation or LBBB, and 65% of non-diabetics. More diabetic patients with a qualifying ECG were not thrombolysed because of late presentation (30% vs 24%), but there was no increase in prior bleeding risk (28% vs 31%). Thirty-day fatality among diabetic patients respectively given or not given thrombolysis (30%, 40%) was significantly higher than for non-diabetics in the same category (9%, 23%). Diabetic patients are disadvantaged with higher case fatality from acute myocardial infarction. They have lower admission rates to coronary care and lower thrombolytic treatment rates.


In patients with coronary artery disease, endothelial dysfunction impairs coronary vasodilation during conditions of increased myocardial oxygen demand. Angiotensin converting enzyme inhibitors prevent bradykinin (BK) degradation which may improve endothelial function. The aim of our study was to assess the effect of intracoronary enalaprilat (EN) on flow mediated epicardial, and metabolic microvascular dilation produced by pacing. Furthermore, we assessed whether any observed improvement in vasomotion with EN was mediated by BK. We studied 19 patients, 17 of whom had mild coronary atherosclerosis or its risk factors. Quantitative angiography was used to measure epicardial coronary diameter (D) and a Doppler wire to measure blood flow velocity. Pacing decreased coronary vascular resistance (CVR) (-27±16%, p<0.001) and increased D (3.7±9%, p=0.056). EN (20 μg/min) produced no change in coronary haemodynamics. However, EN abolished flow-mediated epicardial constriction in segments which initially constricted with pacing alone (n=20), whereas segments that dilated remained unchanged (n=30). In the constricting epicardial segments, BK (62.5 ng/min) at a dose which did not alter baseline diameter, also abolished abnormal pacing induced constriction. In contrast, EN did not improve microvascular dilation in patients with or without depressed pacing induced dilation. These data suggest that EN, by increasing endogenous BK, improves flow mediated epicardial vasodilation in segments with endothelial dysfunction. The lack of effect of EN in the microcirculation may be because the endothelium contributes less to metabolic microvascular vasodilation than to flow mediated epicardial vasodilation.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Pace</th>
<th>Pace + EN</th>
<th>Pace + BK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segments</td>
<td>Distance (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilating</td>
<td>2.01±0.52</td>
<td>2.21±0.61</td>
<td>2.15±0.60</td>
</tr>
<tr>
<td>Constricting</td>
<td>2.13±0.65</td>
<td>2.02±0.62</td>
<td>2.15±0.66</td>
</tr>
</tbody>
</table>

mean ± SD; *Pace v Pace+EN, p<0.005; **Pace v Pace+BK, p<0.001
Chlamydia pneumoniae antibodies, cardiovascular events and azithromycin in post-myocardial infarction patients
S Gupta, EW Leuthardt, D Carrieton, MA Mendlon, JC Kaski, AJ Camm. Departments of Cardiological Sciences, Virology and Medicine, St George's Hospital Medical School, London

Elevated antibody titres to the bacterial pathogen, Chlamydia pneumoniae (Cp), have been associated with myocardial infarction (MI). In male patients with previous MI we investigated whether C pneumoniae antibody titre (Cpt) was an independent risk factor for future cardiovascular (CV) events. In addition, the effect of azithromycin (AZ) therapy on event rates was assessed in a sub-group with high Cpt. Consecutive male patients with remote MI (MI>6 months previously, n=213) were screened for Cpt (IgG class) using a microluminescence/fluorescence assay. Patients were classified according to their serological status: negative (Cpt=0, n=59), intermediate (Cpt=1/64, n=74) and high (Cpt ≥1/64, n=80). Of the high Cpt group, 40 patients were randomised to receive AZ (28 patients receiving single course of 500mg/day for 3 days; 12 receiving double course) or placebo (PL, n=20). Twenty high titre patients were not randomised to AZ or PL (NR, n=20). Over a follow-up period of 18±4 months the total number of CV events (unstable angina, coronary revascularisation, MI, CV deaths) occurring 21% (Cpt=0 vs 49% Cpt=8). The incidence and odds ratios (Odds=59%) for the occurrence of CV events in patients with positive Cpt (with and without AZ) relative to the Cpt negative group are shown. Multiple logistic regression was used to control for the factors age, diabetes mellitus, hypertension, dyslipidaemia, previous coronary revascularisation, and smoking status.

**Group**

**CV events (%)** Unadjusted, Adjusted OR

<table>
<thead>
<tr>
<th>Group</th>
<th>Cpt=0 (n=59)</th>
<th>Cpt=1/64 (n=74)</th>
<th>Cpt=1/64-PLN=80 (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpt=0</td>
<td>4 (7)</td>
<td>11 (15)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Cpt=1/64</td>
<td>2 (0.4)</td>
<td>22 (5.1)</td>
<td>21 (5.3)</td>
</tr>
<tr>
<td>Cpt=1/64-80</td>
<td><strong>2</strong> (5.2)</td>
<td><strong>2</strong> (5.1)</td>
<td><strong>2</strong> (5.2)</td>
</tr>
</tbody>
</table>

**P<0.05 vs 0.02**

The outcome for patients receiving single or double AZ course and Cpt=PL versus Cpt-NR groups was not different. Sixteen out of 40 (40%) patients receiving AZ compared to only 2 out of 20 (10%) in placebo group had a fall in Cpt (p=0.02) at 3-6 months post therapy.

Conclusions: Chlamydia pneumoniae antibody titre may be an independent risk factor for future cardiovascular events in post-MI patients. A short course of azithromycin may attenuate this risk.

RE-DO CORONARY ARTERY SURGERY IN PATIENTS OVER SEVEN: A 5 YEAR FOLLOW-UP
WI Awad, AC De Souza, PG Mages, RK Walesby, JE Wright, RU Uppal
Department of Cardiothoracic Surgery, The London Chest Hospital, London

The objective of this study was to determine the outcome of coronary artery bypass re-operations in patients over the age of seventy. All patients who underwent 're-do' cardiac surgery at our institution, between 1 January 1987 and 31 October 1995 were identified. The case notes of patients over the age of seventy who underwent 're-do' coronary artery bypass surgery were reviewed retrospectively. These patients were subsequently followed-up by telephone. A total of 687 're-do' operations were performed during this period. One hundred and ten (16%) operations were on patients aged 70 years and over and 54 (8%) of these were isolated coronary artery re-revascularisations. Thirty-five (65%) operations were elective, 15 (28%) were urgent and 4 (7%) were emergencies. Forty-five (83%) patients were male and the median age was 72 years (range 70-79 years). Pre-operatively, 25 (46%) patients were New York Heart Association (NYHA) functional class III or IV and 29 (54%) had angiographically impaired left ventricular function (ejection fraction <50%). The overall operative mortality was 2% (of 154 operations).

Median stay in the Intensive Care Unit was 1 night (range 1-21 nights) and hospital stay was 7 days (range 6-35 days). Major in-hospital complications included resternotomy in 2 (4%) patients, permanent stroke in 2 (4%) and acute renal failure requiring haemodialisation in 2 (4%). At a median follow-up of 33 months (range 14-101 months), there were 11 late deaths. Thirty-eight (90%) of the 42 patients alive at follow-up were NYHA functional class I or II. We conclude that 're-do' coronary artery bypass surgery in patients over the age of 70 carries a low operative morbidity and mortality with a good functional improvement at medium term follow-up.

ABNORMALITIES OF INTRACELLULAR Ca++ HANDLING IN ENDOCARDIAL MYOCYTES FROM RABBITS WITH LEFT VENTRICULAR DYSFUNCTION.
P Neary, MA McIntosh, SM Cobbe, GL Smith. Clinical Research Initiative in Heart Failure, West Medical Building, Glasgow University.

Ca++ entry across the sarcolemma and release from the sarcoplasmic reticulum during systole underlie excitation-contraction coupling in cardiac myocytes. Abnormalities of systolic Ca++ release and subsequent diastolic re-uptake have been found in the impaired left ventricular function and may contribute to both diastolic and systolic dysfunction. Ca++ transients were measured using a fluorescent dye, Fura-2, in single endocardial myocytes isolated from rabbit hearts with left ventricular dysfunction produced by ligation of the marginal branch of the left circumflex artery eight weeks prior to sacrifice. Ca++ transient duration was significantly prolonged in endocardial cells from ligated hearts at stimulation frequencies from 0.1-2 Hzs (table) compared to cells from control hearts. The effect of this on the whole heart would be to delay myocardial relaxation during diastole and impair ventricular filling. Peak systolic Ca++ release was markedly reduced in endocardial cells (table). A reduction in systolic Ca++ availability would increase contraction amplitude.

Abnormalities of Ca++ handling which would contribute both to systolic and diastolic dysfunction are therefore observed in endocardial myocytes in this rabbit model of left ventricular dysfunction.


MYOCYTE INOS EXPRESSION IN AUTOIMMUNE MYOCARDITIS IS NOT AN EXPERIMENTAL ARTEFACT AND OCCURS ALSO IN PACING-INDUCED HEART FAILURE
Roger J. Lord, Thomas D. Moore, Malcolm J. Lewis, Michael P. Frenneaux. University of Queensland, Australia and University of Wales College of Medicine, Cardiff

Background. It is controversial whether INOS expression in myocytes occurs clinically in only dilated cardiomyopathy or also in heart failure of other aetiologies. Expression of INOS in cardiomyocytes in viral and autoimmune models of myocarditis has been described but the role of Freund's adjuvant in autoimmune models is unclear. Studies were therefore performed in experimental autoimmune myocarditis and in a canine rapid pacing heart failure model.

Methods. 3 groups of Balb/c mice (n=4 each) were treated with intraperitoneal injections weekly for 3 weeks. Group I received 100 μg cardiac myosin emulsified with Freund's incomplete adjuvant, Group II adjuvant only, and Group III myosin only. Blood was collected weekly for 5 weeks for measurement of anti-myosin antibody (Ab) and TNFα (ELISA). Frozen sections were examined for myocarditis by H&E staining and for TNFα and INOS by immunofluorescence staining. Cardiac tissue from the canine heart failure model (n=3) was stained for TNFα and INOS (Group IV).

Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Myocarditis histology</th>
<th>Serum TNF</th>
<th>Anti-myosin TNF</th>
<th>INOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Yes</td>
<td>58.9 pg/ml</td>
<td>1:1600</td>
<td>Yes</td>
</tr>
<tr>
<td>Group II</td>
<td>No</td>
<td>3.5 pg/ml</td>
<td>absent</td>
<td>No</td>
</tr>
<tr>
<td>Group III</td>
<td>Yes</td>
<td>14.3 pg/ml</td>
<td>1:100</td>
<td>Yes</td>
</tr>
<tr>
<td>Group IV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
</tbody>
</table>

INOS expression is associated with TNFα expression, is not dependent on Freund's adjuvant, and occurs also in an anti-inflammatory model of heart failure.
THE INSERTION / DELETION POLYMORPHISM OF THE ANGIOTENSIN-CONVERTING ENZYME GENE, AND LEFT VENTRICULAR FUNCTION FOLLOWING MYOCARDIAL INFARCTION.

J Byrne, DR Murdoch, SD Robb, MJ Metcalfe, JJ Morton, JJ McMurray, HJ Dargie.
Department of Cardiology, Western Infirmary, Glasgow, UK.

There may be an increased risk of ischaemic heart disease and myocardial infarction (MI) in individuals homozygous for the deletion polymorphism (DD) of the angiotensin converting enzyme (ACE) gene. Increased levels of plasma ACE are observed in patients with this genotype. It has been suggested that the deletion polymorphism may cause adverse ventricular remodeling after MI as a consequence of enhanced activity of the renin-angiotensin system (RAAS).

We have investigated the relationship between the ACE genotype and left ventricular (LV) function in the subacute and late phase of MI in an unselected CCU cohort. The LV ejection fraction (LVEF) was measured by MUGA scan in 291 patients 3-7 days after MI (Normal range: LVEF>40%). Blood was taken to allow genotyping. 181 patients had a second MUGA scan 6 months later to assess changes in ventricular function.

<table>
<thead>
<tr>
<th>ACE Genotype</th>
<th>Patients at baseline</th>
<th>Baseline LVEF% (sd)</th>
<th>6 Month LVEF% (sd)</th>
<th>Change in LVEF% (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>55</td>
<td>28.7 (10.4)</td>
<td>31.1 (11.3)</td>
<td>+2.2 (9.31)</td>
</tr>
<tr>
<td>ID</td>
<td>143</td>
<td>29.5 (9.77)</td>
<td>31.9 (9.97)</td>
<td>+2.4 (6.37)</td>
</tr>
<tr>
<td>DD</td>
<td>93</td>
<td>29.5 (9.97)</td>
<td>32.4 (9.26)</td>
<td>+1.19 (7.70)</td>
</tr>
</tbody>
</table>

*p<0.05, s in all cases

Conclusion: The insertion / deletion polymorphism of the ACE gene has no discernible effect on LV systolic function in the subacute phase of MI, and does not appear to influence subsequent ventricular remodeling, or LV function in the following 6 months.

Acute Effects of Enalapril and Losartan on Autonomic Function in Heart Failure
NER Goodfellow, SJ Laer, AD Flapan. Department of Cardiology, Royal Infirmary, Edinburgh.

The potential mechanisms by which ACE inhibitors (ACEIs) improve prognosis in CCF are diverse and include vasodilatation, improved autonomic tone and improved fibrotic activity. It is unclear whether these effects are mediated by angiotensin II (AII), prostaglandin or bradykinin pathways and therefore whether the new specific AII receptor antagonists have the same properties? We addressed part of this question by looking at the two drugs effects on reflex autonomic activity.

Methods: 10 patients with CCF (NYHA II-III, LVEF<40%) due to IHF were studied. After performing a standard set of autonomic function tests (AFTs), they were randomised to receive enalapril 10mg (E) or losartan 50mg (L), orally. BP and heart rate (HR) were monitored. The AFTs were repeated 5 hours after drug ingestion. The study was repeated 2 days later using the other drug.

Results: AFT's (mean)

<table>
<thead>
<tr>
<th></th>
<th>Pre L</th>
<th>Post L</th>
<th>Pre E</th>
<th>Post E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva Ratio</td>
<td>1.26</td>
<td>1.25</td>
<td>1.21</td>
<td>1.27*</td>
</tr>
<tr>
<td>Postural JHR (30/15 ratio)</td>
<td>1.13</td>
<td>1.13</td>
<td>1.11</td>
<td>1.10</td>
</tr>
<tr>
<td>Respiration JHR (rpm)</td>
<td>11.42</td>
<td>11.74</td>
<td>12.42</td>
<td>12.16</td>
</tr>
<tr>
<td>Postural JBP (mmHg)</td>
<td>-1.95</td>
<td>-4.47</td>
<td>-2.89</td>
<td>-3.95</td>
</tr>
<tr>
<td>Handgrip JBP (mmHg)</td>
<td>14.68</td>
<td>14.68</td>
<td>15.84</td>
<td>15.26</td>
</tr>
<tr>
<td>AFT Score*</td>
<td>3.68</td>
<td>4.84</td>
<td>3.74</td>
<td>3.16</td>
</tr>
</tbody>
</table>

* independent of pretreatment

Conclusion: In contrast to losartan, enalapril significantly improved the Valsalva ratio suggesting improvement in parasympathetic and sympathetic pathways. Losartan on the other hand appears to have neutral effects on all the AFTs. However the overall trend was for enalapril to improve autonomic function, as judged by AFT score, whilst losartan tended to worsen it. This suggests, that in the short term, the beneficial autonomic effects seen with ACE's may not be solely due to inhibition of AII and may not be a feature of specific AII receptor.

EFFECT OF ACE-INHIBITION ON RIGHT VENTRICULAR DIASTOLIC FUNCTION IN RESTRICTIVE LEFT VENTRICULAR DISEASE
MY Henein, CA O'Sullivan, DG Gibson.
Royal Brompton Hospital, London.

Right ventricular function is frequently disturbed in left ventricular disease. To assess possible effects of ACE-inhibition on right ventricular behaviour, we studied 20 patients with restrictive left ventricular physiology, NYHA III-IV, age 62±9 years, before and after symptomatic benefit by Doppler echo measurements of right ventricular systolic and diastolic free wall motion and tricuspid valve flow velocities. Baseline values were compared with 21 normals with similar age. Before ACE-I, Right ventricular systolic excursion, peak shortening and lengthening velocities were reduced compared to normals, p<0.001. The onset of detectable tricuspid flow with respect to P2 was delayed 130±60 vs 30±15 ms (vs normal). E wave velocity was reduced and A wave increased, p<0.001 for each. In 7 patients mild tricuspid regurgitation demonstrated a pressure drop of 30±5 mmHg in the absence of any abnormal shortening of right ventricular free wall. With ACE-I, mechanical right ventricular systolic and diastolic function did not change while the delayed onset of flow regressed from 130±30 to 70±25 ms, after P2, p<0.001. Tricuspid E wave velocity 30±10 vs 13±16 cm/s, and E/A ratio 1.2±0.7 vs 0.5±0.8 increased, p<0.001 for each.

Conclusion: In the absence of free wall incoordination and only moderate elevation of right ventricular pressure, diastolic function is markedly disturbed in LV restrictive disease. Its improvement with ACE-inhibition suggests that right ventricular abnormalities result from raised left ventricular diastolic pressures.

THE EFFECT OF NITRIC OXIDE INHIBITION ON THE RENIN RESPONSE TO FRUSEMIDE IN MAN
AFC Lee, DG Kelly, WJ Castle, AD Struthers. Department of Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee, United Kingdom.

Nitric Oxide (NO) has been demonstrated in animals, and in cell culture to be important in the control of renin release. We wished to see if renin release in man is also dependant on Nitric Oxide. To this end we studied ten normal male volunteers, 26 ± 1.6 years. Following a one hour supine rest to stabilise plasma renin, the subjects received either Nω-monomethyl-L-Arginine (L-NMMA) or volume matched placebo. L-NMMA caused the expected increase in mean arterial pressure (MAP) (96 ± 3 mmHg vs 89 ± 3 mmHg placebo, p<0.05), and a reduction in heart rate (59 ± 4 bpm vs 67 ± 2 bpm placebo, p<0.05). L-NMMA completely blocked the renin rise following the bolus of Frusemide (1.18 ±0.19 ng/ml/hr vs 1.96 ± 0.34 ng/ml/hr placebo p<0.01). In case this effect was due to the observed haemodynamic effects of the L-NMMA, we repeated the experiment, in five of the volunteers, using an equipressor dose of phenylephrine. Phenylephrine 0.5µg/kg/min produced very similar haemodynamic effects to L-NMMA (MAP 91±2 mmHg phenylephrine vs 93±2 mmHg L-NMMA vs 85±4 mmHg placebo [NS], heart rate 92±3 bpm phenylephrine vs 59±2 bpm L-NMMA vs 67±4 bpm placebo [NS]) and also suppressed the renin response to Frusemide (1.43±0.29 ng/ml/hr phenylephrine vs 1.56±0.2 ng/ml/hr L-NMMA vs 2.67±0.34 ng/ml/hr placebo p<0.01).

We conclude that nitric oxide inhibition does block the stimulated release of renin in response to a bolus of Frusemide but that this is a non specific effect due to alterations in arterial pressure.
IS ENDOTHELIN CONVERTING ENZYME ACTIVITY INCREASED IN CHRONIC HEART FAILURE?
MRC Clinic Research Initiative in Heart Failure, University of
Glasgow, *Clinical Pharmacology Unit, University of Cambridge and
*Department of Medicine, Western General Hospital, Edinburgh.

Activation of the endothelin (ET) system leads to an increase in circulating ET immunoreactivity in patients with chronic heart failure (CHF). Plasma levels of mature ET-1, the dominant ET isoform in the human vasculature, are probably a poor index of ET system activity because of the predominant abnormally secreted peptide by the vascular endothelium and its subsequent high affinity receptor binding. It has been suggested that in CHF there may be a predominant increase in circulating levels of big ET-1, the inactive propeptide from which mature ET-1 and a C-terminal fragment (CTF) are generated by ET converting enzyme (ECE), but whether this might be indicative of increased ECE activity in CHF is unclear. We therefore obtained anticoagulated venous plasma samples after at least 30 minutes of supine rest from 10 patients with stable CHF (mean age 65 years, mean ejection fraction 21%) and 10 healthy control subjects (mean age 61 years, mean ejection fraction 62%) for determination of plasma big ET-1, big ET-1 and CTF by specific radioimmunoassay. CHF patients had significantly higher resting levels of big ET-1 and CTF than control subjects (2.5±0.4 vs 1.7±0.1 pmol/l p=0.04) and 2.1±0.3 vs 0.6±0.1 pmol/l p=0.001) respectively but only a tendency to a higher level of ET-1 (7.2±1.6 vs 4.7±0.5 pmol/l p=0.15). The mean CTF/big ET-1 ratio, a putative index of ECE activity, was significantly higher in CHF patients than in control subjects (0.90±0.11 vs 0.45±0.06; p=0.004). The elevation in plasma big ET-1 and CTF coupled with the raised CTF/big ET-1 ratio suggest that ECE activity may indeed be increased in CHF. ECE inhibition may therefore be a particularly attractive anti-ET therapeutic strategy for CHF.

<table>
<thead>
<tr>
<th>IMPAIRED ALVEOLAR-CAPILLARY MEMBRANE FUNCTION PREDISPOSES TO EXERTIONAL ARTERIAL DESATURATION IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Par*, DP Dentka, BL Baker, JMB Hughes, and J G F Cleland**.</td>
</tr>
<tr>
<td>Department of Medicine (Cardiology), RPMS, Hammersmith Hospital, London, **CTC Liverpool and **MRC CRI in Heart Failure, Glasgow.</td>
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<tr>
<td>Many varied factors have been proposed as causes of exercise impairment in heart failure, and it is generally agreed that impaired oxygen delivery to working muscle is important. The prevalence and role of arterial oxygen desaturation in chronic heart failure, however, remains controversial. We studied 55 patients with varying degrees of left ventricular dysfunction (age 50±8 years, ejection fraction 33±9%) with arterial capillary membrane conductance (Dm) and reactive conductance, using the Routledge and Foster method of measuring Dm with a single breath technique at varied inspired oxygen concentrations. All subjects underwent incremental maximal exercise testing on a bicycle ergometer with respiratory gas analysis. Continuous arterial oxygen saturation was recorded by earlobe pulse oximetry (SaO2). 12(22%) patients exhibited significant arterial oxygen desaturation of &gt; 3% from resting (DESAT), while 43(68%) did not (SAT).</td>
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<td></td>
</tr>
<tr>
<td>DESAT</td>
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<td>SAT</td>
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<td>Dm is significantly reduced in the DESAT group compared to the SAT group, and forms a larger proportion of the total pulmonary diffusive resistance (DmDesAT). This indicates that alveolar-capillary membrane resistance to gas transfer is increased in the DESAT group. We conclude that impairment of alveolar-capillary membrane function predisposes to arterial desaturation in patients with left ventricular dysfunction.</td>
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CABG IMPROVES LV ANTERIOR WALL COORDINATION AND INCREASES REGIONAL MYOCARDIAL WORK

TW Koh, JR Pepper, DG Gibson
Royal Brompton Hospital, London

Recovery of LV function after CABG is commonly assessed by indices based on amplitude of wall motion. However, disturbances in the time sequence of ventricular contraction, represent an important mechanism for impairment of LV function that has not been studied after CABG. We studied incoordination by assessing abnormal LV anterior wall (AW) motion during the period of isovolumic rapid pressure rise and fall, when AW thickness should normally remain unchanged, by plotting LV pressure and AW thickness loops. We determined its effect on regional myocardial work (RW) and early wall dynamics. Methods: 25 stable angina pts who underwent grafting of the LAD without previous anterior MI were studied. Transoesophageal echo of LV mid cavity and high fidelity LV pressure measurements were made at prebypass (PRE), 0.5, 1 and 3 hrs after cross clamp release. Results: LV dimensions, fractional shortening and wall thickening fraction did not change after bypass. However, in all but one pt, the prebypass LV pressure thickness loop showed major distortion, wall thinning during isovolumic contraction in 15 pts and thickening in 9. These disturbances in the timing of contraction, produce incoordination and can be quantified by calculating cycle efficiency (CE) defined as the ratio of loop area (useful work transferred to the circulation) to that of the rectangle which just encloses it (maximal possible work that could be done). CE had increased by 0.5hr (69±10 vs 54±11%) from PRE and was maintained at 3 hrs (73±6%). As wall motion becomes more distorted, the loops became more rectangular in shape resulting in increased RW derived from loop area, at 0.5 and 3hrs (4.3±1.1, 3.8±1.1 vs 2.9±0.9 ml/cm2) vs PRE. Improvement in coordination coincided with increase in AW thickening and thinning rates from 0.5 hr onward (3.4±0.9, 3.1±0.8 vs 1.9±0.6, 1.9±0.4 cm/s) and increase in peak AW power production (38±13 vs 24±10 ml/min/cm2) vs PRE, p<0.05 for all. Conclusion: 1) Incoordinate AW motion is commonly present in stable pts undergoing CABG and is restored by revascularisation. 2) This early improvement in coordination is associated with an increase in regional independent indices such as thickening fraction. This mechanism for recovery of function should be considered in any comprehensive assessment of the effect of CABG on LV function.

RECOVERY OF CONTRACTILE FUNCTION IS EQUALLY PREDICTED BY METABOLIC IMAGING AND ASSESSMENT OF CONTRACTILE RESERVE PRIOR TO REVASCULARISATION IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION

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The assessment of the potential for recovery after revascularisation of akinetic myocardial segments in patients with severe left ventricular (LV) dysfunction and CAD has been a challenge. Metabolic imaging with nitrate-enhanced (NTG) Ti-201 provides myocardial viability information, whereas low dose dobutamine echocardiography (DE) provides knowledge of the contractile reserve of akinetic myocardial segments. However, DE has been thought to be insensitive for assessing recovery of function in such segments. We have compared the predictive value of both these techniques in 23 patients with congestive heart failure (CHF) due to CAD with severe LV dysfunction (mean ± SD LV ejection fracture: 26 ± 9%) undergoing revascularisation. Echocardiographic (echo) wall thickening was assessed before and 3 months after revascularisation. The NTG Ti-201 SPECT and Echo images were analysed by matching the images in a 12 segment model and scored (1(normal to 4= absent)) according to reduction in wall thickening or (0 = normal to 4 = absent) according to tracer uptake. Of the total 276 segments (n = 23 patients), 144 were akinetic, of which 73 (51%) improved after revascularisation. Of which, NTG Ti-201 predicted 58(79%) and Echo 55(75%) of the segments, respectively (p = ns). Though the lack of improvement of regional wall thickening is not the only measure of improvement of LV dysfunction following revascularisation, gross improvement in severe regional asynergy is equally predicted by both methods. Further studies may be required to show a synergistic value of both modalities for enhanced prediction of outcome in these patients.
SERUM URIC ACID IS RELATED TO MARKERS OF IMMUNE ACTIVATION IN CHRONIC HEART FAILURE
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Chronic heart failure (CHF) is associated with elevations in circulating uric acid and markers of immune activation. In view of the link between xanthine oxidase activity and leukocyte activation at the level of the endothelium, we sought to determine whether serum uric acid is related to markers of immune activation in patients with CHF, taking into account the hyperuricemic effects of diuretic therapy and insulin resistance. Method: Circulating uric acid and measures of immune activation were measured in 44 male patients with CHF and 16 healthy controls. All patients underwent a metabolic assessment, which provided an insulin sensitivity index (obtained by minimal modelling analysis of glucose and insulin responses during an intravenous glucose tolerance test). Results: Compared to controls, patients with CHF had significantly higher levels of circulating uric acid, interleukin (IL)-6, soluble tumour necrosis factor receptor (sTNFRF1), soluble intercellular adhesion molecule-1 (sICAM-1), (all p<0.001), IL-6, sICAM-1, and sTNFRF2 (both p<0.05), but not tumour necrosis factor (TNFα). In patients with CHF, there was a strong positive correlation between serum uric acid and circulating levels of sTNFR-1 (r=0.75), sTNFR-2 (r=0.63), IL-6 (r=0.65), TNFα (r=0.58), sICAM-1 (r=0.49) (all p<0.001). In stepwise linear regression analysis, serum uric acid emerged as the strongest predictor of sICAM-1, IL-6, TNFα, sTNFR1, sTNFR2, independently of diuretic dose, age, adiposity, alcohol intake, serum creatinine, plasma insulin and glucose, and insulin sensitivity. Conclusions: Serum uric acid is strongly related to circulating markers of immune activation in patients with CHF. This is consistent with a role for increased endothelial xanthine oxidase activity in the immune activation in patients with CHF.

Incidence and aetiology of heart failure in the general population
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The contemporary incidence of heart failure in the UK is not known. A prospective survey of incident cases of heart failure presenting to 81 general practitioners and a district general hospital serving a population of 151 000 was conducted over 15 months. Cases were identified from hospital admissions and through a daily rapid access heart failure clinic to which GP's referred all new cases of suspected heart failure. Following a standardised interview, physical examination, ECG, CXR and echocardiogram all cases were reviewed by a panel of 3 cardiologists who determined whether the clinical case definition of heart failure was met and the aetiology. 171 incident cases of heart failure were identified (94M:77F) with no case aged under 35 years. Thirty five cases (20%) were identified from 122 referrals to the clinic, the remainder being acute hospital admissions. The incidence increased dramatically with age from 0.2 per 1000 population per annum in those aged 35-44 years to 11.6 in those aged 85 years or over and was higher in males than females (comparative incidence ratio 1.9 [95% CI 1.5-2.4] p<0.0001). The median age at presentation was 76 years. Aetiology were ischaemic heart disease (36%), hypertension (15%), valve disease (6%), other (7%) but in 36% of cases the aetiology was unknown. Randomised controlled trials of heart failure are conducted in highly selected hospital cases with a strong bias towards younger patients and those with coronary artery disease as the aetiology. However, in the general population new cases of heart failure largely arise in the elderly and in over a third of cases the aetiology cannot be determined from non-invasive investigation. These findings have important implications for the investigation and management of new cases of heart failure in the general population.

LEFT VENTRICULAR HYPERTROPHY AND CORONARY MICROVASCULAR ENDOTHELIUM: PHENOTHIAZINE CHANGES AND ANGIOTENSIN CONVERTING ENZYME ACTIVITY
JP Bell, D Lang, BD Prannegar, MJ Lewis Cardiovascular Disease Research Group, UWC, Cardiff.

Left ventricular hypertrophy (LVH) is associated with coronary microvascular endothelial dysfunction. We investigated the nature of this dysfunction in CMVE isolated from a guinea pig pressure overload model of LVH and assessed nitric oxide (NO) synthase and angiotensin converting enzyme (ACE) activity. In CMVE freshly isolated from control animals, exposure to bradykinin (BK) and the calcium ionophore A23187 (both 1µM for 90 sec) induced significant (p<0.01) increases in cGMP from 0.82±0.07 to 1.63±0.13 & 2.57±0.25 fmol/mg protein respectively (all n=7). In CMVE freshly isolated from animals with LVH, the basal cGMP levels were significantly lower (p<0.05) (0.41±0.05 fmol/mg protein, n=7) compared to control animals, as were the cGMP responses to BK and A23187 (both 1µM for 90 sec) exposure (0.95±0.15 & 1.06±0.14 fmol/mg protein [p<0.01 cf. LVH basal levels, both n=7] respectively). The increases in cGMP were completely inhibited by pretreatment with the NO synthase inhibitor L-nitro arginine benzyl ester (L-NAME, 1µM for 20 min) in cells from both groups of animals. CMVE from both groups of animals responded to exposure to sodium nitroprusside (SNP, 1µM for 2 min) with similar increases in cGMP (4.5±0.54 & 4.37±0.48 fmol/mg protein [n=10] for control and LVH animals respectively). Finally isolated CMVE exhibited elevated ACE activity (3.6±0.04 U/mg protein, n=6), which was significantly (p<0.01) higher in the LVH animals (1.06±0.11 U/mg protein, n=8). In this model of LVH CMVE exhibit impaired NO release and increased ACE activity. It is likely that these changes contribute to the development of LVH following aortic banding in the guinea pig.
INDUCTION OF NITRIC OXIDE IN HUMANS IN VIVO FOLLOWING EXPOSURE TO CYCLOXIDIN
K Bhogat and P Vallance, Rayne Institute, UCL, London WC1N 6JU

Nitrergic (NO) is an important mediator of a wide variety of physiological processes. It is synthesised by a family of enzymes known as NO synthases (NOS). Three members of the NOS family have been identified: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). There has been particular interest in the role of eNOS in mediating cardiovascular responses to vasoconstriction, hyperresponsiveness to angiotensin, hyper tension, vascular leakage and vessel damage. Increased generation of NO also appears to contribute to the cardiovascular changes that occur in response to systemic inflammation in humans. Most studies demonstrating induction of NO have used rodent models. However, large details exist in the human and murine/rodent NO synthase gene. In the present study we explored the effects of key inflammatory eNOS (CTX) on the reactivity of a human blood vessel perfused with blood, at rest. Methods: Subjects lay with one hand placed on an angled support above the level of the heart. The diameter of a single dorsal hand vein was recorded by measuring the linear displacement of a light weight probe placed on the skin overlaying the vein when the pressure in a constricting cuff placed around the upper arm was deflated from 40 mmHg. To instil CTX, a length of the vein under study was isolated from the circulation by means of 2 wedges placed 2 3cm apart. N'Eth (1mg), Il 1b (1mg) or Il 6 (100pg) were infiltrated through the skin in two individual or together (dose response curves to noradrenaline [NA] were used to normalize the results) and of 1, 6, 74, and 49h after instillation of CTX. In order to explore the effects of Il 1b on endogenous NA mediated constriction, the deep breath venoconstrictor response was studied before and 6h after instillation of Il-1b. Sympathetic venoconstriction was induced by occluding subjects to take a single deep inspiration over a period of 5 sec, to hold this for a comfortable period (approximately 10 sec), and then to breathe out slowly before returning to normal breathing. Results and summary: Il-1b (1mg) produced a dose-dependent increase in hyperresponsiveness to NA which was greatest 6h after instillation (maximum constriction to NA before instillation was 84±5% and 94±3% 6h after cytokines). Neither Il-6 nor Il6A alone had any effect. The NO synthase inhibitors L-NMMA and L-NAME (10µM) markedly reversed the hyperresponsiveness induced by Il 1b. Prior administration of hydromorphone (100mg) inhibited the effects of Il-1b. Instillation of Il1b virtually abolished endogenous venoconstriction due to activation of the sympathetic nervous system. Local infusion of L-NAME restored the ability of the sympathetic nervous system to cause venoconstrictor. Our results show for the first time that NO mediated dilation following exposure of a human blood vessel in vivo to CTX and b) that Il 1b is a key cytokine for increasing vascular NO generation in humans.

ENDOGENOUS NITRIC OXIDE FACILITATES THE FRANK-STARRING RESPONSE
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The Frank-Starling response contributes to the regulation of cardiac output. The major underlying mechanism is a length-dependent change in myocardial responsiveness to Ca2+. Recent studies indicate that nitric oxide (NO) decreases myocardial responsiveness to Ca2+, and modulates myocardial relaxation and left ventricular ejection fraction. We therefore investigated the interaction between NO and the Frank-Starling response. Isolated buffer-perfused ejection guinea-pig hearts (1µM isothiocyanate, 37°C, constant afterload (70mM NaCl) and heart rate) were studied before and after interventions. Under baseline conditions, elevation of filling pressure from 10 to 20 cm H2O increased cardiac output (24.5±2.7%, coronary flow (11.1±1.4%), LV end-diastolic pressure (LVEDP) (40.5±3.6%) and peak LV pressure (LVP max) (4.2±0.8%); all p<0.0001), but not LV dp/dt max (2.5±1.7%, p>NS). In the presence of N-nitro-L-arginine (L-NAME, 10 µM; n=10) or the NO scavenger, hemoglobin (Hb, 1 µM), cardiac output at a preload of 10 cm H2O was unaltered but the preload-induced increase in cardiac output was markedly attenuated (Table). Neither agents altered preload-induced rise in LVP max (L-NAME, 2.0±0.4 mll/min/Hb, -2.1±0.7mll/min; Time controls, 0.5±0.3 mll/min/P<NS). L-NAME effects were also observed in the concurrent presence of L-arginine (100 µM; n=6). In the presence of the exogenous NO donor, sodium nitroprusside (SNP, 1 µM; n=6), cardiac output at a preload of 10 cm H2O was significantly reduced (by 14%, P<0.01), but the preload-induced increase in cardiac output was no longer observed. A cardiac output increase from 10 cm H2O was also observed in the presence of SNP. These data indicate that basal intrinsic production of NO facilitates the Frank-Starling response in the isolated ejection guinea-pig heart. The mechanism may be NO-induced improvement in diastolic function, changes in cardiac myofibrillar Ca2+ response, and/or length-dependent changes in NO activity.

IN VIVO PULMONARY ARTERY ADENOVIRAL GENE TRANSFER OF NITRIC OXIDE SYNTHASE ENHANCES NATURAL NITRIC OXIDE PRODUCTION
KM Channon, AP Kypson, CW Daggett, MA Blazing, WJ Koch, SE George. Division of Cardiology, Duke University Medical Center, Durham, USA.

Nitric oxide (NO), generated by nitric oxide synthase (NOS), has key regulatory roles in the normal pulmonary circulation, and also inhibits pathological processes such as platelet aggregation, neutrophil adhesion and smooth muscle cell proliferation. NO production is defective in disease states such as pulmonary hypertension or enhancing NO production, by gene transfer of NOS, may therefore offer a potential therapeutic strategy. We used a recombinant adenoviral vector, Ad.nNOS, containing the neuronal isoform of NOS (nNOS), to carry out in vivo gene transfer to the pulmonary vasculature in the rabbit.

Methods: Rabbits underwent left thoracotomy to expose the left pulmonary artery (PA). Recombinant adenovirus, either Ad.nNOS (n=6) or, as a control, Ad.cDNA (n=3) was diluted in 4 ml saline and injected rapidly into the left PA, which was occluded for 5 minutes. Lungs were harvested after 5 days. The left and right lungs were processed for NOS protein analysis by Western blotting and for NOS activity determination by 3H-Arginine conversion. The left lung was also divided for analysis into left upper (LLL) and lower (LLL) lobes.

Results: Immunoblotting demonstrated high level nNOS protein expression in LLL and LUL, but barely detectable in RL. No nNOS protein was seen in Ad.Gal-infected lungs. NOS activities (Mean ± SD, in pmol NOS/mg protein) are shown in the table (*p<0.05): Left Lung Left UL Left LL Right Lung Ad.Gal 6.3±2.7 5.05±2.7 7.5±2.6 6.1±3.3 Ad.nNOS 18.6±12.8* 14.0±14.5 23.3±10.2 8.5±3.4

Specificity of NOS activity was demonstrated by inhibition in the presence of N-methyl-L-arginine (1 mM), a specific NOS inhibitor.

Conclusions: In vivo adenoviral gene transfer of NOS via the pulmonary artery results in efficient recombinant protein expression and significantly augments NO production in the lung, by 3-fold. These findings highlight the investigative and therapeutic potential of NOS gene transfer strategies in pulmonary vascular diseases.

IN VIVO ADENOVIRAL GENE TRANSFER OF NITRIC OXIDE SYNTHASE AUGMENTS OR RESTORES VASCULAR NO PRODUCTION
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Nitric oxide (NO) has key regulatory roles in the cardiovascular system. NO production is defective in injured or diseased vessels and restoration of NO production inhibits the sequelae of vessel injury. The nitric oxide synthase (NOS) gene is promising as a potential therapeutic agent for gene transfer to the vessel wall. Using a recombinant adenoviral vector, Ad.nNOS, containing the neuronal isoform of NOS (nNOS), we carried out in vivo gene transfer to rabbit carotid arteries (CA), with and without balloon denudation. Methods: Rabbits underwent balloon denudation of the left CA (2F Fogarty). Recombinant adenovirus (5 x 10^9 pfu/ml), either Ad.nNOS (n=4) or, as controls, Ad.Gal or no virus (n=6) was instilled into the lumen and onto the adventitia of both CA, for 15 minutes. Vessels were harvested after 3 days, and analysed as follows: 1) NOS protein analysis by Western blotting. 2) Staining of cytoskeletons by NADPH diaphorase and NOS immunohistochemistry (3) NOS activity determination in intact vessels by 3H-Arginine conversion. (4) Isometric tension studies in organ baths for determination of vasomotor responses.

Results: Western blotting, diaphorase and NOS immunostaining revealed nNOS protein expression in intact and denuded CA infected with Ad.nNOS, but not in control CA. NOS activities (Mean ± SD, in pmol NO/mg protein) are shown in the table (*p<0.05).

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<th>Treatment</th>
<th>Intact</th>
<th>Denuded</th>
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<tr>
<td>Ad.Gal+No Virus</td>
<td>35.8±48.2</td>
<td>22.9±20.6</td>
</tr>
<tr>
<td>Ad.nNOS</td>
<td>85.2±10.8**</td>
<td>44.4±7.2*</td>
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Vasomotor responses to phenylephrine and nitroprusside were unaffected by gene transfer. Ad.nNOS-infused arteries showed profound relaxation was augmented in intact CA, and A23187-induced paradoxical contraction was reduced in denuded CA.

Conclusions: In vivo adenoviral gene transfer of NOS restores or augments NO production in denuded or intact CA, respectively, with corresponding changes in vessel physiology. Gene transfer strategies using NOS may potentially provide novel investigative and therapeutic approaches to vascular diseases.
ENDOTHELIAL DYSFUNCTION IN MICROVASCULAR ANGINA (MVA): BENEFICIAL EFFECTS OF ORAL L-ARGININE
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Whether MVA is associated with endothelial dysfunction remains controversial. Ten well characterised patients (age 38-64 yr, 4 male) with MVA (angina, positive stress test, reversible radionuclide perfusion defect, normal coronary arteriogram), selected to exclude known cause of endothelial dysfunction (active or healed passive smoking, cholesterol>6.5mmol/l, total homocysteine>15mmol/l, BFS>150/90mmHg, diabetes) were studied. Arginine can prevent/restore endothelial dysfunction in some conditions. Accordingly the study included a randomised double-blind placebo-controlled cross-over trial (no washout phase) of oral L-arginine (7g bd for 4 weeks). Brachial artery diameter was measured by ultrasonic “wall tracking”. Flow-dependent dilatation during hand hyperaemia was absent (+0.7±1.9 [SD%], cf. +2.8±2.3% in normal age, sex and cholesterol matched subjects), but was restored on arginine (+3.3±3.5%, p<0.05), whereas sublingual glyceryl trinitrate-induced dilatation (+11.5±6.2%) was normal and unaltered by arginine (+11.9±5.0%). Arginine did not alter heart rate, blood pressure or blood flow responses. Symptom (angina)-limited Weber protocol exercise duration was increased on arginine (422±170 to 519±273 sec, p<0.05) without change in peak rate-pressure product. The study showed loss of flow-dependent systemic conduit artery dilatation in MVA, indicating endothelial dysfunction despite absence of known cause, a conclusion supported by arteriographically observed improvement in flow-dependent dilatation and in the angina threshold. It suggests that generalised endothelial dysfunction underlies MVA.

THE ROLE OF ANGIOTENSIN II IN MEDIATING BASAL AND SYMPATHEICALLY STIMULATED PERIPHERAL ARTERIAL TONE IN HEALTH AND DISEASE
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Objectives: To determine the contribution of angiotensin II (Ang II) to basal and sympathetically stimulated arterial tone in chronic heart failure (CHF), cirrhotic liver disease (CLD) and healthy sodium replete and deplete men.
Methods: Ten healthy sodium replete and 6 sodium deplete men, 8 patients with chronic CHF (ejection fraction <35%; temporarily withdrawn from ACE inhibitor therapy) and 8 patients with CLD (Child’s grade C) were studied with age & sex matched controls. Following brachial artery cannulation, forearm blood flow (FBF) was measured using venous occlusion plethysmography. In healthy volunteers, FBF responses to intra-arterial infusions of angiotensin I and II, noradrenaline and bradykinin were determined +/- co-infusion of losartan. In all groups, FBF was measured +/- lower body negative pressure (LBNP) of -15mmHg during saline and losartan infusions. FBF responses to noradrenaline and angiotensin II were determined in the patient and control groups.
Results: Losartan inhibited responses to angiotensin I and II, but had no effect on responses to bradykinin or noradrenaline. In the sodium replete men and patient control groups, losartan alone caused no significant changes in basal FBF (95% CI: -7.2 to + 8.0%), vascular resistance or sympathetically stimulated forearm vasoconstriction. Sodium depletion more than doubled plasma angiotensin II concentrations after which losartan increased forearm blood flow in a dose dependent manner by 69% (p<0.001). Both patient groups demonstrated significant vasodilatation to losartan (CHF 25%, CLD 29%; p<0.001 for both) and had a significantly reduced LBNP response compared to controls (p<0.001). Unlike CHF, CLD patient groups demonstrated significantly reduced vasoconstriction to angiotensin II compared to controls (p=0.01). Both patient and control groups had similar responses to noradrenaline.
Conclusions: Angiotensin II does not contribute to basal forearm resistance vessel tone except under circumstances of renin-angiotensin system activity such as sodium depletion and CHF. Despite normal responsiveness to noradrenaline, CHF and CLD are associated with impaired reflex sympathetic nervous system vasoconstriction. ACE inhibition may protect against hyporesponsiveness to angiotensin II.

THE ROLE OF VASOACTIVE MEDiators IN PRIMARY AND SECONDARY PULMONARY HYPERTENSION.
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The role of vasoactive mediators in the pathophysiology of primary and secondary pulmonary hypertension (PPH and SPH) remains undefined. Endothelin-1, thromboxane, nitric oxide and prostacyclin are thought to be regulators of vasomotor tone in the pulmonary vasculature. We investigated 14 patients (6 females, 8 males), (mean age 42.8±3.3 yrs) with pulmonary hypertension. Eight patients had PPH with a mean pulmonary artery pressure of 67±8.7 mmHg and 6 patients had SPH with a mean pulmonary artery pressure of 52±4.5 mmHg. All patients had a pulmonary artery flotation catheter and a radial arterial line inserted. Arterial and mixed venous samples from the pulmonary artery were taken at 14.00, 20.00, 24.00 and 8.00 hrs. for the measurement of endohepin-1, 6-keto-prostaglandin F1α, thromboxane B2 and nitrate/nitrite. Blood samples were also taken from 5 control patients with normal pulmonary artery pressure (16±1.3 mmHg) at cardiac catheterisation. Within each of the 3 groups, there was no significant difference between mixed venous and arterial levels of any of the vasoactive mediators. No significant diurnal variation was seen. Although endohepin-1 levels tended to be higher during the night, this difference was not significant. When compared to the control group, PPH and SPH patients had significantly higher mixed venous (8.7±1.0 and 7.6±1.6 cf. 0.5±0.4 mmol/l, p<0.05) and arterial (8.0±1.4 and 6.8±0.9 cf. 1.2±0.6 mmol/l, p<0.05) levels of endohepin-1. In contrast, PPH patients tended to have lower mixed venous and arterial levels of nitrate/nitrite when compared to the control subjects (0.0509±0.0192 and 0.059±0.0258 cf. 0.1326±0.0187 and 0.1516±0.0042 μM, p=NS). There was no significant difference between the groups for the other levels measured. We conclude that pulmonary hypertensive patients have increased circulating levels of endohepin-1 which may contribute to the increased pulmonary vascular resistance. The role of prostacyclin, nitric oxide and thromboxane, in controlling vascular tone in these patients is less certain.

PULMONARY ARTERY PRESSURE AT LOW AND HIGH ALTITUDE IN SUBJECTS SENSITIVE TO HIGH ALTITUDE PULMONARY OEDEMA AND CONTROL SUBJECTS
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Royal Brompton Hospital, London, Triemli Hospital, Zurich, Institute of Physiology, University of Zurich, Switzerland and Department of Sports Medicine, Karl-Ruprechtss University, Heidelberg, Germany.

Some people who ascend to high altitude develop pulmonary oedema which is reproducible on repeated exposure. The pathophysiology may be related to pulmonary hypertension. Twelve mountaineers, 7 high altitude pulmonary oedema sensitive (HAPE-S) subjects (age 45.0 years) and 5 control subjects (age 39.8 years) underwent 50 h ambulatory pulmonary artery pressure recording in a barochamber. After a day at 4800 m altitude (Zurich), an ascent was made over 6 to 4000 m where the next day was spent. Average pulmonary artery pressure was calculated for day and night at 480 m and 4000 m. Systolic and diastolic pulmonary artery pressure (mm Hg) were compared between control and HAPE-S subjects using analysis of variance:

<table>
<thead>
<tr>
<th>Control</th>
<th>HAPE-S</th>
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<tr>
<td>Systolic</td>
<td>Diastolic</td>
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<tr>
<td>Day 480m</td>
<td>7.36</td>
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<tr>
<td>Night 480m</td>
<td>10.39</td>
</tr>
<tr>
<td>Day 4000m</td>
<td>14.26</td>
</tr>
<tr>
<td>Night 4000m</td>
<td>14.05</td>
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* p<0.02, ** p<0.001, *** p<0.0001

There was no significant difference between the groups in heart rate, oxygen saturation, end tidal carbon dioxide or maximum rate of oxygen consumption. In conclusion, pulmonary artery pressure is higher in HAPE-S than control subjects and while this is marked at 4000 m it is also present at 480 m. This finding suggests gene polymorphism.
Vascular smooth muscle cells from human atherosclerotic plaques are highly susceptible to p53-mediated apoptosis or growth arrest


Myocardial infarction (MI) is caused by rupture of an atherosclerotic plaque at an area deficient in vascular smooth muscle cells (VSMCs), with subsequent thrombosis. We have recently shown that apoptosis occurs at higher rates in plaques than in normal vessels, and that the suppressor gene p53 regulates apoptosis of VSMCs following deregulated cell cycle control. We therefore analysed p53 function in VSMCs derived from human coronary plaques or the media of normal coronary arteries. VSMCs with reduced or increased p53 activity were created using retroviruses containing a dominant-negative p53 minigene or Human Papilloma Virus E6 (which degrades p53), or a chimaeric p53 protein which could be activated pharmacologically (p53 ERTM). Apoptosis and cell proliferation were determined and quantified by time-lapse video microscopy and flow cytometry. Basal levels of p53 expression or activity were similar in plaque or normal VSMCs, as determined by Western blot or transient transfection of a p53 reporter. Suppression of p53 activity blocked growth arrest but not apoptosis in response to DNA damage (etoposide treatment) in plaque and normal VSMCs. Apoptosis of plaque or normal VSMCs in low or high serum conditions was not suppressed by low levels of p53 activity. However, p53 overexpression induced arrest and apoptosis in plaque, but not normal VSMCs. Furthermore, arrest by p53-dependent mechanisms in plaque VSMCs suppressed subsequent apoptosis in these cells, indicating that the presence of the cell in the cell cycle per se determines sensitivity to p53-mediated growth arrest, p53-mediated apoptosis of plaque VSMCs was independent of new RNA or protein synthesis. We conclude that VSMCs from human plaques have a markedly increased sensitivity to p53-mediated apoptosis. However, the mechanism of p53-mediated plaque VSMC apoptosis may be distinct mechanistically from that inducing growth arrest.
Publication bias in medical research, particularly of new therapies, is recognised but the possible magnitude of its effect on statistical overviews of trials is not always appreciated. Incomplete overviews can give a very misleading impression of effect size. Eleven controlled trials of rehabilitation following myocardial infarction compared psychological therapy and counselling (independently of other modalities) with 'usual care' (2209 patients). Eight reported total mortality, one to five years after trial entry; 123 deaths among 1954 patients. An initial statistical overview of these trials suggests a 'relative risk' (RR) of mortality of 0.65 with 95% confidence interval (CI) of 0.46-0.91, a greater mortality reduction than aspirin, a 2 blocker or thrombolysis. A 'funnel plot' suggests some publication bias. Correspondence with principal investigators of those trials that did not report total mortality provides a revised estimate of RR = 0.73 (95% CI 0.53-1.00) corroborating the suspicion. Individual trials were mostly small and many were self-evaluations by therapists. When 9 of the above 11 were published, a multicentre trial was designed with sufficient power to detect a 20% reduction in one year mortality. This multicentre trial, with larger numbers than all previous trials combined, found no difference in mortality RR = 1.01 (95% CI 0.75 - 1.37).

AN AUDIT OF THROMBOLYSIS FOR SUSPECTED ACUTE MYOCARDIAL INFARCTION: EXPERIENCE WITH UROKINASE IN GENERAL PRACTICE
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Urokinase is a long-established thrombolytic agent which is convenient for use by general practitioners because it is given by bolus injection, is non-antigenic, and does not need refrigerated storage. However, experience with its use in acute myocardial infarction is limited, and urokinase is not licensed for this indication in the UK.

In an audit of the early management of suspected acute myocardial infarction, 278 administrations of thrombolytic therapy were identified in patients from practices ≥30 minutes travelling time from hospital. Of these, 98 (35%) were by general practitioners, at a median time after onset of 120 minutes; in 180 (65%) cases administration of thrombolytic therapy was deferred until after admission to hospital, at 240 minutes. Median call-to-needle times were 45 (94% ≤90 min) and 163 (0% ≤90 min) minutes respectively. Of the thrombolytic given prehospital, 80 doses (82%) were of urokinase 2MIU, 10 (10%) anistreplase, and 8 (8%) streptokinase. In 6 cases venous fibrillation was reported within an hour of administration of urokinase; 5/6 rescusitations were successful; one patient had a fatal aortic arrest. Transfusion of 2 units of blood following haematemesis and melena was necessary in one patient. Hypotensive reactions to urokinase have not been seen. One year following urokinase the estimated mortality was 18%, the same as after other thrombolytic agents given prehospital; for patients given thrombolysis in hospital it was 31%.

Conclusion The results from this audit provide reassurance that urokinase is a safe, effective, and convenient thrombolytic agent for use in acute myocardial infarction by general practitioners.

ECONOMICS OF MYOCARDIAL PERFUSION IMAGING IN EUROPE - THE EMPIRE STUDY
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Physicians use myocardial perfusion imaging (MPI) to a variable extent in patients presenting with possible coronary artery disease (CAD). There are few clinical data on the most cost-effective strategy although computer models predict that routine use of MPI is cost-effective. We have studied 400 patients presenting to 8 hospitals for the diagnosis of CAD. The hospitals were regular users or non-users of MPI with one of each in 4 countries (F, D, I, UK). Information was gathered retrospectively on presentation, investigations, complications, and clinical management, and patients were followed up 2 years in order to assess outcome. Costs and prices were estimated in each hospital. Pre- and post-test probabilities of CAD were computed for diagnostic tests and each test was also assigned as diagnostic or part of management. Diagnostic strategies defined were 1: Ex-ECG/angio, 2: Ex-ECG/MPI/angio, 3: MPI/angio, 4 angio. Primary outcome measures were the cost and accuracy of diagnosis, the cost of subsequent management, and clinical outcome. Secondary measures included prognostic power, normal angiography rate, and rate of angiography not followed by revascularisation. Mean diagnostic costs per patient were: Strategy 1: £333, 2: £339, 3: £288, 4: £775 (P<0.001). Mean diagnostic cost in the MPI user centres was £373 and in the non-users £519 (P<0.001). Mean probability of the presence of CAD when the final clinical diagnosis was CAD present was 1: 0.89, 2: 0.91, 3: 0.95, 4: 0.97, and when CAD was absent, 1: 0.22, 2: 0.11, 3: 0.12, 4: 0.05 (P<0.001). Thus quality of diagnosis for the scintigraphic strategies (2 and 3) was higher than strategy 1 and almost equal to the angiographic strategy (4). Prognostic power at diagnosis was higher (P=0.001) and normal coronary angiography rate was lower (P=0.001) in the scintigraphic centres and strategies. We conclude that diagnostic strategies routinely using MPI are cheaper and equally effective compared with strategies that do not use MPI.

DIPYRIDAMOLE-THALLIUM SCANNING AND THE PREDICTION OF PERIPHERAL MYOCARDIAL INFARCTION: A PROSPECTIVE, BLINDED STUDY.
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Dipyridamole-thallium scanning is usually considered as the 'gold-standard' investigation for assessment of peripertative risk in patients undergoing peripheral vascular surgery, but recent studies have cast doubt on its value. The aim of this study was to determine whether semi-quantitative dipyridamole-thallium scanning and gated blood-pool imaging can predict perioperative myocardial infarction. 333 patients underwent preoperative dipyridamole-thallium scanning and a stress and redistribution perfusion score were devised. Right and left ventricular ejection fraction were obtained from technetium-labelled blood pool scans. Surgeons were blinded to the results of scanning, except in 3 of 40 cancelled operations. Out of 293 patients who underwent surgery there were 21 perioperative myocardial infarctions or cardiac deaths as determined by daily ECG and CK-MB screening. Median reversibility score was higher in those with events (12 v 6, p=0.0001 Mann-Whitney). 25 patients had a moderate to large reversible defect on thallium scanning, of whom only 3 had events (sensitivity 14%, specificity 85%, PPV 12%, NPV 93%). Right ventricular ejection fraction did not correlate with perioperative cardiac events, but left ventricular ejection fraction was lower in those with events (31 v 38, p=0.015).

Semi-quantitative dipyridamole-thallium scanning, coupled with gated blood-pool imaging, predicts perioperative cardiac risk. However the sensitivity and positive predictive accuracy of a reversible defect are low, and the cost of routine dipyridamole-thallium scanning in unselected patients is considerable. Improved methods of risk prediction are required.
Dobutamine Stress MRI as a Pre Operative Predictor of Myocardial Viability in areas of Regional Wall Motion Abnormality
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Abstract: We have examined dobutamine stress MRI as a predictor of functional recovery after coronary artery bypass grafting (CABG) in subjects with areas of akinetic or severely hypokinetic myocardium. Seventeen patients with multivessel coronary disease and at least one substantial wall motion abnormality demonstrated at ventriculography were studied before, and 3-6 months after revascularisation. Rest and dobutamine stress MRI were performed using a 26 segment model. The mean dobutamine dosage used was 15µg.kg.min⁻¹, with a mean heart rate achieved of 95 bpm. Radial wall thickening (RWT) analysis was performed in comparison to our normal reference range (n=33), and semi-subjective regional wall motion (RWM) observer analysis was scored on a 0 to 3 scale. Reduced RWT was taken as >1 SD below normal, and reduced RWM as a score of <2. At rest, 147 segments had reduced RWT and 97 reduced RWM. 55/147 segments had improved RWT with stress, and 20/97 an improved RWM. Post operative improvement in RWT and RWM was seen in 33 and 57 segments respectively, with a maximal predictive sensitivity and specificity of 52% and 88%.

Conclusion: Dobutamine stress MRI is highly specific, though at best moderately sensitive as a predictor of functional recovery after CABG in akinetic or severely hypokinetic myocardium.

ADENOSINE STRESS MYOCARDIAL PERFUSION IMAGING USING ECHO-PLANAR MRI WITH A 0.5T SCANNER
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Myocardial perfusion imaging assesses the physiological significance of coronary stenosis. Current techniques involve the use of ionising radiation and have a relatively poor resolution. We compared magnetic resonance imaging (MRI) perfusion studies with radionuclide SPECT scans. In 22 patients with abnormal SPECT (18 males, 4 females, mean age 65, range 46-77) single shot echo-planar imaging with an acquisition time of between 50-100 ms, was performed on a mobile 0.5T scanner. End systolic gating was used with a pixel size of 3.9 x 3.9 mm giving several pixels across the myocardium. Fat suppression reduced the signal from surrounding tissues, and a preparatory inversion pulse was used to null the myocardial signal. For the perfusion study, a bolus of 0.05mmol/kg Gadolinium DTPA was given through a right atrial catheter placed using intravenous electrocardiography via the right antecubital fossa. Two scans were performed, the first at rest and another during the infusion of adenosine at a dose of 140 µg/min to induce maximal coronary hyperaemia. Images were interpreted by visual analysis of the contrast wash-in, and by drawing signal intensity curves obtained from 16 regions of interest around the myocardium. Of the 22 patients, 20 (91%) had interpretable results, the other 2 being hindered by gating problems during acquisition. Of 320 segments, 112 were abnormal by SPECT, of which 94 were reversible and 18 fixed. By MRI, 96 segments were abnormal with 80% concordance with SPECT studies. MRI is fast in comparison to nuclear imaging (1 hour vs typically 4-6 hours) and the use of multislice imaging, which has now been implemented, will enable complete coverage of the myocardium.

ADENOSINE MYOCARDIAL PERFUSION SCINTIGRAPHY: CAN CLINICAL OBSERVATIONS PREDICT ISCHAEMIA?
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Chest pain during dynamic exercise is a specific sign of myocardial ischaemia but clinical observations during adenosine stress may have a different significance. We have studied 300 patients undergoing adenosine myocardial perfusion scintigraphy, in order to assess the relationship between the presence, extent and severity of ischaemia and the presence of pain, and whether clinical observations or features of pain can distinguish ischaemic from non-ischaemic pain. Clinical variables included were age, sex, medication, and prior angina, infarction, revascularisation or heart failure. Haemodynamic response and cardiac symptoms were recorded. The site, extent and severity of perfusion abnormalities were assessed quantitatively from stress and redistribution thallium tomograms. Pain was more likely to be experienced in those aged 65 and over (P<0.05), those with prior angina (P<0.0001), and those on angina medication (P<0.0001). Pain was less likely to be experienced in patients with heart failure (P=0.02), and if adenosine was combined with exercise as opposed to adenosine alone (P=0.05). In patients who experiences pain, this pain was more likely to be ischaemic following coronary bypass grafting (P=0.004), and it was less likely to be ischaemic in females (P=0.03). Features predictive of myocardial ischaemia were any pain (P=0.03), central chest pain (P=0.03), pain similar to symptoms in everyday life (P=0.005), and pain described as “tight” (P=0.03). Features that were not predictive of ischaemia were pain in sites other than the chest, the severity of pain, the time of onset of pain, and the presence of associated ST segment depression. Despite these statistically significant findings, many of the individual features had poor sensitivity and specificity for predicting pain, and for distinguishing between ischaemic and non-ischaemic pain. Therefore, in terms of using clinical features to assist with image interpretation, there is little to be gained from a rigorous consideration of clinical observations.

EXERCISE TRAINING FOLLOWING MYOCARDIAL INFARCTION IMPROVES MYOCARDIAL PERFUSION ASSESSED BY QUANTITATIVE TI-201 SCINTIGRAPHY.
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Aims: We assessed the effects of a six week exercise programme following myocardial infarction(MI) on myocardial perfusion abnormalities using quantitative TI-201 scintigraphy. Methods: Twenty-five patients(23M,2F, median age 61 yrs), all having acute MI diagnosed by standard ECG criteria, were randomised to one of two groups: i) those undergoing a supervised six week exercise protocol(n=15 patients) and ii) a control group not undergoing exercise(n=10). All underwent 3 sequential TI-201 myocardial perfusion scans: within 10 days of MI, after 6 weeks, and at 3 months. Myocardial stress was performed in an identical fashion on each occasion by infusion of 140µg/kg/min of adenosine coupled with 25W of ergometer pedalling for 6 minutes. At 4 minutes, 80 Mbq TI-201 was administered and images acquired on a dual headed gamma camera, immediately after stress and 4 hours later. Polar map analysis of the images was performed using a computer assisted algorithm comparing stress and redistribution. Values for defect extent, severity and degree of reversibility were generated. Results: A total of 29 perfusion defects were identified, 18 in the exercise group and 11 in the control group. Study population(n=25 patients)there was a decrease in mean extent and severity of defects from 118±5 to 114±10 pixels and from 651±3 to 640±5 SD(p<ns) respectively. Percentage reversibility increased from 11±3 to 14±5,% Exercise group(n=15)there was a decrease in the mean extent and severity of the defects from 10±1 to 6±2 and 581±98 to 485±80 SD(p<0.05). Reversibility increased from 14.6±3 to 17±5.3,. Control group(n=10);mean extent and severity increased from 133±13 to 144±12 pixels and 765±93 to 877±101 SD(p<0.05). Reversibility increased from 5.2±1 to 9.6±3%. Conclusion: Following acute MI, patients undergoing a six week exercise programme display improved myocardial perfusion characteristics. In patients not exercising, the perfusion defect size and severity increases.
ASSMENT OF NITROGLYCERINE ENHANCED Tc-99m SESTAMIBI SPECT FOR THE DETECTION OF VIABLE MYOCARDIUM IN CONGESTIVE HEART FAILURE

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Tc-99m sestamibi imaging (MiBi) is widely used to assess coronary artery disease but its value for the detection of myocardial viability remains controversial. We prospectively evaluated 52 consecutive patients with congestive heart failure (NYHA II-IV) due to coronary artery disease with left ventricular ejection fraction < 35%. Both thallium-201 and Tc-99m sestamibi SPECT imaging were performed at rest following 0.5 mg of sublingual nitroglycerin. Systolic wall thickening was assessed by echocardiography. Left ventricular shortening was divided into 12 matching segments for all 3 imaging modalities. Tracer uptake was scored semiquantitatively (0 = normal, 4 = absent) and viability was present when 50% tracer uptake was seen in a severely dysfunctional segment. The tracer uptake was also calculated in the dysfunctional segments using the semiquantitative score for both Tc-99m sestamibi imaging and thallium-201. Of a total of 624 segments, 459 (74%) showed severe dysfunction; of these, Tc-99m sestamibi imaging showed viability in 318 (65%) and thallium-201 imaging in 289 (61%) segments (P < NS). Concordance between thallium-201 imaging and Tc-99m sestamibi imaging was 81% (kappa = 0.60). The mean score of thallium-201 and Tc-99m sestamibi imaging were 1.89±0.74 and 1.92±0.66 (P < NS). Thus, nitroglycerin enhanced Tc-99m sestamibi imaging is comparable to thallium-201 for the detection of viability in severely dysfunctional myocardium.

THE UTILITY OF REST THALLIUM IMAGING IN PREDICTING IMPROVEMENT IN SEGMENTAL LEFT VENTRICULAR FUNCTION AFTER REVASCULARISATION

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Segmental Left Ventricular (LV) contractile dysfunction is common in patients with coronary artery disease (CAD), especially in the setting of previous myocardial infarction (MI). However, some of these areas will be "hibernating" and have the capacity to improve their function after coronary revascularisation. Various methods have been described for the detection of such "hibernating" segments; of these potentially the most widely available to Cardiologists is thallium-201(Tl) perfusion imaging. We set out to prospectively investigate the accuracy of this method at the segmental LV level. Methods. We studied 16 patients with angiographically confirmed CAD and a previous Q-wave MI. All patients had been selected for coronary revascularisation on clinical grounds (CABG in 15, PTCA in 1). At rest all patients were injected with 74 MBq of Tl-201 with SPECT imaging at 15 mins and after 4 hours further rest. The patients also had 2D echocardiography to assess LV function prior to revascularisation and then 2 months after. LV wall motion was scored on a 4 point scale using a standard 16 segment model. The SPECT images were also assessed on a similar 16 segment map and the presence of viable tissue was scored using predetermined criteria. Results. A total of 256 segments were analysed. 108 segments had abnormal wall motion prior to revascularisation; of these 27 showed improvement in motion by at least 1 point after. The total sensitivity and specificity of TL SPECT for detecting these "hibernating" segments was 80% and 88% respectively. The positive predictive accuracy of the technique was 72%. Conclusion. Rest TL perfusion imaging is a useful and sensitive method for the detection of myocardial hibernation in CAD patients. Any Nuclear Medicine department with experience in SPECT perfusion imaging could perform such studies and hence this method could be widely available to practising Cardiologists.

ENHANCED DETECTION OF MULTIVESSEL DISEASE BY SIMULTANEOUS INOTROPIC STRESS Tc-99m SESTAMIBI SPECT IMAGING AND ECHOCARDIOGRAPHY.

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Exercise electrocardiography (ETT) is sub-optimal for the identification of high risk patients with multivessel disease. The aim of this study was to assess whether inotropic stress testing in conjunction with either Tc-99m sestamibi SPECT imaging (MiBi), echocardiography (echo) on both, could enhance the detection of multivessel disease in association with clinical variables and ETT. Accordingly, 100 patients underwent simultaneous inotropic stress MiBi and echo, using either dobutamine or adrenaline. Rest and stress MiBi and echo studies were analysed using a 12 segment left ventricular model. Five anterior and anteroseptal segments were assigned to the left anterior descending artery, 5 inferior and inferoseptal segments to the right coronary artery and 2 lateral segments to the left circumflex artery. Reduced tracer uptake or wall thickening in at least 2 coronary artery territories at peak stress were considered diagnostic of multivessel disease for MiBi and echo, respectively. ETT criteria for the detection of multivessel disease included workload ≤ 110 mets, ST depression ≥ 1.5 mm or hypotension. Coronary angiography was used as the reference standard and a ≥ 50% stenosis at least one of the major coronary arteries was considered significant. On this basis, 51 patients had multivessel disease, 23 had single vessel disease and 26 had normal coronary arteries. Univariate analysis showed age, previous MI, MiBi and echo, but not ETT, to be predictive of multivessel disease. The addition of either MiBi or echo to clinical variables enhanced the detection of multivessel disease (p<0.001; R^2=0.29) and adding both had further incremental value (p<0.001; R^2=0.35). Therefore, the assessment of both perfusion and function by inotropic stress testing is an advantage in the non-invasive detection of multivessel disease. This has important implications for techniques such as gated SPECT imaging and myocardial contrast echocardiography which take both of these factors into account.

THE PREVALENCE OF HIBERNATING MYOCARDIUM IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION.

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Introduction: Severe left ventricular (LV) dysfunction is an important determinant of poor prognosis in ischaemic heart disease (IHD). The prognosis could be improved with revascularisation if hibernating myocardium is present. However, the proportion of patients (pts) likely to benefit from this intervention is controversial. Therefore, we studied the prevalence of hibernating myocardium in pts with severe LV dysfunction and IHD. Methods: From a consecutive series of 302 pts undergoing coronary angiography, 36 pts with IHD and severe LV dysfunction were identified. Hibernation was defined as areas of significant metabolic-perfusion mismatch on positron emission tomography (PET). The perfusion marker is F-18-fluorodeoxyglucose. The images are displayed on polar maps. Each polar map is divided into five regions. Results: Of the 36 pts with IHD & severe LV dysfunction, 9 pts were excluded due to: emergency revascularisation (n=3), death (n=1), loss to follow up (n=1), inability to give consent (n=3) and age 40 years (n=1, ethical committee guidelines). Of 27 pts imaged, 15 pts (55.5%) had hibernating myocardium, including 6 patients in whom more than one region was involved. The imaged and the excluded groups were similar. Conclusion: More than 50% of patients with IHD and severe LV dysfunction have hibernating myocardium. This reflects a higher prevalence than previously predicted.
NEURAL NETWORK APPLIED TO SPECT THALLIUM PERfusion IMAGING AS A DIAGNOSTIC AID
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Neuronal computational methods that "simulate" the brain's decision processes can be used for diagnostic problems that involve pattern recognition. We have tested this technique for the interpretation of SPECT thallium perfusion scans. Scans were obtained from male patients undergoing routine stress perfusion imaging for the assessment of chest pain. Polar plots, reconstituted from short axial slices definitely containing left ventricular myocardium, were encoded to a 32x32 matrix by use of D4 wavelet transforms, which preserve spatial resolution. These plots were presented to the neural network which was subsequently trained on a set of data classified by an experienced cardiologist on the basis of ECG and images as either normal, anterior or inferior inact. The network was then tested on new scans; a further 21 normal males, randomly mixed with 37 who had evidence of myocardial infarction. In distinguishing normal from abnormal, the accuracy, sensitivity and specificity were all 95% while the positive predictive value was 97%. Site of abnormality was correctly designated in 95% or inferior/lateral in 89%. Four patients had both anterior and inferior perfusion defects; in 2 both defects were recognised, in 1 neither, and in 1 the anterior alone. Thus as with human observers, most difficulty arises in assigning inferior perfusion defects. In summary, neural networks offer potential when applied to thallium perfusion scans, and may be of use as a clinical computational aid.

NEW VASCULAR INJURY MODELS IN MICE
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Transgenic mice have emerged as powerful tools for studying genetic influences on diseases, including cardiovascular disease. Arterial responses to injury include neointimal hyperplasia, as a non-reproducible method of inducing this is required for vascular studies. The aim of this study was to find a simple method of injury which could reliably produce neointimal lesions in the mouse carotid artery. Method: Six different techniques were compared. 1. Crush, 2. cryo-injury, 3. endoluminal abrasion with a coronary guidewire (diameter ~ 0.35mm, after Lindner et al '93, Circ.Res.73:792-6), 4. endoluminal abrasion with a fine tungsten wire (diameter = 0.12mm) using a Selinger technique, 5. application of a non-constrictive collar, 6. lumen reduction with ligatures or a constrictive cuff. The left carotid artery of ICR mice was injured (n=5 for each method), harvested two weeks later and processed for light microscopy. Sections were taken every 0.1 mm through the whole tissue and stained with H & E and EVG. Uninjured right carotid artery served as control. Results: Crush injury induced an adventitial-medial reaction with islands of neointima seen only in 2 of 8 vessels examined. Cryo-injury caused smooth muscle cell depletion and stimulated neointimal lesions in 2 of 5. Endoluminal abrasion with a coronary guidewire resulted in reactive medial changes without appearance of a neointima. In contrast, the fine sharper tungsten wire disrupted elastic laminae and produced neointimal lesions not dissimilar to those seen in the 32x32 matrix angioplasty model (4 of 5). The non-constrictive collar attracted a mono-nuclear inflammatory exudate between the cuff and artery but did not cause a neointima. Lumen reduction consistently produced a neointima in the region of stenosis (5 in 5). Conclusion: Creating a stenosis in the carotid artery endoluminally caused neointimal proliferation in the mouse carotid artery.

HIGH RESOLUTION M.R.I. OF THE POPILITEAL ARTERY WALL IN NORMAL SUBJECTS AND PATIENTS WITH ATHEROSCLEROSIS

Conventional Xray arteriography visualises the arterial lumen only. There is a need for a non-invasive technique to image the vessel wall. We describe high resolution M.R. imaging of the wall of the popliteal artery in volunteers and patients with popliteal atherosclerosis. Seven volunteers (3 male, 4 female aged 35 to 47) and ten patients with popliteal artery atheroma demonstrated on X-ray arteriography were imaged. Examinations were performed on a 1.5T clinical M.R. system using a 3 inch surface coil. An initial 2D time of flight angiogram was used in the patient group to match the level of the T1 weighted acquisition to the site of atheroma, the popliteal arteries of the volunteers were imaged at the level of the mid patella. Images of the arterial wall were obtained with a standard cardiac gated T1 weighted spin echo sequence and the following parameters: TE 25 msec, slice thickness 3mm, gap 1.5 mm, 6 cm FOV, 512 x 256 matrix, 2NEX, RRBW 8 kHz, superior, inferior and anterior spatial preturbation was applied. Acquisition times were approximately 4 minutes. Cine phase contrast acquisition was performed to define the optimal gating trigger delay and provide flow volume data from the vessel immediately above the stenosis in the patients. In all subjects the arterial wall was clearly visible. In the patients, the thickened atheromatous wall and narrowed lumen were well defined and dimensions could be correlated with conventional angiographic findings. Focal variations in plaque signal intensity were seen in several patients - these may be genuine or artefactual. This work shows that M.R.I. can provide non-invasive imaging of the vessel wall in vivo. Serial imaging of the popliteal artery wall may be useful to monitor effects of treatment and interventions such as angioplasty.

EFFECTS OF INHIBITION AND STIMULATION OF NITRIC OXIDE SYNTHESIS IN FOREARM PERFUSION VASCULARITY OF MEN AND WOMEN
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Nitric oxide (NO) has potential anti-atherogenic actions. Increased NO synthesis may explain the lower incidence of atheromatous disease in pre-menopausal women compared with men. We investigated gender differences in NO synthesis in forearm volunteers. Basal NO synthesis was assessed by comparing vasoconstrictor responses to brachial arterial infusion of NO-monomethyyl-L-arginine (L-NMMA, an inhibitor of NO synthesis) with those to nonforearm (NA) in 20 men and 20 pre-menopausal women. Stimulated NO synthesis was assessed by comparing vasoconstrictor responses to substance P (sP, acting through endothelium-derived NO), nitroprusside (NP), and verapamil (Vrp) (sP) in 10 men and 10 women. Inter-individual variation (e.g. in forearm geometry) was thus controlled for by intra-subject comparison of responses to endothelium-dependent with endothelium-independent agents. Subjects were matched for age, mean blood pressure, and cholesterol, and were on no medication (including the oral contraceptive pill). Forearm blood flow was measured in both arms by transonic occlusion plethysmography and drugs administered via the left brachial artery. Responses to drugs were expressed as percent change in the ratio of blood flow in the infused to that in the control arm. Repeated measurement analysis of variance was used to test for an interaction between the responses to infused drug and gender. In men, vasoconstrictor responses to NA (50-240 pmol min^-1) were 26-37%, greater than those to L-NMMA (1-4 pmol min^-1) (P=0.0007), Vasodilator responses to sP (0.2-10 pmol min^-1), NP (3-26 pmol min^-1), and Vrp (20-160 pmol min^-1) were similar (P=0.76 in men (sP: 63-302%, NP: 71-1212%, Vrp: 68-267%) and women (sP: 62-283%, NP: 47-1692%, Vrp: 51-243%). The differences in vasoconstrictor responses to inhibition of basal NO synthesis (relative to the comparator vasoconstrictor NA) between men and women suggest that basal NO synthesis is greater in women compared to men. There are no gender differences in vascular dilator responses to the NO-dependent agonist sP (relative to comparator vasodilators NP and Vrp) in men and women. Women suggest the gender difference in basal NO synthesis is greater than that for stimulated NO synthesis. Increased basal synthesis of NO may, at least in part, protect pre-menopausal women from atheromatous disease.
Increased Nitric Oxide Activity by Converting Enzyme Inhibition Improves Endothelial Dysfunction in Humans
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Angiotensin converting enzyme inhibitors (ACEI) have vasculoprotective effects. We hypothesized that this is due to their ability to reduce bradykinin (BK) degradation and thus increase nitric oxide activity. In the femoral circulation of 45 pts, 41 of whom had demonstrated or at risk factors, we studied endothelin-1-dependent vasodilation with BK (250 ng/min) and acetylcholine (ACH, 300 μg/min), and endothelin-1-independent vasodilation with sodium nitroprusside (SNP, 40 μg/min) before and after enalaprilat (EN, 20 μg/min). In 16 pts, we repeated the infusions in the presence of L-Nω monomethyl arginine (L-NMMA, 64μmol/min), an inhibitor of nitric oxide synthase. Femoral artery flow velocity was measured using a Doppler flow wire and the resistance index (RI= mmHg cm-1 sec) calculated as mean arterial pressure ×flow velocity. EN did not alter resting RI (p=0.1; mean±SD) but enhanced BK mediated dilation (2.7±1.0 to 2.0±0.7 RI, p<0.001). The potentiation of ACh mediated dilation with EN was inversely proportional to the baseline ACh response (r=−0.5, p<0.005). EN did not potentiate SNP mediated vasodilation. L-NMMA inhibited the effect of BK (p<0.07) and ACh (p=0.02), but not SNP (p=0.7). Furthermore, in the presence of L-NMMA, EN did not potentiate BK (3.1±1.1 to 3.5±1.1 RI) and ACh (5.3±2.6 to 5.4±3.1 RI) responses. These findings suggest that ACEI selectively improve endothelin-1 dependent vasodilation in patients, particularly those with endothelial dysfunction. Increased nitric oxide activity with ACEI is in part responsible for this beneficial effect.

ABNORMAL SENSITIVITY TO ENDOTHELIN-1 IN PATIENTS WITH SYNDROME X
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The induction of "microvascular angina" in patients with syndrome X has been attributed to a generalised disorder of vascular and endothelial cell function. We tested this hypothesis by assessing the endothelin system in the forearm vascular bed in such patients. Ten syndrome X patients were compared with healthy age and sex matched controls. Following brachial artery cannulation, forearm blood flow (FBF) was measured in both arms using venous occlusion plethysmography. On separate days, at least one month apart, BQ-123 (endothelin A receptor antagonist) at 100 nmol/min, and endothelin-1 at 5 pmol/min, were infused for 90 min each. BQ-123 caused a slow onset vasodilatation (p<0.001; both groups) with no significant differences between the groups. However, endothelin-1 caused a slow onset vasoconstriction (p=0.001; both groups) with a peak mean reduction in FBF of 21 ± 4% in patients with syndrome X compared to 35 ± 3% in the control group (p<0.001; between groups). Vasocostriction to endothelin-1 was negatively correlated with plasma endothelin-1 concentrations (r=−0.51; p<0.04).

OPTIMISING ADENOVIRAL VASCULAR GENE TRANSFER IN VIVO: IMPACT OF EARLY ACUTE INFLAMMATION ON TRANSGENE EXPRESSION AND VASOMOTOR FUNCTION.
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Recombinant adenoviruses are attractive vectors for in-vivo vascular gene therapy, although chronic inflammation and transgene loss results from host immunity to viral proteins. However, early acute effects of adenovirus may also have important implications for in vivo vascular gene transfer. We aimed to assess the mechanism and functional significance of endothelial injury after adenoviral gene transfer. We performed B-Galactosidase (B-Gal) gene transfer to rabbit carotid arteries (CA), using increasing viral titers. Arteries were either left in place in-vivo, or removed and incubated ex-vivo. After 3 days, we determined: (1) B-Gal protein levels, by ELISA: (2) endothelial VCAM-1 and ICAM-1 expression, and inflammation, by immunohistochemistry; or (3) endothelial function, by isometric vasomotor studies. The importance of neutrophils (PMN) was examined by inducing neutropenia with vinblastine.

Results: A total of 68 rabbit CA were studied. (1) B-Gal expression was reduced 4-fold in in-vivo CA compared with paired ex-vivo CA (n=18, p<0.001). Increasing viral titer > 5 x 10^9 pfu/ml had little effect on B-Gal expression in-vivo. (2) Endothelial PMN were not seen ex-vivo but increased with viral titer in-vivo (21 ± 4.2 ± 0.7 x 10^7 pmf/ml). PMN section at 8 ± 10^7 pmf/ml vs. 2 ± 0.7 ± 4.1 x 10^2 pmf/ml; p<0.01. (3) Phenylephrine-induced contraction was unaffected by gene transfer. In contrast, endothelial dependent relaxation to acetylcholine (ACh) was greatly impaired (31 ± 6 ± 6 % relaxation at 1 x 10^7 pmf/ml vs. 53 ± 5 ± 8 % in control CA, at 10 μM ACh; p<0.001). (4) Vinblastine-induced neutropenia virtually abolished PMN infiltration in CA, and improved ACh dependent relaxation.

Conclusions: In vivo vascular adenoviral gene transfer can result in endothelial injury, impaired vasomotor function, and greatly reduced transgene expression. Acute endothelial toxicity is mediated largely by PMN. However, we identify a "window" of viral titer for optimal vascular adenoviral gene transfer, between 1 and 5 x 10^9 pfu/ml, when transgene expression is high but vessel injury is minimized.

Inhibition of Regrowth of Arterial Endothelium in the Apolipoprotein E Knockout Mouse
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Acute endothelial cell loss is commonly observed after balloon angioplasty and vein bypass grafting, and is followed by healing of the endothelial monolayer by a combination of cell migration and cell proliferation. Although animal studies indicate that endothelial regrowth is critical for restoring normal function to injured blood vessels, the factors controlling it are not known. Studying the process is difficult because specific inhibitory drugs or antibodies are generally not available. We have therefore developed a novel marine model of endothelial injury in order to take advantage of the availability of genetically modified animals. Fine PTFE tubing (diameter 250μm) is introduced into the left common carotid artery via the external branch and then advanced to the aortic arch. The tubing is slowly withdrawn to the carotid bifurcation with constant rotation, four times. This procedure removes all of the endothelium from the common carotid artery, as determined by administration of Evan’s Blue dye in vivo and by en face staining of the artery ex vivo. There is no significant loss of medial smooth muscle cells and no evidence of thrombosis. Endothelial regrowth is first detectable four days after injury, and complete restoration of a continuous endothelial monolayer is observed seven to eight days after injury.

The technique has been applied to mice homozygous for disruption of the gene for apolipoprotein E (apoE), a possible regulator of endothelial growth. Normal C57Bl6 mice were used as wild-type controls, and endothelial regrowth was quantified seven days after injury. Results are expressed as mean±SEM.

These results show that endothelial regrowth is significantly inhibited in apoE knockout mice, suggesting that this protein is an endogenous stimulant of endothelial regrowth in injured arteries.

We have previously shown that cultured endothelial cells tonically release low molecular weight factor(s) that reduce myocyte shortening (by ~20%). We studied the effect of endothelial cell hypoxia and reoxygenation on release of cardioactive substances. Porcine cultured aortic endothelial and right ventricular endocardial endothelial cells were superfused with normoxic (Po₂ >160 mmHg) or hypoxic (Po₂ <60 mmHg) physiological buffer. Single-pass superfusates were collected, stored at -70°C, and tested on adult rat ventricular myocytes after reequilibration (Po₂ >160 mmHg, pH, temperature). Myocyte twitch contraction (video edge detection) and intracellular Ca²⁺ (Fura-2 ratio) were recorded. Hypoxic superfuse from both cell types induced a rapid, reversible reduction, or a total abolition, of twitch contraction (-44.9±7.3%; mean±SEM; n=1005; n=106) and decrease in cell diastolic length (2.1±0.6%; n=85), but no significant change in Ca²⁺ transients, (-12.3±3.0%; P=0.05; n=106). The figure shows the effect of duration of endothelial hypoxia (left) and reoxygenation (right) on myocyte contractility. Thus, cultured endothelial cells reversibly respond to acute moderate hypoxia by releasing an unidentified substance(s) which inhibits myocyte contractility predominantly through effects on myofilaments rather than changes in cytosolic Ca²⁺. Such a mechanism may contribute to the regulation of oxygen supply-demand balance in the heart.

**Synergistic Regulation of MMP-1, MMP-3 and MMP-9 Expression by Inflammatory Cytokines and Growth Factors in Rabbit Vascular Smooth Muscle Cells and Dermal Fibroblasts.**

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The matrix metalloproteinases (MMPs) are a group of closely related zinc-dependent endopeptidases thought to be important for matrix turnover during normal physiological processes. Overexpression of MMPs has been implicated in a number of pathological processes including the migration and proliferation of smooth muscle cells (SMCs) during the development of atherosclerosis. Previous work conducted in our department has demonstrated that IL-1α acts synergistically with PDGF(BB) in upregulating MMP-9 mRNA and protein secretion in rabbit SMCs. Here we demonstrate that other inflammatory cytokines (TNF α) and growth factors (NGF) can act synergistically to upregulate MMP-9 expression and extend the study to MMP-1 and MMP-3 expression in both rabbit SMCs and rabbit dermal fibroblasts. Denatometric analysis of gelatin zymograms demonstrated that either interleukin-1 alpha (IL-1 α) or tumour necrosis factor alpha (TNF α) were able to act synergistically with either PDGF(BB) or NGF to induce secretion of MMP-9 in both cell types. Western blots probed with specific antibodies demonstrated that IL-1 strongly synergised with either PDGF(BB) or NGF to induce MMP-1 and MMP-3 expression, whereas alone they had little or no effect. These results were confirmed with gelatin zymography for MMP-9 and casein zymography for MMP-3. Northern blotting analysis of rabbit dermal fibroblast total RNA demonstrated that MMP-1, MMP-3 and MMP-9 steady state mRNA levels were also increased synergistically at 4 hours and 8 hours after cytokine and growth factor stimulation. These data demonstrate the co-ordinate and synergistic regulation of MMP-1, MMP-3 and MMP-9 by inflammatory cytokines and growth factors in rabbit dermal fibroblasts and rabbit SMCs.

The mechanisms underlying synergistic induction of MMP-9, MMP-1 and MMP-3 are unknown. However, the requirement for both growth factors and inflammatory cytokines to achieve maximal induction may be an important mechanism underlying metalloproteinase expression during the development of atherosclerosis or at the site of injury.
Z-VAD BUT NOT Z-DEVD INHIBITS SERUM WITHDRAWAL INDUCED APOPTOSIS OF HUVEC IN VITRO

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Serum withdrawal induces apoptosis of HUVEC (human umbilical vein endothelial cells) in vitro but the mechanism of this induction is unknown. Proteins belonging to the ICE (Interleukin-1β converting enzyme)-related family of proteases are believed to have a role in apoptosis. ICE activity can be inhibited by Z-VAD (Valine-Alanine-Asparagine) which is an irreversible, specific peptide inhibitor, and the protease CPP32/Apopain can be inhibited by the peptide Z-DEVD (Aspartagine-Glutamine-Valine-Asparagine).

We have investigated whether these inhibitors could prevent HUVEC from undergoing apoptosis in response to serum withdrawal in vitro. Using a triated thymidine apoptosis assay, Z-VAD gave 82% inhibition of apoptosis over 24 hours of serum deprivation (n=5) and 61% inhibition over 48 hours (n=1). This was confirmed by time-lapse video microscopy. However, by time-lapse video microscopy, Z-DEVD gave no inhibition of apoptosis compared with a replicate culture which was filmed at the same time with serum withdrawal but no inhibitors.

In conclusion, it would appear that ICE is involved in serum withdrawal induced apoptosis of HUVEC in vitro, but CPP32 may not be involved.

A DOUBLE BLIND COMPARISON OF ENOXAPARIN (A LOW MOLECULAR WEIGHT HEPARIN) WITH STANDARD HEPARIN IN THE TREATMENT OF UNSTABLE CORONARY ARTERY DISEASE - THE ESSENCE TRIAL: KAA Fox, M Cohen, C Denman, E Gurfinkel, G Prenell, P Bigoni, J Premmerer, A Langer, S Goodman, R Califf, AOG Turpie* for the ESSENCE Group

Background: Combination therapy with aspirin plus heparin reduces the risk of recurrent ischaemic events in patients with unstable angina (UA) and non-Q MI. Low molecular weight heparin (LMWH), with high anti Xa activity, has advantages over unfractionated heparin (UFH) that may result in greater efficacy and safety.

Methods: In 3171 patients we compared fixed dose subcutaneous enoxaparin (LMWH) (n=1607) 1mg/kg q 12H + ASA with intravenous UFH (n=1564) adjusted by a predetermined nomogram + ASA in the initial treatment of UA in a double blind randomised trial.

Results: At 14 days, the primary end-point of the study, the composite risk of death, myocardial infarction, or recurrent angina with BCG changes or prompting intervention, was significantly lower in patients assigned to enoxaparin compared to UFH (16.5% vs 19.8%; odds ratio 0.80 [95% CI 0.49-0.95]; p=0.019). At 30 days, the composite outcome remained significantly lower in the enoxaparin group (19.8% vs 23.3%; p=0.017). The rate of readmission procedures by 30 days was also significantly lower in patients in the enoxaparin group compared to the UFH (27.7% vs 32.4%; p=0.01). There was no difference in the incidence of major bleeding complications (6.5 vs 7.0%; p=NS) but minor bleeding (largely at injection sites) was more common with enoxaparin (total: 18.4% vs 14.1%; P=0.001).

Interpretation: Antithrombotic therapy with subcutaneous enoxaparin (LMWH) plus aspirin is superior to UFH plus aspirin in patients with unstable angina or non-Q wave myocardial infarction at 14 days, with effects sustained at 30 days, and without an increase in clinically important bleeding. The trial has implications for the practical management of patients with Acute Coronary Syndromes.

AORTIC VALVE STRANDS : A TRANSESOPHAGEAL ECHO STUDY
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Post-mortem studies have recognised the occurrence of fibrous strands on otherwise normal cardiac valves. It is now possible to image these structures by transoesophageal echo (TOE). They appear as highly mobile fine filamenous lesions approximately 1mm in diameter and 1cm in length particularly noted on aortic valves. These strands are felt to represent a degenerative process but could be misinterpreted as vegetations. We therefore performed a prospective study of 100 consecutive patients (age 19-83 years, mean 38) referred for TOE to determine the incidence of aortic strands in clinical practice. Indications for TOE included suspected endocarditis (25), mitral disease (38), source of embolus (10) and other (27). Strands were detected in 30%; 17/48 (35%) males and 13/52 (25%) females; mean age 57 years (range 20-76). In 29% they occurred on the left ventricular aspect of the aortic valve and were most easily identified on the longitudinal 120° view. We diagnosed strands in 625 (24%) patients investigated for endocarditis; these were patients in whom the clinical suspicion of endocarditis was low and the valvular lesions detected were identical to those seen in patients with no suggestion of infection. Follow-up TOE in these patients did not reveal any change in the echo appearances of these filamentous processes. They were detected in 6/10 (60%) with suspected cardiac source of embolus. Conclusion: In this series aortic valve strands were detected in 30% of patients by TOE. They were seen in all age groups and were more frequent in males. Their recognition is important as they may be mis-diagnosed as vegetations. Caution is recommended in the interpretation of these lesions in patients with a low likelihood of endocarditis and serial TOE in these patients may be of value. The incidence in patients with suspected source of embolism was high and further studies to examine the association of valve strands and thromboembolic events are indicated.

A COMPARISON OF THE ACUTE HAEMODYNAMIC EFFECTS OF ENDOTHELIN ETA AND ETB RECEPTOR BLOCKADE IN CHRONIC HEART FAILURE
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Further to the evidence that endothelin (ET) system activation contributes to the elevation in vascular resistance characteristic of chronic heart failure (CHF), speculation has arisen that ET receptor antagonists may be therapeutically useful as vasodilator agents in CHF. However, the relative function of the two primary ET receptor subtypes, ETA and ETB, in mediating the constrictor effects of endogenous ET are unclear. We therefore compared the acute haemodynamic effects of the selective ETA receptor antagonist BQ-123 and the selective ETB receptor antagonist BQ-788 in 10 patients with treated NYHA II-III CHF (mean age 65, mean ejection fraction 21%) and 10 healthy control subjects (mean age 61, mean ejection fraction 62%). On separate days at least one week apart, subjects received brachial arterial infusion of locally active doses of each antagonist for 90 minutes while forearm blood flow (FBF) was measured by venous occlusion plethysmography. The absence of significant changes in heart rate and blood pressure confirmed that drugs had no systemic haemodynamic effects. BQ-123 (5μg/min) caused slow onset vasodilatation in CHF patients and control subjects, increasing FBF by 30±3% (p<0.001) and 5±10% (p=0.001) respectively after 90 minutes of infusion (CHF vs controls p=0.05). Conversely, BQ-788 (5μg/min) caused slow onset vasoconstriction in CHF patients and control subjects, reducing FBF by 9±4% (p=0.006) and 15±5% (p=0.036) respectively after 90 minutes of infusion (CHF vs controls p=NS). ETA receptor analogues appear to play an important role in regulating peripheral vascular resistance in healthy subjects and patients with CHF. The vasoconstrictor effect of BQ-788 suggests that endothelial ETB receptors mediating vasoconstriction are functionally more important than smooth muscle ETB receptors mediating vasoconstriction in the peripheral subjects and patients with CHF. Non-selective ET receptor antagonists may therefore be less effective vasodilator agents than ETA selective antagonists.
CARDIOPULMONARY INTERACTIONS AFTER FONTAN OPERATIONS: AUGMENTATION OF CARDIAC OUTPUT USING NEGATIVE PRESSURE VENTILATION

Royal Brompton Hospital, London

The low cardiac output state can complicate the post-operative course of patients undergoing Fontan-like operations. In the absence of a sub-pulmonary ventricle, pulmonary blood flow and hence cardiac output (CO) are closely related to the mean airway pressure. We investigated the effect of negative pressure ventilation (NPV) using the Hayek oscillator on the CO of 17 fully sedated intubated children (median age 6 years) who had undergone Fontan-like operations. 9 patients (acute) were studied on the intensive care unit in the early post-operative period, and 8 convalescent patients (conv) were studied following cardiac catheterisation under general anaesthetic. All patients were initially receiving intermittent positive pressure ventilation (IPPV). CO was measured using the direct Fick method during IPPV, and after 15 minutes' NPV. Oxygen consumption (VO2) was measured using respiratory mass spectrometry.

CO (l/min/m²) VO₂ (ml/min/m²) mixed venous sat (%) IPPV NPV IPPV NPV IPPV NPV
all 2.5±1.1 3.6±0.5* 129±25 153±49 60±21 65±17** acute 2.4±1.2 4.5±1.3* 156±15 156±15 56±17 62±18* conv 2.6±0.9 3.6±0.8* 131±19 129±26 70±17.9 78±13* Results are shown (mean±SD) for the group as a whole (all), and for the two sub-groups. *p<0.05; **p<0.001. NPV increased CO in all patients by 44±26%. There was no significant difference in the increase in CO in the acute (41±18%) and convalescent (47±25%) groups. Conclusion: By reducing the mean airway pressure, NPV exploits the important cardiopulmonary interactions which are present in the Fontan circulation, and may therefore be a useful haemodynamic tool in these patients.

IS ALTERED CENTRAL PROCESSING OF AFFERENT SIGNALS THE CAUSE OF CHEST PAIN IN SYNDROME X? SD Rosen, E Pauli, RFS Frackowiak and PG Camici.
MRC Clinical Sciences Centre and Royal Postgraduate Medical School, Hammersmith Hospital, London

The aetiology of syndrome X (SX, anginal pain and ischaemic-like changes in the stress ECO despite a normal coronary arteriogram) remains to be elucidated. There is increasing doubt over the myocardial ischaemia hypothesis of chest pain in SX, whereas abnormalities of pain perception have been shown. To investigate the latter factor, we have used positron emission tomography with H2 15O to measure regional cerebral blood flow (rCBF) changes as an index of neuronal activation: a) during chest pain in SX patients and b) during angina pectoris in coronary artery disease (CAD) patients. Nine SX patients (7 female, age 56±11) and 9 CAD patients (7 male, age 61±7) were studied. No patient had diabetes or other systemic disease. WCO2, stress, normal ventricular function was demonstrated in the SX patients despite an ischaemic-like ECG, but there were reversible wall motion abnormalities in the CAD patients. Intravenous dobutamine (D) was used to induce the chest pain. rCBF was measured during the following scan sequence: 1) rest; 2) placebo; 3) rest; 4) low dose D; 5) high dose D (provoking chest pain); and 6) rest. PET images were transformed into a standard stereotactic space and comparisons made across conditions by Statistical Parametric Mapping. Chest pain occurred in response to low dose D in 4/9 SX but in no CAD patients (p=NS). During scan 5 (high dose D) chest pain was reproducibly compared by both groups (6.3 in CAD vs 7.6 in SX; p=NS). During scan 5, ischaemic-like ECO changes were noted in 5/9 CAD and 9/9 SX. The maximal D dose was equivalent for both groups. During chest pain, SX patients showed significantly greater increases in rCBF in the midbrain, right thalamus and right insular cortex and bilaterally in the frontal and perifrontal cortex. The central nervous areas activated are similar in both SX and CAD, suggesting that in SX the afferent pain signals do originate from the heart. However the degree and extent of activation is disproportionately greater in SX and occurs in the absence of correlates of myocardial ischaemia such as ventricular wall motion abnormalities.

EVALUATING RISKS AND PERFORMANCE IN CARDIAC SURGERY

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INTRODUCTION: The Parsonnet scoring system has been widely adopted in cardiac surgery but is recognised to systematically over-estimate risk. The aim of this study was to develop firstly an alternative scoring system, which better reflects risk based on contemporary data and which can provide estimates of in-hospital mortality rates; and secondly, graphical methods that allow mortality figures, adjusted for risk mix, to be displayed and regularly updated. SCORING SYSTEM: We analysed the records of 4,318 consecutive cardiac surgery patients treated between 1992 and 1995. The analysis identified risk factors that were associated with in-hospital mortality. Logistic regression was used on a random sample of 80% of the data to derive an additive 'risk score' for expected mortality. Initially this was done using only patients who had undergone isolated coronary artery bypass grafting as they represented the majority of cases (2,980/4,318). The same technique was then applied to the second most common procedure, isolated valve surgery (1,694/4,318), before being applied to all remaining procedures. The simple formula derived expresses risk in terms of significantly associated factors, such as LV function and type and urgency of procedure. This 'risk score' was then validated against the remaining 20% of the data. GRAPHICAL DISPLAY: The Cumul method plots cumulative in-hospital deaths against the number of operations and can be used to monitor results in a run of cases (de Level ITCVS 1994: 107:914). However it has no account of variable risk in a mixed practice. Our 'Variable Life Adjusted Display' or VLAD incorporates expected mortality as derived by the above 'risk score'. A surgeon is regarded as being notionally in credit or debit according to how his actual in-hospital death rate compares with the death rate that would have been expected based on the scores for his caseload. This credit/debit is plotted against a count of the surgeon's consecutive cases. We have developed a system for displaying these plots on a computer which allows trends, learning curves, and changing performance, to be monitored in real time, corrected for case mix.

DO THE ATRIA "REMEMBER" PREVIOUS PAROXYSMS OF ATRIAL FIBRILLATION?
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There is good evidence that atrial fibrillation (AF) becomes self-perpetuating due to AF-induced shortening of atrial refractoriness ("AF begets AF"). It is not known, however, if the atria are still affected by a previous episode of AF once atrial refractoriness has returned to normal. We examined the possibility that previous episodes of AF can precondition the atrial myocardium in the conscious goat model of AF. The study protocol consisted of repeated 5-day periods of pacing-maintained AF separated by 2-3 days of sinus rhythm, which was sufficient for atrial refractoriness to return to control values. Comparison of the time course of development of sustained AF during consecutive episodes of pacing-maintained AF in 5 goats revealed no evidence for a preconditioning effect of previous episodes (mean AF duration/time slopes: 0.23±0.09, 0.21±0.09, 0.21±0.08; NS; example shown below).

Conclusion: The atria do not "remember" previous episodes of AF once atrial refractoriness has returned to normal. This may have important implications for the effects of paroxysmal AF on the atrial myocardium and for the design of experimental protocols to assess the efficacy of antiarrhythmic interventions.
NEW INSIGHT INTO QT DISPERSION
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There is currently controversy over the clinical value of measuring QT dispersion given problems associated with accuracy of measurement as well as interpretation. The present computer based study presents new data derived from a series of databases of ECGs analysed by the Glasgow Program. Using ECGs from 1,501 adult normals, it was found that there was no significant difference in QT dispersion between males and females (24.67 ± 8.2 vs. 24.35 ± 8.2ms). The upper limit of normal in each case was 44 milliseconds. There was no gradient with respect to age. In a subset of the conventional 12-lead ECG, viz. 6 precordial leads plus leads I and II, the QT dispersion was reduced to 20.76 ± 20.0ms. In a group of 1,785 healthy children aged from birth to adolescence, QT dispersion varied little with age with a mean of 24.52 ± 8.7ms. and an upper normal limit of 44ms. as in adults.

It is often argued that QT dispersion is in large measure due to the projection of cardiac electrical activity on to different lead axes. To study this problem, 1,220 normal and abnormal ECGs from the CSE Database were used. Both the conventional 12-lead ECG and the 3-orthogonal lead XYZ lead ECG were available from each patient. From the latter, it was possible to derive the conventional 12-leads as linear combinations of leads X, Y and Z. The mean QT dispersion for the conventional and derived 12-lead ECG was 29.1 ± 10.2ms and 27.5 ± 10.2ms respectively. On the other hand, the mean QT dispersion in the 3-lead ECG was only 17.1 ± 20.0ms.

The repeatability of the automated technique was shown in the same 1,220 ECGs to be excellent by using a splitting technique which created 2 ECGs from each original. The mean difference in QT dispersion between corresponding pairs of ECGs was 0.28 ± 9.7ms. These new data provide information on QT dispersion throughout the age spectrum and show that it is not related solely to dispersion of repolarisation but to the number of leads used in its measurement.

PREDICTORS OF SURVIVAL IN OUT-OF-HOSPITAL CARDIAC ARREST
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We studied the predictors of outcome in 9805 patients who underwent resuscitation following cardiac arrest due to presumed heart disease to assess the impact of site of arrest, bystander cardiopulmonary resuscitation (CPR) and other variables on survival. Cardiac arrest was witnessed by the ambulance crew in 714 (7.3%) cases, of which 272 (38%) survived. For the remainder, the median 999 call - on scene interval was 7 mins (IQR 5-10); 5269 of patients in VT/VF (survival 9.1%) and 3726 were in other rhythms (survival 0.7%). Independent predictors of survival to hospital discharge were analysed by logistic regression, excluding crew witnessed arrests.

<table>
<thead>
<tr>
<th>Variable</th>
<th>%</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bystander CPR</td>
<td>38</td>
<td>2.662 (1.6, 3.27)</td>
<td>&lt;0.001</td>
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<tr>
<td>Witnessed Arrest</td>
<td>67</td>
<td>5.27 (3.0, 8.42)</td>
<td>&lt;0.001</td>
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<td>999 Call - Arrival (per min)</td>
<td>0.930 (0.91, 0.95)</td>
<td>&lt;0.001</td>
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<tr>
<td>Site of Arrest (not home)</td>
<td>1.71 (1.40, 2.09)</td>
<td>&lt;0.001</td>
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The same four variables were the principal predictors of the presence of VT/VF, with the addition of Health Board region, younger age and male gender. Social deprivation category did not influence outcome of resuscitation. The effect of potentially achievable changes in the 999 call - arrival interval such as a reduction in median delay from 7 mins to 5 mins would be expected to increase overall survival from 5.7% to only 6.5%. In contrast, a doubling in the provision of bystander CPR from 38% to 76% should increase survival to 15.2%.

LONG-TERM EFFICACY OF IMPLANTABLE ANTI-TACHYCARDIA DEVICES IN THE CONTROL OF MONOMORPHIC VENTRICULAR TACHYCARDIA
M. Clarke, K. Wilmer. North Staffordshire Hospital, Stoke on Trent

Twenty-three patients with recurrent sustained monomorphic ventricular tachycardia (VT) refractory to multiple drug therapy were treated by implantable cardiac defibrillators with antitachycardia pacing (ATP) facilities. None of the patients had experienced spontaneous ventricular fibrillation (VF). The devices were implanted between 1991 to 1993 and the shortest long term follow up in this cohort was thirty-two months (maximum fifty-seven months).

Prior to implantation of the devices the twenty-three patients had required a total of ninety-six admissions to hospital for between two to sixteen days to control their arrhythmia. Subsequently all have been free from symptoms with a total of nearly two thousand episodes of VT terminated by ATP. One patient required admission to hospital for replacement of a fractured pace/sense lead three years after implantation. A single episode of VF was recorded in one patient two years after the implantation. None of the other patients has required defibrillation shocks.

Audit has indicated that ATP therapy in this group of patients is a satisfactory mode of treatment both in terms of efficacy and cost. Because defibrillation has not been required the patients have been able to retain their driving licences.

MAPPING AND ABLATION OF VENTRICULAR TACHYCARDIA USING A NOVEL NON-CONTACT MAPPING SYSTEM
R Schilling, N Peters, W Jackman, W Davies St Mary's Hospital, London, UK, University of Oklahoma, OK USA.

A novel 9F non-contact mapping system was deployed in the left ventricle (LV) of 13 patients (pts) with ventricular tachycardia (VT). It comprises a multi-electrode array (MEA) - a 64 wire braid around an 8ml balloon, allowing mathematical reconstruction of more than 3,300 electrograms superimposed onto a computer model of the endocardium creating isopotential and isochronal maps. 11 pts had ischaemic heart disease, 1 had cardiomyopathy and 1 had fascicular tachycardia in a normal heart. 5 pts had implantable defibrillators. During these initial investigational studies the MEA was deployed for a mean of 4.25hrs, without hemodynamic effect, to acquire LV data during VT and sinus rhythm before and after ablation (RF).

During the procedures a total of 43 sustained VTs (mean 3.3 per pt) and 2 nonsustained VTs were recorded. A total of 6 clinical VTs were not induced. 101 RF applications were used to ablate 27 VTs (3.7 RF per VT). Maps of VT were analysed on-line and guided ablation in the last 8 pts. Analysis of the maps identified exit sites for all 45 VTs. Of these, activation consistent with diastolic pathways was detected in 31 over a mean of 76% of the diastolic interval, being traced over the entire circuit in 16 VTs. 6 VTs were seen to share diastolic pathways, 4 using the same one in contrarotation and 2 having different exits from the same pathway.

Unique data of diastolic components of VT circuits have been obtained in the majority of VTs studied and new insights attained into multiple VTs occurring in the same pt. The maps created by this novel system helped direct successful RF in 8 pts.
THE UNITED KINGDOM PACING & CARDIOVASCULAR EVENTS (UKPACE) STUDY: DESIGN, FEASIBILITY AND PILOT EXPERIENCE
WD Toff for the UKPACE Pilot Study Investigators
Department of Cardiology, Glenfield Hospital, Leicester

Published guidelines recommend physiological pacing modes for patients with high-grade atrioventricular (AV) block, with restoration of AV synchrony and rate adaptation whenever possible. Despite this, the majority of such patients in the United Kingdom receive fixed rate ventricular pacing systems and there is evidence of ageism, with a higher proportion of physiological pacing systems in younger patients. Current practice is thought to reflect uncertainty as to whether optimal pacing is appropriate or cost-effective for all of the, predominantly elderly, paced population. The UKPACE study will randomly allocate 2,000 patients aged ≥70 years with high-grade AV block to VVI (25%), VVIR (25%) or DDD (50%) pacing. Patients with established atrial fibrillation, severe cognitive dysfunction, total immobility, class IV heart failure or advanced malignancy will be excluded. Patients will be followed for a minimum of 3 years to assess quality of life, functional capacity (assessed by a 6 minute walk), cardiovascular events and cost-utility. The primary and only end-point will be all-cause mortality. A pilot study to assess feasibility was initiated in August 1995. During a mean recruitment period of 9 months, a total of 168 patients were enrolled between 3 centres. This represented 53.3% of the eligible population (≥70 years, high-grade AV block) in those centres and 18.9% of their total pacing practice. The mean age of the enrolled patients was 80.8 years; 56% were male and 44% female. 77.9% were symptomatic, with syncope in 34.1% and dizziness in 25.6%. Bradycardia was intermittent in 32.9% and constant in 67.1%. Of the total, 53% were able to undertake a baseline 6 minute walk with a mean distance walked of 235.9 m. The pilot study experience indicates a high level of acceptability to patients and physicians and suggests that the proposal to recruit 2,000 patients over a one year period will be feasible with extension of the study to some 40 additional centres.

IS SURGICAL COVER STILL NECESSARY WITH THE ADVENT OF CORONARY ARTERY STENTS?
J L Williams, M R Thomas, R J Wainwright, D E Jewitt.
King's College Hospital, London

In the UK surgical back up has traditionally been required for PTCA, although this is not the case in some other European centres. It has been argued that the use of coronary artery stents to correct obstructive dissections may obviate that need in certain circumstances. We have analysed the reasons for which patients have been referred directly from the catheter lab for emergency bypass grafting in a high volume centre with operators experienced in the use of coronary artery stents. Between 1 January 1995 and 31 October 1996 1309 interventional procedures were performed in this centre. Of these 20 (1.5%) patients required emergency surgery. One declined surgery. Five patients were considered to be low risk (stable angina, AHA grade A/B lesions and good or fair LV function) pre-procedure and 10 were considered to be high risk (unstable angina and/or poor LV function and/or). The target lesion was the LAD in 12, RCA in 4 and circumflex artery in 4. Six of the vessels were occluded. Indications for referral for surgery were, obstructive coronary dissection at the PTCA site which could not be corrected by stent insertion in 8, guide catheter dissection in 3, vessel rupture in 3, guide wire dissection in 2, no reflow in 2, dissection past stenting in 1 and acute stent thrombosis in 1. This was despite further attempts at stent insertion in 12 patients. One patient had no coronary grafts (artery over-sewn during emergency chest opening in catheter lab), 9 had grafts to one vessel only, 8 had grafts to 2 vessels and 1 had grafts to three vessels. Of the 20, 3 (15%) died and 17 (85%) were discharged home, of whom none had a Q wave MI and 4 had a non-Q wave MI. In conclusion, indications for emergency cardiac surgery still exist despite the availability of intra-coronary stents. Surgery will be required in a small number but significant number of patients. That requirement is unpredictable and can occur in patients with an anticipated low risk, including those undergoing PTCA of an occluded artery. PTCA without surgical cover should not be encouraged.

IS REPEAT REvascularisation FOR Restenosis determined by the Site of Initial Angioplasty.
A S Kuraan, T J Bowker, A F Rickards (on behalf of the CABRI investigators)
Royal Brompton Hospital / I CSTM, London, UK

In analysing the determinants of post angioplasty reintervention for restenosis it is important to determine the influence of the initial revascularisation site(s).

Methods: In the CABRI population those patients who underwent conventional balloon angioplasty for multivessel CAD had their angiographic findings assessed before and immediately following initial intervention. Target lesions were categorised according to 15 coronary sites (American Heart Association classification). Clinical restenosis was defined as initial revascularisation success followed by a subsequent revascularisation within 10-35 days, either by repeat angioplasty at the initial site or by coronary bypass grafting at or distal to the initial site.

Results: 1195 coronary sites in 541 patients were attempted. Successful revascularisation was achieved in 85.3% (150 = 19.1%) of lesions. The likelihood of successful angioplasty was similar in all sites. The overall clinical restenosis rate (as defined by the need for a subsequent intervention as defined above) was 16.5%. However, the probability that the proximal LAD required further intervention was much higher than for other vessels (relative risk 1.9, 95% confidence interval 1.3-2.7, P<0.005). There were no significant differences between other sites.

Conclusions: Lesion recurrence following angioplasty in the proximal LAD (as part of multivessel angioplasty) increases the likelihood of repeat revascularisation for recurrent symptoms (and conversely recurrent symptoms requiring repeat revascularisation). The distribution of the angioplastied sites should be taken into account when assessing the results from trials to reduce bias in re-intervention rates due to unequal distribution of initial target lesions.

IMMEDIATE AND MEDIUM TERM OUTCOME FOLLOWING THE USE OF MULTIPLE STENTS IN THE TREATMENT OF VERY LONG (≥55mm) CORONARY LESIONS
J L Williams, M R Thomas, A de Belder, R J Wainwright, D E Jewitt.
King's College Hospital, London

The clinical outcome of the use of multiple stents to treat very long coronary lesions is unknown. Between 1 January 1995 and 31 October 1996 1309 interventional procedures were performed in this centre. Of these, 59 patients had ≥55 mm of stent implanted into a single coronary artery. We analysed their in-hospital outcome and subsequent target vessel revascularisation rate at 6 months. Of the stented lesions, 44 (75%) were in the right coronary artery, 11 (18%) in a saphenous vein graft and 4 (7%) in the left anterior descending artery. Thirty nine patients had stable angina and 20 unstable angina. The mean stent length was 72mm (±16mm). A total of 152 stents (68 Wallstents, 51 AVE, 17 Palmaz Schatz, 7 ACS, 7 NIR, 1 GRII, 1 Cordis) were deployed with a mean length per lesion of 2.6 (range 2-6). All were considered to be adequately deployed as assessed by angiography. Anticoagulation with Warfarin was used in 27 post procedure and aspirin/Ticlopidine 32. Primary in-patient success occurred in 55/59 patients (93%). Complication rates and target lesion revascularisation rates (TLR) at 6 months for the group were:

<table>
<thead>
<tr>
<th>In-Patient Complications</th>
<th>Death</th>
<th>SAST</th>
<th>MI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>1/59</td>
<td>3/59</td>
<td>2/59</td>
<td>4/59</td>
</tr>
<tr>
<td>(1.6%)</td>
<td>(5.0%)</td>
<td>(3.3%)</td>
<td>(6.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Target lesion revascularisation at 6 months:

<table>
<thead>
<tr>
<th>TLR</th>
<th>PTCA</th>
<th>CABG</th>
<th>TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/58</td>
<td>(13.7%)</td>
<td>(6.9%)</td>
<td>(20.6%)</td>
</tr>
</tbody>
</table>

In conclusion, this difficult group of patients can be treated with multiple overlapping stents. There is an increased in-hospital complication rate when compared with the deployment of a single short stent, but the subsequent 6 month TLR rate is acceptably low.
(73) ANGIOGRAPHIC AND CLINICAL RESTENOSIS FOLLOWING THE USE OF LONG CORONARY WALLSTENTS.

I L Williams, M R Thomas, N M K Robinson, R J Wainwright, D E Jeuitt, King's College Hospital, London.

From May 1995 to October 1996 148 patients were discharged from our hospital after the deployment of a long coronary Wallstent. There were 117 men and 31 women with a mean age of 63 (range 40-83 yrs). Wallstents (172) were deployed in 154 vessels. An additional 81 stents were deployed to improve the initial angiographic appearance (34% of vessels). The target vessel was the RCA in 80, saphenous vein graft in 35, LAD in 28 and CX in 11. Single vessel PTCA was performed in 142 patients and 43% of patients had unstable angina. Mean lesion length was 34 mm (range 16-97) and mean stent length 49 mm (range 22-94). Clinical events and target lesion revascularisation (TLR) for the whole group at a mean follow-up of 8 months (range 2-18 months) are:

<table>
<thead>
<tr>
<th>Death</th>
<th>MI</th>
<th>rtp PTCA</th>
<th>CABG</th>
<th>TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/148</td>
<td>0/148</td>
<td>19/148 (13%)</td>
<td>5/148 (3.3%)</td>
<td>25/148 (16.2%)</td>
</tr>
</tbody>
</table>

Angiographic follow-up at 6/12 is available in 73/94 (78%) eligible patients (76/97 vessels). Clinical events, TLR and angiographic restenosis (RS) for those patients with 6/12 follow-up is as follows:

<table>
<thead>
<tr>
<th>Death</th>
<th>MI</th>
<th>rtp PTCA</th>
<th>CABG</th>
<th>TLR</th>
<th>Angio RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/94</td>
<td>0/144</td>
<td>19/94 (19%)</td>
<td>5/94 (5%)</td>
<td>23/97 (23.7%)</td>
<td>28/73 (36.8%)</td>
</tr>
</tbody>
</table>

Angiographic RS in the Wallstent alone occurred in 23/76 (30%) vessels (5 episodes were in other stents). Angiographic data for the 6/12 group is as follows:

<table>
<thead>
<tr>
<th>Prox ref</th>
<th>Distal ref</th>
<th>In-stent MLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8 mm</td>
<td>3.1 mm</td>
<td>3.5 mm</td>
</tr>
<tr>
<td>6/12 angio</td>
<td>3.5 mm</td>
<td>2.9 mm</td>
</tr>
</tbody>
</table>

In conclusion clinical and angiographic RS following deployment of long Wallstents range from 16.2-36.8%. These rates may represent the coronary morphology rather than the stent but this needs to be confirmed by trials with other long stents. The optimal treatment of diffuse in-stent restenosis is important in order to establish the efficacy of this and other long stents in this type of disease.

(74) COLLATERAL CHANNELS ARE MAXIMALLY RECRUITED AT AN EARLY STAGE DURING SINGLE VESSEL CORONARY ANGIOPLASTY.

M Mason, N Jepsen, DJ Patel, S Brant, VE Paul, CDJ Ilsley. Department of Cardiology, Harefield Hospital, Harefield, Middlesex.

Studies have previously shown that there is significant diversity between patients in the degree of collateralisation at angiography. To date, however, the time course of collateral recruitment during each balloon inflation has not been established in humans. This study was designed to assess both the degree and time course of collateral recruitment during coronary angioplasty. Patients with single vessel disease (n=11), who had no angiographic evidence of collaterals and normal ventricular function were selected. Four 90 second low pressure balloon inflations were performed with angiographic confirmation of vessel occlusion. Inflations were separated by a sufficient time period to allow for complete resolution of ECG changes and chest pain. Collateral channels were assessed by contralateral injections at 30, 60 and 90 seconds during each inflation. Films were recorded on both cine and digital imaging, and collateral channels were graded by an independent observer according to Rentrop criteria. Collateralisation was demonstrated in 6 out of 11 patients. In all 6, maximal collateral recruitment was achieved by 30 seconds of the first inflation. There was no further change in 'Rentrop' grade of collaterals with time, or with successive inflations. The level of collateralisation varied between patients: 4 had grade 1, one grade 2 and one grade 3 collaterals. ST segment analysis demonstrated a trend towards a longer time to 2 mm ST segment elevation with successive inflations (1st inflation: mean 30 ± 16.9; 4th inflation: mean 44.5±28.6), with no difference between patients with and without collateralisation. This study supports the assertion that collateralisation varies widely between patients and that in those who do collateralise, this is maximal at an early stage (by 30 sec). Since the duration of ischaemia required to induce preconditioning in this setting is greater than 30 seconds, collateral recruitment is unlikely to play a major role in the observed 'preconditioning' response at angioplasty.

(75) LESION MOULDING CATHETERISATION IN THE ASSESSMENT OF STENT DEPLOYMENT.

S Eccleshall, P Jordan, J Townsend, N Buller, Dept of Cardiovascular Medicine, Queen Elizabeth Hospital, Birmingham.

Assessment of stent deployment by angiography is imperfect, whilst intravascular ultrasound is of limited availability. We have imaged stents deployed in coronary artery phantoms using a new lesion moulding balloon catheter (LMBC). By deploying the "deformation memory" of the balloon polymer luminal diameters and stenoses in the range 2.5 - 4.0 mm are accurately reproduced. Six LMBCs were inflated (20 PSI for 20 seconds at 37°C) a total of 26 times within perspex phantoms containing a 9 mm NIH stent (deployed at 8 atmospheres). Phantom stenoses were concentric (internal diameters of 3.5 and 4.0 mm) and eccentric (internal diameter 2.6 mm). The balloon was removed after each inflation, refilled (5 PSI) and photographed (with 3.33 magnification). The stent was identifiable in each case as struts indentations on the balloon mould in 1 or more views; diameters and length were measured with Vernier callipers. The results are shown below.

<table>
<thead>
<tr>
<th>Stent size</th>
<th>Mean diameter</th>
<th>Range</th>
<th>2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric</td>
<td>2.85</td>
<td>2.89</td>
<td>2.77-2.84</td>
</tr>
<tr>
<td>Concentric</td>
<td>3.30</td>
<td>3.12</td>
<td>2.94-3.33</td>
</tr>
<tr>
<td>Eccentric</td>
<td>2.50</td>
<td>2.70</td>
<td>2.52-2.88</td>
</tr>
<tr>
<td>Stent length</td>
<td>9.0</td>
<td>9.49</td>
<td>8.8-10.1</td>
</tr>
</tbody>
</table>

*% recoil allowed

Conclusion: The Lesion Moulding Catheter enables accurate assessment of stent diameter and length in coronary artery phantoms. Poorly deployed stents are highlighted by indentation of the LMC balloon. In vivo studies are warranted.

(76) IN VIVO AND IN VITRO ARTERIAL GENE TRANSFER OF TIMP-1 USING AN ADENOVIRAL VECTOR.

CM Dollery, A McClelland, M Rolleston, SC Stevenson, DS Latchman, AM Hemsey, SE Humphries, JR McEvoy. Department of Medicine (Division of Cardiology), University College London Hospitals Medical School, London, W1E5DB, England and Genetic Therapy Inc, Guttenberg, MD, USA.

Extraocular matrix breakdown is likely to be essential for the migration and proliferation of vascular smooth muscle cells (VSMC) in angioplasty restenosis. Tissue inhibitor of metalloproteinases-1 (TIMP-1) potently inhibits the matrix metalloproteinase enzymes. A recombinant replication deficient adenoviral vector Avl.TIMP-1 containing the cDNA for human TIMP-1 and the Rous Sarcoma virus promoter was constructed. Its ability to express TIMP-1 was assessed in rat primary VSMC versus cells infected with a β galactosidase expressing adenovirus Avl.βGal and control cells. Western blotting showed a dose dependant protein expression in response to Avl.TIMP-1. Reverse zymography showed biologically active protein. VSMC have constitutive activity of TIMP-1 but an increase proportional to the multiplicity of infection (MOI) of Avl.TIMP-1 was seen (figure 1). TIMP-1 is a mitogen in some cell types but no change in H4 thymus expression was seen versus control cells. Balloon injured rat carotid arteries in vivo were exposed to Avl.βGal and Avl.TIMP-1 and transgene expression was shown at 2 and 14 days post inflation. Western blotting (n=4) and immunohistochemistry (n=3) demonstrated human TIMP-1. Studies are on going to establish the effect of transfer of TIMP-1 on neointimal generation after vascular injury. Conclusion: We have generated an adenoviral vector which overexpresses biologically active TIMP-1 in vascular cells. This vector does not cause cell proliferation and successful protein expression follows in vivo administration after vascular injury.
**EFFICIENCY OF LOCAL DELIVERY OF ANTI-PLATELET DERIVED GROWTH FACTOR-BB ANTIBODY INTO INJURED ARTERIAL VESSEL BY MICROPOROUS BALLOON CATHETER**

WA Martin, R Aggarwal, M Salame, C Rutherford, GAA Fenn and AH Gershlick. Division of Cardiology, University of Leicester, William Harvey Research Institute, Charterhouse Square, London & School of Biological Sciences, Surrey University, Guildford.

Restenosis following PTCA/stent placement remains problematic. We are investigating the potential of locally delivered anti-PDGF antibody in limiting this phenomenon. 7 anaesthetized male New Zealand White rabbits underwent left external iliac artery balloon injury with a 2.5mm diameter non-compliant angioplasty balloon. A 3mm nominal diameter Cordis microporous balloon catheter was advanced to the injury site and 5 ml solution containing 125-iiodine labelled sheep anti-PDGF IgG in PBS pH7.4 (total IgG protein 5mg; total radioactivity delivered 0.42MBq) was infused by manual pressure over 30 secs. The animals were terminated with phenobarbitone overdose 5 minutes (n=3), 4 hours (3) and 24 hours (1) after local delivery. The treated artery, contralateral artery, segments of aorta & IVC proximal to the bifurcation were excised, weighed, rinsed gently in PBS & immersion-fixed. Samples were gamma-counted and IgG protein content determined. The minimum IgG level required to neutralize PDGF-BB released at injury site was estimated to be 1.2 ng.mm-1 vessel length.

**Results:** Data presented as mean (ng.mm-1 vessel length)+SE.

<table>
<thead>
<tr>
<th>IgG content</th>
<th>5 minutes</th>
<th>4 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>treated</td>
<td>17.6±4.7</td>
<td>3.2±0.1</td>
<td>3.7</td>
</tr>
<tr>
<td>control</td>
<td>3.1±1.4</td>
<td>0.7±0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>aorta</td>
<td>3.1±0.6</td>
<td>2.2±0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>IVC</td>
<td>14.8±10.1</td>
<td>0.8±0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The mean delivery efficiency to treated vessel wall compared to total IgG delivery was: Delivery efficiency is low but sufficient levels of neutralizing antibody can be deposited at the target site and despite wash-out, effective levels exist up to 24 hours.

**CORONARY ANGIOPLASTY FOR THE TREATMENT OF CHRONIC LEFT VENTRICULAR DYSFUNCTION: PREDICTIVE VALUE OF POSITRON EMISSION TOMOGRAPHY**

F. Fath-Ordoubadi, JK Beattie, N Spyrou, PG Camici. MRC CSC, RPMS, Hammersmith Hospital, London, UK.

Coronary artery bypass can restore function in hibernating myocardium (H). To ascertain whether coronary angioplasty (PTCA) is also effective in restoring function in H, we studied 15 patients (pts); age: 62±9 with at least one chronically dysfunctional (D) segment (S) supplied by a stenotic artery. Myocardial viability was assessed with positron emission tomography (PET) and 15F-deoxyglucose during euglycemic hyperinsulinemic clamp. PET viability, based on our previous studies, was defined as a metabolic rate of glucose >0.25μmol/min/g in each S. Echocardiography was performed before and 4 months after PTCA. A total of 68 D-S were revascularised, 36 (53%) S improved after PTCA, 35 of which were PET viable (sensitivity: 97%), and 32 (47%) remained unchanged of which 25 were PET non-viable (specificity: 78%). However, 10 (33%) of unchanged S were found to be supplied by a reseeded artery of which 5 (50%) were PET viable. Exclusion of these S improved the specificity of PET to 90% and the positive predictive accuracy (PA) from 82% to 93%. Ejection fraction improved from 42±11% to 45±11% (p=0.08), the improvement became significant only if pts with restenosis were excluded (41±10% to 45±10%, p=0.04). Wall motion score improved from 1.4±0.28 to 1.39±0.41, (p=0.09) and only just fell to reach statistically significant after exclusion of restenosed pts (1.50±0.31 to 1.38±0.42, p=0.06). In conclusion: PTCA can improve the function in viable but D-S. Restenosis may hinder this recovery and lead to an apparently worse specificity and positive PA of PET.

**ANEURYSM FORMATION AFTER BALLOON DILATION OF AORTIC RE-COARCTATION**


The aim is to examine the frequency and type of aneurysm formation after balloon angioplasty of aortic re-coarctation (BAAC) in children. In the period from 1990 to 1996, 33 patients underwent BAAC (33 re-coarctation). Their ages at BAAC ranged between 6 months to 18 years (median of 7 years). All patients had pressure measurements and angiography immediately before and after angioplasty. Echocardiographic and Doppler examinations were performed before, 24 hrs after angioplasty and during follow up. The gradient across the site of coarctation was 30 - 120 mmHg (median 65 mmHg) before BAAC and 0 - 60 mmHg (median 20 mmHg) after wards (p<0.05). During follow up, the gradient was reduced to 0-30 mmHg (median 10 mmHg) at 3 - 8 months after BAAC (p<0.05). Aneurysms, downstream of the site of coarctation, occurred in 4 patients (4/33, 12%) and were identified immediately after the procedure. The immediate angiographic appearances of post BAAC aneurysms were upward tear (type 1, 2 patients), downward tear (type 2, 1 patient) and saccular aneurysm (type 3, 2 patients). The patient with a downward tear and saccular aneurysms showed evidence of enlarging aneurysm, became haemodynamically unstable and required urgent surgical resection. To date (6 months to 6 years after BAAC), no further complications occurred in these patients. Thus, balloon angioplasty of aortic re-coarction can relieve the stenosis. Three types of aneurysms occurred downstream of the coarctation site in this experience. Management of these aneurysms may include immediate surgical intervention. These results should be compared with reported aneurysm incidence following BAAC of "native" coarctation.

**TEMPORAL CHARACTERIZATION OF PRECONDITIONING IN HUMAN MYOCARDIUM AT PTCA AND THE CONTRIBUTION OF COLLATERALS TO PROTECTION**

NS Jepson, MJ Mason, DP Patel, B Katzen, VP Paul, CJB Bailey. Department of Cardiology, Harefield Hospital, Middles.

The validity of PTCA as a clinical model of preconditioning is debated. As the duration of myocardial ischaemia is relatively brief and there is potential for acute recruitable collateral (ARC) channels to open. The aim of this study was to determine the minimal ischaemic interval to induce a protective response at PTCA whilst monitoring ARC flow by intravascularr doppler. Eighteen patients (14 male, 4 female) aged 54.5±5.8 with normal LV function and absent spontaneous collaterals undergoing PTCA to proximal LAD lesions were assessed. Patients were assigned to one of three treatment protocols (6/group), (1)3x30sec inflations, (2)3x60sec and (3)3x90sec. ST segment shift asssisted over precordial leads and anginal intensity (0-10 scale) were recorded at peak ischaemia prior to each period. Three procedures in each group were performed with a 0.014" 12MHz doppler-tipped guidewire to monitor intracoronary flow velocity. Flow velocity signals distal to the balloon during inflation defined recruitable collaterals.

<table>
<thead>
<tr>
<th>Collateral</th>
<th>30sec</th>
<th>60sec</th>
<th>90sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow (cm/s)</td>
<td>3.1±1.3</td>
<td>4.9±2.1</td>
<td>6.4±2.3</td>
</tr>
<tr>
<td>p&lt;0.05 vs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARC flow was detected in 7 of 9 cases. Maximal peak collateral velocity integral values for serial 30sec inflations were 5, 6 and 6 units. Corresponding results for 60sec occlusions were 7, 8 and 7 units and 7, 8 and 6 units for 90sec inflations respectively. ARC flow was maximal by 30sec of balloon inflation in all cases and did not increase with repeated or longer occlusions. There was no attenuation of ischaemia with serial 30 and 60 sec inflations. A threshold occlusion duration of 90 sec is needed to induce an adaptive or preconditioning response at PTCA. The observed reduced ischaemic injury following successive 90 sec inflations occurs without collateral recruitment.

Heart: first published as 10.1136/hrt.77.Suppl_1.i on 1 May 1997. Downloaded from http://heart.bmj.com/ on September 15, 2023 by guest. Protected by copyright.
WHOLE BODY HYPERTERMIA (HEAT STRESS) INDUCES DELAYED MYOCARDIAL PROTECTION AGAINST ISCHAEMIA. THE MECHANISM IS UNCLEAR. SLOW DEPLOYMENT OF ATP SENSITIVE POTASSIUM CHANNELS (KATP) IN HEART MUSCLE MIGHT BE RESPONSIBLE FOR THE PROTECTIVE EFFECT.

The role of protein kinase C (PKC) in ischaemic preconditioning is controversial. This controversy is not surprising, as PKC has been implicated in cell death by both pro- and anti-apoptotic pathways. Furthermore, PKC is activated by different agents that are also used in the clinical treatment of ischaemic cardiac injury.

**Transfer to Myocytes of the Gene Encoding a Mutationally Active Protein Kinase C-8 Mimics Ischaemic Preconditioning**

J Zhao, O Renner, DS Latchman and SM Marber. Dept of Cardiology, UMDS and Dept of Molecular Pathology, UCLMS, London.

The role of protein kinase C (PKC) in ischaemic preconditioning is controversial. This controversy arises in part from difficulties with both measurement and interpretation of the biological manipulation of PKC. We therefore investigated preconditioning by expressing isotypes of PKC in isolated neonatal rat cardiomyocytes.

Ischaemia was simulated at 37°C in low volumes of media, pH 6.2, 16mM K+, 20mM lactate, lacking metabolic substrate, at 37°C, in an hypoxic chamber (G5%O2). Six hours of simulated ischaemia increased dead myocardium, unable to exclude trypan blue, from 15.0±5.8 to 70.3±2.1% (p<0.001) and decreased transfected β-galactosidase activity to 60.5±4.1% (p=0.0001) of the pre-ischaemic value. Observations at differing durations of simulated ischaemia suggested β-galactosidase activity reflected viability within transfected myocytes. Preconditioning with 90 minutes of simulated ischaemia significantly increased β-galactosidase activity and myocyte survival after 6 hours of simulated ischaemia. This effect was abolished by the PKC inhibitors staurosporine or chelerythrine. After liposome-mediated cotransfection with plasmids encoding β-galactosidase and either constitutively active mutants of PKC δ, PKC-α, wild type PKC δ or empty vector, cardiomyocytes were subjected to 6 hours of simulated ischaemia. Only PKC-δ, rendered constitutively active by a limited deletion within the pseudosubstrate domain, increased resistance to ischaemia such that β-galactosidase activity was 85.6±11.9% rather than 53.7±2.5% (p<0.001) of the pre-ischaemic value while the other PKC isoforms were unable to exclude trypan blue decreased from 68.7±2.8% to 46.8±13.4% (p<0.01).

Since transfection efficiency was only 3.8%, the marked increased survival of cells within the monolayer was likely secondary to a bystander effect. This effect was confirmed by co-culturing cardiomyocytes transfected with isotypes of PKC above an untransfected monolayer sharing the same medium.

These results provide an insight into the mechanism and possible avenues for therapeutic exploitation of ischaemic preconditioning.

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**Transfer to Myocytes of the Gene Encoding a Mutationally Active Protein Kinase C-8 Mimics Ischaemic Preconditioning**

J Zhao, O Renner, DS Latchman and SM Marber. Dept of Cardiology, UMDS and Dept of Molecular Pathology, UCLMS, London.

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Current classification identifies α1-adrenoceptor (AR) subtypes as α1A, α1B, and α1D-ARs, which correspond respectively to the recombinant subtypes previously referred to as α1A, α1D-AR, and α1D/α1A-ARs; transcripts for all three receptors are present in rat ventricular myocytes. Our objectives were to determine the roles of (i) α1-AR subtypes, and (ii) extracellular-regulated kinase (ERK) activation, in α1-adrenergic stimulation of sarcosomal Na+/H+ exchange (NHE) activity in these cells. As an index of NHE activity, acid efflux rates (3H) were determined in single myocytes loaded with pH-sensitive fluorophore carboxy-SNARF-1, following two consecutive intracellular acid pulses in bicarbonate-free medium. In control cells, ∆pH (pH6.9) did not change significantly during the second pulse relative to the first. When the second pulse occurred in the presence of 10 or 100 μM phenylephrine (non-selective α1-AR agonist), ∆pH increased by 142% (p<0.05) and 171% (p<0.05), respectively. The increase in ∆pH, induced by 100 μM phenylephrine was unaffected by pretreatment with 3 μM chloroethylcholine, which inactivates α1B-ARs, but was abolished by pretreatment with 3 μM WB-4101, an α1A/α1D-AR antagonist. The phenylephrine-induced increase in ∆pH was also abolished by pretreatment with 30 μM 5-methylurapidil, an α1A- AR-selective antagonist. Phorbol 12-myristate 13-acetate (PMA) mimicked the effect of phenylephrine and increased ∆pH by 45% (p<0.05) and 186% (p<0.05) at 10 and 100 μM PMA, respectively. The inactive stereoisomer was without effect. Pretreatment with 100 mM bisindoylmaleimide, a selective PKC inhibitor, abolished the increase in ∆pH induced by 100 μM PMA but only partially attenuated that induced by 100 μM phenylephrine. These results suggest that (i) α1-adrenergic stimulation of sarcosomal NHE activity is mediated by the α1A-AR subtype, and (ii) PKC activation is sufficient to increase sarcosomal NHE activity, but is not the sole mechanism underlying the α1A-AR-mediated response.

**STIMULATION OF CARDIAC GENE EXPRESSION IN NEONATAL RAT VENTRICULAR MYOCYTES BY Ga13**

SJ Fuller, SG Fiss and SG Plonk.

Imperial College School of Medicine at NTHI (Cardiac Medicine), London and Vanderbilt University Medical Centre, Nashville, USA.

In the heart cellular stresses such as ischaemia/reperfusion activate the Jun kinase but not the extracellular-regulated kinase (ERK) members of the mitogen-activated protein kinase (MAPK) superfamily. This selective pattern of MAPK activation is seen in NIH 3T3 cells in response to an active GTPase-deficient mutant of Ga13, Gα13Q226L, suggesting that activation of Ga13 may be an early event in the response of the heart to cell stress. The aim of the current experiments was to determine whether, Gα13 can induce transcriptional changes associated with a hypertrophic response, as has been shown for agents which activate the Jun kinase. To test this, cultured neonatal rat ventricular myocytes were transfected with wild type Gα13, Gα13Q226L or vector control. The effect on genes known to be upregulated in hypertrophy was monitored with luciferase (LUX) reporter constructs under the control of promoters for atrial natriuretic factor (ANF), β-myosin heavy chain (β-MHC), skeletal muscle α-actin (Ska) and the c-fos serum response element (c-fos-SRE). Transfection efficiency was corrected for using a co-transfected β-galactosidase (β-gal) reporter gene. Transfection with 1, 3 or 10 μg Gα13Q226L stimulated ANF-LUX expression to 2.02±0.77, 1.70±0.17 and 3.20±0.76 of vector control respectively (n=4 transfections, p<0.05 for all). Similarly, β-MHC-LUX and Ska-LUX expression was increased by transfection with 1 μg of Gα13Q226L (1.54±0.16 and 1.54±0.28 of control, respectively), but not by wild type Gα13 (1.38±0.42 and 1.01±0.22 of control, respectively). In contrast, neither wild type Gα13, nor Gα13Q226L had any effect on c-fos-SRE expression (1.05±0.05 and 0.92±0.09 of control, respectively). These studies show that active Ga13 can stimulate expression of a subset of genes associated with a hypertrophic response in cardiac myocytes and suggest that Gα13 may play a role in the response of the heart to cell stress.

**MITOGEN-ACTIVATED PROTEIN KINASES ARE ACTIVATED BY OXIDATIVE STRESS AND CYTOKINES IN NEONATAL RAT VENTRICULAR MYOCYTES**

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The three subfamilies of mitogen-activated protein kinases (MAPKs), namely the extracellularly-responsive kinases (ERKs), the c-Jun N-terminal kinases (JNKs) and the p38-MAPKs. ERKs are involved in cell growth and differentiation, whereas JNKs and p38-MAPKs are important responses to cell stress. We have previously shown that ischaemia/reperfusion in the perfused heart activates JNKs and p38-MAPKs. We have now assessed the potential for oxidative stress (a component of ischaemia) to activate the MAPKs. Hearts were perfused with H2O2 at concentrations of up to 2 μM. Activation of MAPKs in extracts was determined using in-gel kinase assays with myelin basic protein (for ERKs), GST-c-Jun1-13 (for JNKs) or GST-MAPKAPK2 (for p38-MAPKs). ERK activation was also assessed after Fast Protein Liquid Chromatography on a Mono Q column. p54 and p66 JNKs were activated maximally after 30 min perfusion with 0.5 mM H2O2. Immunoprecipitation with specific antibodies followed by in-gel kinase assays indicated that approximately 70% of these activities resulted from JNK1 activation. The remainder presumably resulting from activation of other JNK isoforms. p38- MAPK was also activated maximally after 30 min perfusion with 0.5 mM H2O2. Only about 50-60% of the in-gel kinase activity was immunoprecipitated with antibodies to the C-terminus of mouse p38-MAPK. However, all activity was inhibited by SO42- or H2O2 (30 μM) (p38-MAPK family) suggesting that more than one isoform of p38-MAPK may be activated. The hydroxyl radical scavenger, dimethyl sulfoxide, inhibited the activation of JNKs and p38-MAPKs by H2O2. Activation of the ERKs was detected after 5 min perfusion with 0.5 mM H2O2. Thus reactive oxygen species stimulate the activities of stress-regulated MAPKs (JNKs and p38-MAPKs) and this may be relevant to the activation of these kinases in pathological situations.
 Recent studies indicate that nitric oxide (NO) regulates cardiac contractile functions, eg, relaxation, β-adrenergic response. A constitutive type NO synthase (NOS3) has been identified in the heart in coronary microvascular endothelial cells (CMVE) as well as cardiac myocytes. As abnormalities of the NO pathway are reported in hypertension, we compared the expression of NOS3 in left ventricular (LV) cardiac myocytes and CMVE of 12 week old male spontaneously hypertensive rats (SHR) and matched normotensive Wistar rats. LV/body weight ratio was significantly greater in SHR compared to Wistar rats (3.8±0.2 cf 2.8±0.1 mg/g, p<0.0002). As the expression of NOS3 in CMVE was downregulated by culture only freshly isolated CMVE were used. Both CMVE and LV myocytes were freshly isolated by retrograde Ca²⁺-free collagenase digestion; purity was >95%. Total RNAs were extracted by the guanidinium isothiocyanate method, and NOS3 and GAPDH transcripts were amplified by RT-PCR (35 cycles) using species-specific primers. Semi-quantitative analyses of PCR products were performed by Southern blotting and hybridisation with radioactively labelled NOS3 and GAPDH cDNA probes, followed by densitometry of autoradiograms and normalisation of NOS3 levels by GAPDH. LV hypertrophy did not alter the expression of GAPDH mRNA in either cell type. Expression of NOS3 mRNA was 3.22±0.1 fold greater in SHR relative to Wistar myocytes after normalisation for GAPDH (n=9; p<0.0001). However, NOS3 expression in freshly isolated SHR CMVE was unaltered compared to Wistar CMVE (1.25±0.85, p>NS). Thus, NOS3 mRNA is selectively upregulated in SHR cardiac myocytes but not in CMVE. This upregulation may be relevant to the pathophysiology of hypertensive LVH and could be adaptive for example through effects on diastolic function, O₂ consumption and/or anti-hypertrophic action.

**UPREGULATION OF TYPE 3 NITRIC OXIDE SYNTHASE IN CARDIAC MYOCYTES NOT CORONARY ENDOTHELIAL CELLS OF HYPERFONERED HEARTS**

**U Baytrakutun, Z Yang, A Waltera, AM Shah**

Department of Cardiology, UWCMD, Heath Park, Cardiff CF4 4XN

In some studies, the deletion (D) polymorphism of the ACE gene has been identified as a possible risk factor for myocardial infarction (MI). Apo-E e4 allele has been associated with premature atherosclerosis. Apo-E C2 alleles have been considered to be "protective" atherosclerosis and have been found to exhibit a higher frequency in controls. The purpose of this study was to evaluate possible differences in ACE and apoE genotype distributions in patients with cardiovascular disease (CAD) in relation with MI.

We studied 139 patients (mean age 55 yr, 85% males) with CAD based on angiographic criteria. Previous MI diagnosis was based on complete hospital charts. Lipid profile, (Total Cholesterol, Triglycerides, HDL, and Lp(a)) was evaluated. ACE and apoE gene polymorphic fragments were amplified by the polymerase chain reaction. ACE genotype was visualized after direct agarose gel electrophoresis of PCR fragments while apoE genotype was determined after flaim digestion of PCR products and subsequent polyacrylamide gel electrophoresis.

**MYOCARDIAL INFARCTION IS ASSOCIATED WITH APOLOPROTEIN-E (apoE) BUT NOT WITH ANGIOTENSIN-CONVERTING ENZYME (ACE) GENE POLYMORPHISM**


Oxides Cardiac Surgery Center, Athens, Greece, and The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus.

We studied 139 patients (mean age 55 yr, 85% males) with CAD based on angiographic criteria. Previous MI diagnosis was based on complete hospital charts. Lipid profile, (Total Cholesterol, Triglycerides, HDL, and Lp(a)) was evaluated. ACE and apoE gene polymorphic fragments were amplified by the polymerase chain reaction. ACE genotype was visualized after direct agarose gel electrophoresis of PCR fragments while apoE genotype was determined after flaim digestion of PCR products and subsequent polyacrylamide gel electrophoresis.

Distribution of apoE and ACE (D/I) genotypes between the 2 groups of patients (68 pts with and 71 pts without MI) are summarized below.

<table>
<thead>
<tr>
<th>APOE</th>
<th>ACE</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>D</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>D/I</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
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<tr>
<td>2</td>
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<tr>
<td>1</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>D/I</td>
<td>6</td>
</tr>
</tbody>
</table>

* A positive association that reached statistical significance (P=0.03) was observed between myocardial infarction and apoE 4 allele. The significant decrease in e2 allele frequency among patients with MI is compensated by an almost equal increase in e4 frequency, while the frequency of e3 allele remains unchanged. No difference in D/I allele frequencies was observed in relation to MI. The same applies to the comparison between CAD patients and 25 age and sex matched controls (D/I frequency % 58.3/41.7 in patients vs. 56.1/43.9 in controls). TC and LDL-C levels were higher in e4 carriers but these differences did not reach statistical significance. These results are in accordance with the aforementioned hypercholesteremic effect of e4 allele and a probable protective role of the e2 allele. Thus, we conclude that apolipoprotein E and not ACE gene polymorphism was found to be predisposing to MI.

**ANALYSES OF RECOMBINANT MUTANT CARDIAC TROPONIN I IN VITRO AND IN MYOCYTE CULTURE**

C Redwood¹, G Esposito², HL Sweeney¹, H Watkins¹, University of Oxford¹ and University of Pennsylvania, Philadelphia, USA².

Mutations in six cardiac contractile protein genes cause hypertrophic cardiomyopathy (HCM). Most HCM mutations are missense mutations likely to encode stable peptides that incorporate into the sarcomere but then interfere with function (dominant negatives). However, as HCM can also be caused by truncation mutations which may encode no stable protein (null alleles), alterations of the relative amounts of contractile proteins may also cause cardiac hypertrophy.

Wild type and truncated human cardiac troponin I (TnI) were expressed in a novel quail myotube system. Antibody-staining demonstrated incorporation of both wild-type and truncated TnI into the sarcomers. Ca²⁺-activated force of contraction was normal in transfected myotubes expressing wild type human cardiac TnI, but 80% reduced with the truncated TnI. Thus the truncated TnI is not a null allele, but acts as a dominant negative.

In view of this, and a recent report of a missense TnI (Ile79Asn) producing increased velocity in the (unloaded) motility assay, we have studied 3 missense TnI peptides that cause HCM. All 3 were stable and incorporated into the sarcomere. The Ile79Asn mutant caused both depression of max. Ca²⁺-activated force (by 25%) and a shift of the pCa curve (decreased Ca²⁺ sensitivity). With increased velocity, but decreased force, we suggest that the mutant TnI acts by shortening the cross-bridge cycle. This is the first indication that the troponin complex can regulate the actin/myosin interaction beyond acting as an on/off switch.

To begin to dissect this mechanism we have expressed the mutant TnIs (together with troponins C and I) in E. coli. Analyses of the purified proteins will allow us to examine the TnI-tropomyosin interaction and, by reconstitution, the impact of TnI mutations on the function of the thin filament.

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YOUNG RESEARCH WORKERS PRIZE

ATP-SENSITIVE POTASSIUM CHANNELS AND VENTRICULAR REPOLARISATION

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Increasing extracellular K+ accumulation shortens the action potential duration (APD) during ischaemia, so promoting arrhythmias. Activated ATP-sensitive potassium (KATP) channels may be important, in spite of [ATP] remaining relatively unchanged during early ischaemia. We have investigated the hypothesis that acidosis is involved in activation of KATP channels in the canine ventricle. The technique employed was glibenclamide: a K+ electrode. We investigated whether the extracellular K+ concentration following ischaemia (7.5% control) was measured by using 262 ± 7.5 ms (n=11; p<0.01) followed by shortening to 262 ± 7.5 ms at 5 minutes (p=0.01 compared to resting APD). During APD shortening there was a significant increase in the FER of new pH and potassium levels. Glibenclamide abolished K+ channel shortening with a 0.5% reduction in the FER (n=10, p<0.05) after 5 minutes of ischaemia (control: 10.1 ± 1.9 x 10^(-3) mmHg; glibenclamide: 5.2 ± 1.2 x 10^(-3) mmHg; n=6; p<0.05). Metabolic and respiratory acidosis caused a similar initial increase in APD (111 ± 2% and 111 ± 2% respectively) followed by recovery to 106 ± 1% and 107 ± 2% respectively after 6 min acidosis which was inhibited by glibenclamide. This study has shown that during ischaemia APD lengthening precedes increased K+ efflux, which itself is associated with marked APD shortening. This supports the hypothesis that K+ efflux is secondary to a net inward current. KATP channel activation abolishes ischaemia-induced K+ efflux, suggesting that channel activation occurs despite a constant [ATP]. Furthermore acidosis activates a glibenclamide-sensitive conductance consistent with acidosis being an important contributor to the increased K+ channel conductance during ischaemia.

ABNORMAL MECHANICAL FUNCTION, CALCIUM HANDLING AND REPOLARISATION IN ISOLATED HEARTS FROM RABBITS WITH HEART FAILURE

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The underlying pathophysiological mechanisms in heart failure (HF) are not well understood and not thoroughly studied in the whole heart. A coronary artery ligated in this study in the New Zealand White rabbits (3.1-4.2kg). The degree of cardiac dysfunction in vivo was quantitated with echocardiography 8 weeks after ligation of the marginal branch of the left anterior descending coronary artery. The hearts were isolated and perfused with Tyrodes' solution at 37°C and we examined (a) the haemodynamic function in the working heart mode (b) calcium transients from regions of the left ventricular (LV) epicardial surface after loading with the fluorescent calcium indicator Indo-1 and (c) monophasic action potentials (MAPs) from similar regions on the epicardial LV surface. The results were compared with those from sham-operated rabbits. Results: Rabbits with HF had a significantly lower in-vivo ejection fraction compared to controls (41±2% vs 74±2%, p<0.001). (a) Measurements of LV systolic pressure (Sys P), end-diastolic pressure (EDP), aortic flow (Flow) and isovolumic relaxation time (IVRT) are shown below in the table.

| HF (n=9) | 87 ± 3 | 16 ± 1 | 90 ± 6 | 52 ± 8 ± 17 |
| Sham (n=8) | 96 ± 3 | 84 ± 2 | 133 ± 9 | 39.7 ± 1.2 |

Drill LV weights were higher in HF (0.41±0.2 vs 0.3±0.02g/kg, p<0.05). (b) Abnormal long calcium transients were observed in HF hearts (n=14) but not in the control group (n=11). Time to 50% decay of the calcium transient was 157±12±0.6ms in HF hearts compared to 122±12±5ms in controls (p=0.001). This was associated with a slower relaxation in HF hearts with a maximal rate of pressure decline of 0.76±0.6mmHg/min (n=17) vs 1.26±0.26mmHg/min in controls (0.05). There was also increased dispersion of the calcium transient durations in HF hearts (p=0.001). (c) MAP duration was longer in HF hearts (n=14) as measured by the MAP time to 33.5±5.8ms, p<0.001) and there was more dispersion when compared with controls (n=3, p=0.05). There was a significant correlation between the time course of calcium transient duration and MAP duration in both HF and controls (R=0.75, p=0.03). No conclusions: Cardiac hypertrophy/remodelling occurs in this rabbit model of HF with significant systolic and diastolic dysfunction similar to human ischaemic heart disease. Calcium handling is abnormal in the HF hearts which is directly related to mechanical dysfunction. Epicardial repolarisation is delayed in these hearts and dispersions are demonstrated in both the isocromatic and calcium transient durations. These abnormalities may form the basis of the arrhythmogenic tendency in HF.

NITRIC OXIDE CAN INCREASE HEART RATE BY STIMULATING THE HYPERPOLARIZATION-ACTIVATED INWARD CURRENT, If

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Background Nitric oxide (NO) can modulate myocardial contractility and relaxation but it is not clear whether its effects on heart rate are mediated by a direct action on the cardiac pacemaker or from a reflex response to the concurrent changes in arterial blood pressure.

Methods and Results In guinea pig isolated spontaneously beating atria we investigated the chronicotropic effect of increasing concentrations of two NO donors (NO3: sodium nitroprusside (SNP), n=8) and 3-morpholino-sydnonimine (SIN-1, n=6). We found that exogenous NO modulates the beating rate in a concentration-dependent biphasic fashion, with a gradual increase in beating rate for low concentrations of NO and a decrease in beating rate for high concentrations (millimolar). The positive chronotropic effect of 10µM SNP was 28±9% (n=28) and of 30µM SNP the (n=16) was unaffected by IC50 antagonist with nifedipine (0.2µM/L) but was abolished after blockage of the hyperpolarization-activated inward current, If, by Cs+ (2µM/L) or D72788 (1µM/L).

The involvement of If in the positive chronotropic response of exogenous NO was also tested in rabbit isolated patch-clamped SAN cells (n=17) where 5µM SIN-1 caused a reversible, Cs+-sensitive, increase in this current (+ 130% ± 70 mMV and + 225% ± 100 mMV). Conclusion: Exogenous NO can directly affect pacemaker activity in a concentration-dependent biphasic fashion. The increase in beating rate with low doses of NO is unaffected by IC50 antagonist but is abolished in the presence of If blockade. Direct recordings in SAN cells confirmed that this current is markedly increased by NO.

Our results suggest that stimulation of If by NO might play a part in the sinus arrhythmia which accompanies pathological conditions associated with an increase in myocardial production of NO (e.g. heart failure and septic shock).

THE IMPORTANCE OF SLEEP DISTURBANCE IN CHRONIC HEART FAILURE

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Background: Seep disordered breathing (SDB) is common in severe heart failure, but its overall prevalence is unknown. I have studied the prevalence, predictors and treatment of SDB in patients with optimally treated heart failure, and the effect of SDB on somnolence and cognitive impairment. The prevalence of SDB was determined in 125 heart failure patients, compared with 45 normals using the Epworth Sleepiness Scale (ESS). Cognitive function was assessed using a battery of tests including the "Steer Clear" driving simulator. Overnight home pulse oximetry was performed in 85 patients (with ECG monitoring) and 15 normals to determine the prevalence of SDB and its relationship with arrhythmia, left ventricular function and cognitive impairment. 10 patients with Cheyne-Stokes respiration (CSR) entered a double-blind, crossover study of nocturnal oxygen vs air. Sleep quality was assessed by polysomnography. Results: Mean (SEM) ESS score was higher in patients than controls (8.30±0.4) vs 6.50±0.6 (P<0.05). Patients reported more somnolence, hangover and nocturnal myoclonus (P<0.05). Witnessed episodes of SDB and apnoea during sleep were also common in patients (P<0.05). Patients with a poorer NYHA class complained of more symptoms of daytime sleepiness assessed by ESS score (P<0.01). Patients had slower reaction times (1.00±0.3) vs 0.60±0.04 sec; P<0.01) and they hit more obstacles on the driving simulator (77±1 vs 33±4; P<0.01). Desaturation was more severe in patients than controls, 23/85 patients had CSR. The desaturation index correlated with cognitive function in SDB patients, but there was no correlation between either desaturation or ejection fraction and the level of cognitive impairment. Serious arrhythmia was not observed. Overnight oxygen stabilised breathing and improved sleep quality.

Conclusions: Nocturnal desaturation, somnolence and impaired cognitive function are common in heart failure. Arousal from sleep rather than desaturation may determine sleepiness and cognitive impairment. The time has come to investigate further the influence of sleep on heart failure.
CANDOXATRIL IMPROVES EXERCISE CAPACITY IN PATIENTS WITH CHRONIC HEART FAILURE RECEIVING ANGIOTENSIN CONVERTING ENZYME INHIBITION

DE Newby, TJ McDonagh, PC Currie, BB Northridge, NA Boos, HJ Dargie. Departments of Cardiology, Royal Infirmary & Western General Hospital, Edinburgh, and Western Infirmary, Glasgow

Aims To assess the effect of candoxatril, a novel neutral endopeptidase (EC 24.11) inhibitor, on exercise capacity, clinical status and quality of life in patients with mild to moderate chronic heart failure receiving angiotensin converting enzyme inhibition.

Methods Patients were recruited from 16 centres throughout the United Kingdom. All patients had NYHA grade II or III chronic heart failure with an ejection fraction of < 45% or a shortening fraction of < 20% and were receiving maintenance angiotensin converting enzyme inhibitor therapy. They were eligible for recruitment if their treadmill exercise tolerance was between 4 and 7 METS. Following a 4 week single blind placebo "run-in" phase of weekly exercise tests, patients underwent double blind randomisation to receive either candoxatril (100 mg bd) or placebo for the next 84 days. Patients were then reassessed every 28 days.

Results Of 110 patients randomised, 56 received candoxatril and 54 placebo. Over the study period, the overall improvement in mean total exercise time in the candoxatril group in comparison to the placebo group was 34.1 s (p=0.02: 95% confidence intervals: 5.1 to 63.0). There were no significant changes in functional class, clinical status or quality of life scores between the two groups. There was a trend for a small reduction in blood pressure in the candoxatril group.

Conclusion Candoxatril confers an improvement in exercise capacity in patients with chronic heart failure and represents a novel therapeutic adjunct to ACE inhibition in these patients.

THE PROGNOSTIC SIGNIFICANCE OF AN INCREASED VENTILATORY RESPONSE TO EXERCISE IN CHRONIC HEART FAILURE

T P Chan, D Harrington, P Postkowsi, S D Anker, K WebbPeploe, P A Poole-Wilson, A J S Cost

Royal Brompton Hospital and National Heart & Lung Institute, Imperial College School of Medicine, London

The ventilatory response to exercise as characterised by the regression slope relating minute ventilation to carbon dioxide output (VE-VCO2 slope) is high in many chronic heart failure patients. The objective of this study was to investigate the prognostic significance of the VE-VCO2 slope in chronic heart failure. One hundred and seventy-three consecutive chronic heart failure patients (155 men; age 59.8±11.5 years [mean±SD]; radionuclide left ventricular ejection fraction 28.4±14.6%) who had a cardiopulmonary exercise test performed (peak oxygen consumption 18.5±7.3 ml/kg/min; VE-VCO2 slope 34.8±10.6) were studied. Using 1.96 standard deviations above the mean level of the VE-VCO2 slope of 68 healthy age-matched controls (56 men; age 56.4±7.5 years; peak oxygen consumption 32.5±6.3 ml/kg/min; VE-VCO2 slope 26.3±4.1), we defined an abnormally high ventilatory response to exercise as a slope >34. Using this value, 83 chronic heart failure patients (48%) had an increased VE-VCO2 slope (mean 43.1±6.9). In the multivariate Cox proportional hazards model using several variables (age, peak oxygen consumption, VE-VCO2 slope, left ventricular ejection fraction), the VE-VCO2 slope was an independent prognostic marker and gave additional prognostic information (P=0.018) beyond peak oxygen consumption (P=0.022). When Kaplan-Meier survival curves censored at 18 months were constructed, patients with a normal VE-VCO2 regression slope had a survival of 95% compared with 69% for patients with a high slope (P<0.0001). In conclusion, the VE-VCO2 slope is useful in the prognostic assessment of chronic heart failure patients.

PULMONARY AND SYSTEMIC RESPONSES TO EXOGENOUS ENDOTHELIN-1 IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

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Plasma levels of endothelin-1 are raised in heart failure and correlate with pulmonary haemodynamics in this setting. We administered endethelin-1 into a distal pulmonary artery of patients with left ventricular dysfunction with or without overt heart failure in an attempt to study local pulmonary vascular effects. Intra-vascular Doppler ultrasound was used to assess local pulmonary blood flow in the first 4 patients. Haemodynamics were measured by thermodilution catheter and arterial line. Endothelin-1 was infused at 1.5 and 15pmol/min. No side effects occurred but 2 patients did not receive the 15pmol/min infusion (due to a rise in systolic BP >20mmHg or a fall in cardiac output of >15%).

Systemic haemodynamic changes occurred in a dose dependent fashion. Data are given as mean ± standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Peak</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>70±15</td>
<td>71±14</td>
<td>ns</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>97±8</td>
<td>106±11</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Pulmonary wedge pressure</td>
<td>13±6</td>
<td>16±4</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.4±0.6</td>
<td>2.2±0.5</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>167±39</td>
<td>204±45</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>151±56</td>
<td>142±44</td>
<td>ns</td>
</tr>
<tr>
<td>Resistance ratio (PVR/SVR)</td>
<td>0.09±0.03</td>
<td>0.07±0.02</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Exogenous endothelin-1 causes systemic but not pulmonary vasocostriction in patients with left ventricular dysfunction. Raised plasma endothelin-1 may be a marker, as opposed to a mediator of pulmonary hypertension in heart failure.

PRIMARY RESULTS OF THE UK HEART STUDY: HEART RATE VARIABILITY INDEPENDENTLY PREDICTS RISK IN AMBULANT CHRONIC HEART FAILURE

J Nolan, PD Batn, R Andrews, P Brooksby, S Lindsay, M Mullan, M Baig, AJ Cowley, R Prescott, AD Flapan, JMM Neilson, KAA Fox

Patients with severe heart failure have markedly diminished survival, but among ambulant, apparently compensated heart failure, it is necessary to define the factors which independently predict prognosis. There are difficulties in identifying such predictors using currently available clinical measurements. Measurement of heart rate variability (HRV) can be used to determine the degree of autonomic dysfunction present in CHF, but has not previously been tested in trials powered for death. The aim of the UK-HEART study was to determine, in a prospective and adequately powered study, whether reduced HRV provides additional independent prognostic information when added to conventional echo, radiological, biochemical and holistic variables. We studied 433 ambulant outpatients with signs and symptoms of CHF (age 62+/-10 years, NYHA 2.4+/-0.5, frusamide 73+/-69mg, EF 42+/-17%, 82% treated with ACEI) follow up interval: 482+/-161 days, during which 52 cardiac deaths occurred. 24 hour standard deviation (SDNN) was the only HRV parameter associated with outcome in univariate analysis (survivors = 116+/-39 ms, dead = 92+/-47 ms, P<0.001). In multivariate analysis 5 variables provided independent prognostic information.

<table>
<thead>
<tr>
<th></th>
<th>SODIUM</th>
<th>SDNN</th>
<th>NYHA</th>
<th>CREATININE</th>
<th>CARDIOTHORACIC RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.5</td>
<td>33.5</td>
<td>17.6</td>
<td>14.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Odds ratio for death for SDNN of 50-100 ms was 2.2 (95% CI 1.4-4.9), and for less than 50 ms: 10.9 (95% CI 5.1-23.4). These results demonstrate, for the first time, that reduced HRV independently predicts survival. This measurement may provide useful prognostic information when added to clinical assessment of heart failure.</td>
<td>0.0001</td>
<td>0.001</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.02</td>
</tr>
</tbody>
</table>
The predictive value of natriuretic peptide estimation for detecting new heart failure in general practice

MRC Cowie, AD Struthers, DA Wood, A Coats, SG Thompson, PA Poole-Wilson, GC Grieves, Cardiac Muscle, National Heart & Lung Institute, Imperial College School of Medicine, London; Ninewells Hospital & Medical School, Dundee; Medical Statistics & Evaluation, Royal Postgraduate Medical School, London; and EIBBS Hospital, Uxbridge, Midls.

The validity of a clinical diagnosis of heart failure in general practice is known to be poor, leading to inappropriate treatment in as many as two thirds of such patients. However, confirming the diagnosis is time consuming requiring further clinical assessment by a specialist and investigation including echocardiography. Since elevation of plasma atrial (ANP and NT-ANP) and brain natriuretic peptides (BNP) occur in patients with heart failure we assessed the utility of measuring these peptides in 122 consecutive patients referred to a rapid access heart failure clinic with a new primary care diagnosis of heart failure. On the basis of clinical examination, chest x-ray and echocardiography a panel of 3 cardiologists confirmed 35 of the 122 (29%) referred patients had new heart failure. The median level of ANP, BNP & NT-ANP (pmol/l) were much higher in those in heart failure compared with those not in heart failure (30.6 vs 13.0, 60.8 vs 11.9, 1271.3 vs 417.0 respectively, all p<0.0005). The Table displays the sensitivity, specificity and positive predictive value of the three peptides for cut-off levels where the negative predictive value was 98%.

<table>
<thead>
<tr>
<th>BNP</th>
<th>ANP</th>
<th>NT-ANP</th>
</tr>
</thead>
<tbody>
<tr>
<td>pmol/l</td>
<td>pmol/l</td>
<td>pmol/l</td>
</tr>
<tr>
<td>&gt;22</td>
<td>&gt;186</td>
<td>&gt;575</td>
</tr>
<tr>
<td>sensitivity (%)</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>specificity (%)</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>positive pred. value (%)</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>negative pred. value (%)</td>
<td>98</td>
<td>98</td>
</tr>
</tbody>
</table>

A multiple logistic regression model was used to determine the independent contribution of natriuretic peptides in detecting the presence of heart failure and there was significant improvement in fit by adding either ANP (p=0.18) or NT-ANP (p=0.55) to a model containing BNP only.

A plasma BNP level in patients with symptoms which are thought to be due to heart failure by a general practitioner may be a useful (and relatively inexpensive) screening test for selecting patients who require assessment by a cardiologist.

CHARACTERISATION OF HUMAN ATRIAL FLUTTER USING A NOVEL NON-CONTACT MAPPING SYSTEM

R Schilling, N Peters, A Kadish, W Davidoff, St Mary's Hospital, London, UK. Northwestern Memorial Hospital, Chicago, IL, USA.

Atrial flutter (AFI) results from macroreentry in the right atrium (RA) and was analysed in detail in 5 patients (pts) by high resolution mapping with a non-contact multielectrode (MEA) catheter. It is a 64 wire braid around an 8ml balloon, on a 9F catheter allowing mathematical reconstruction of more than 3,300 electrograms which are superimposed onto a computer model of the endocardium creating isopotential and isochronal maps. Maps of AFI were used to guide successful ablation (RF) in all pts with more detailed analysis performed later. 3 pts had failed previous RF. The entire AFI circuit was shown in 1 pt with, and both pts without, previous RF. The isthmus (IS) between tricuspid annulus and inferior vena cava was closely examined. There was attenuation of signal in part of the IS in 2 pts with previous RF but clear entry and exit points to and from the IS identified. Conduction time within the IS was long and was quantified as a percentage of AFI cycle length (IST). Mean IST was 38% in pts with and 26% in pts without previous RF. IST prolonged during creation of a line of block (LB) to 64% prior to completion of a LB. Activation split around the coronary sinus in 2 pts, the posterior of the activation fronts blocking and turning at the eustachian ridge (ER) to fuse with the anterior front. In 1 pt with and 1 without previous RF, activation was predominantly posterior, blocked and turned at the ER. In 4 pts activation progressed towards the lateral LA from the surrounding RA suggesting that the circuit was not dependent on rotation around the TA. It could not be clearly discerned in the remaining pt. This new system has given unique and applicable insights into human atrial flutter and into the changes occurring in the circuit during successful RF therapy.

STRESS INDUCED LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION-A POTENTIAL CAUSE OF DYSPNEA IN THE ELDERLY

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Limitation of exercise tolerance by breathlessness is common in the elderly and has been ascribed to diastolic dysfunction when LV systolic function has deteriorated. Dobutamine stress echocardiography to identify disturbed LV physiology when symptoms develop in 30 such patients, aged 70±12 years, 21 female. Resting results were compared with 12 normals, age 69±10 years. Before stress LV dimensions were normal, fractional shortening increased and basal septum 2.3±0.5 vs 1.3±0.2 cm and posterior wall 1.2±0.2 vs 0.9±0.1 cm were thickened, p<0.001 (vs normal).

Isovolumic relaxation time was prolonged. Peak LV posterior wall thinning rate was reduced 8.1±3.5 vs 10.4±2.6 cm/s, p<0.05 and transmitral A wave velocity increased 0.86±0.1 vs 0.62±0.1 m/s, p<0.001, all indicating diastolic dysfunction. At peak stress: heart rate rose from 80±12 to 132±26 bpm and systolic blood pressure from 135±15 to 170±24 mmHg, p<0.001, but LV cavity dimensions did not change. Peak LV outflow tract velocity increased from 1.5±0.5 m/s to 4.2±1.2 m/s, systolic mitral leaflet septal distance fell from 13.4±5 to 2.2±1.9 mm, p<0.001, and SAM appeared in 24 (80%) patients. Measurements of diastolic dysfunction showed no significant change. All patients developed dyspnea at peak stress, but none developed a new wall motion abnormality or mitral regurgitation. Conclusion: Although our patients fulfilled the criteria for 'diastolic heart failure', diastolic dysfunction was not aggravated by pharmacological stress. Instead, high blood velocities appeared in the LV outflow tract, associated with basal septal hypertrophy and abnormal mitral valve motion. Their presence correlated closely with the development of symptoms.

A NEW TECHNIQUE FOR CONFIRMING BIDIRECTIONAL BLOCK IN THE LOW RIGHT ATRIUM TO CONFIRM SUCCESSFUL CATHETER ABLATION OF TYPICAL ATRIAL FLUTTER

AM Zdzi, MJ Galloway, KJ Lipscombe, NJ Linker, A Fitchet, AP Fitzpatrick. Manchester Heart Centre, The Royal Infirmary, Manchester M13 9WL.

Background. It is established that typical atrial flutter (AFL) is caused by a macroreentrant circuit in the right atrium (RA), propagating in an anticoxrdial direction around the tricuspid annulus, with a protected zone of slow conduction in the inferior vena cava-tricuspid annulus isthmus (IVC-TAI). Delivery of radiofrequency catheter ablation (RFCA) to the IVC-TAI is effective in ablating AFL with immediate success defined by termination of the tachycardia. However, recurrences of AFL remains a major problem, with rates up to 44%. This is thought to reflect a failure to create bidirectional conduction block in the IVC-TAI.

Methods. To confirm bidirectional block in the IVC-TAI, we arranged decapolar catheters along the right atrial free wall and right atrial septal wall at the tricuspid annulus. Following successful termination of AFL, the decapole were used to map the right atrial activation sequence during proximal coronary sinus (CS) pacing. If conduction in the IVC-TAI persists after termination, as is common, further RFCA applications are made during CS pacing. If local block in the IVC-TAI has been established, then the wavefront will propagate clockwise up the septum and down the free wall, but the postero-lateral RA (PLRA) activates late. If conduction persists, the PLRA activates early via the IVC-TAI. After unidirectional (anticoxrdial) block is established, bidirectional block is confirmed by pacing in the posterolateral RA and demonstrating late activation of the proximal CS.

Results. In 5 patients (5 male, age 42±10.6 years) with 18.6±36.6 months of chronic AFL, RFCA terminated AFL but bidirectional conduction was still present. 8.0±8.4 further applications of RFCA were required to successfully abolish bidirectional conduction.

Conclusions. Termination of AFL during RFCA is not evidence of successful ablation. This technique is likely to reduce recurrences and improve long-term success.
THE FINAL ACTIVATION WAVE PRECEDING SPONTANEOUS TERMINATION OF SUSTAINED ATRIAL FIBRILLATION HAS AN EPICARDIAL BREAKTHROUGH SITE AT BACHMAN’S BUNDLE.


The atrial events associated with spontaneous termination of sustained atrial fibrillation (AF) have been little studied. We analysed the atrial activation sequence, electrogram morphology and cycle length changes for 4 seconds preceding spontaneous termination of sustained AF in 5 female goats. Recordings were made from 83 silver disc electrodes on the epicardial atrial surface. 23 on Bachman’s bundle (interelectrode distance 6-10mm) and 30 on both the right and left free walls (interelectrode distance 4mm). AF had been artificially maintained for a mean of 7 days and the duration of the analysed episodes was 10.4±5.1 minutes. Atrial cycle length progressively increased at all recording sites from a mean of 98±10ms to 153±26ms (p<0.001) immediately prior to termination, associated with a marked decrease in electrogram fragmentation. Initially the mapped atria were activated by 2 or more wave fronts with varying degrees of conduction block. breakthrough sites changing from beat to beat. Activation patterns during the last 5 beats became much more uniform however, and strikingly similar in 4/5 goats. Epicardial breakthrough occurred at the centre of Bachman’s bundle and was followed by rapid activation of both free walls.

Conclusion: Termination of AF in the goat is preceded by a reduction in the number of propagating waves of activation, the final wave having an epicardial breakthrough site at the centre of Bachman’s bundle. These findings provide support for the suggestion that the atrial septum is particularly important in the perpetuation of AF and may be an appropriate site for a limited catheter ablation procedure for cure of this arrhythmia.

THE USE OF ATROPINE TO ENHANCE SUCCESSFUL CARDIOVERSION FROM ATRIAL FIBRILLATION

AGC Sutton, ED Grech, D Price, R Graham, C Hirling, A Davies, J Hall, M de Belder. Cardiothoracic Division, South Cleveland Hospital, Middlesbrough

It has been postulated that the use of atropine prior to direct current (DC) cardioversion in patients with resistant atrial fibrillation may enhance cardioversion to sinus rhythm. However, there have been no large studies to examine this hypothesis.

We report a series of 140 elective cardioversions performed for atrial fibrillation in 105 patients (76 males, 29 females, age range 30-84 years, mean age 62.2 years). We used paddles in the sternal and apical positions and incremental shock strengths up to a maximum of 360 Joules repeated up to three times. 109 (78%) cardioversions in 88 patients were successful. 31 (22%) cardioversions in 28 patients were unsuccessful. 43% of the successful and 42% of the unsuccessful cardioversions were preceded by treatment with prophylactic anti-arrhythmic agents.

When DC cardioversion using the above techniques was unsuccessful, the patient was considered for a repeat shock after intravenous atropine. Atropine at a dose of 600mcg was administered on 23 occasions to 22 patients. In this group, sinus rhythm was obtained on 9 occasions in 9 different patients. Thus, 28 of 105 patients had atrial fibrillation resistant to DC cardioversion using the standard techniques. With the selective use of atropine on 23 occasions (in 22 patients), we were able to achieve cardioversion to sinus rhythm in 9 patients.

Larger scale trials assessing the use of atropine for attempted DC cardioversion are indicated.

ELECTROGRAM FRACTIONATION IN THE LONG QT SYNDBOME AND AS MODELLED IN PERFUSED HEART BY INHIBITION OF SCN5A-ENCODED ION CHANNELS

RC Saumarez, J Hall, MD Lowe, PF Ludman, SA Rowland, AA Grace. Department of Cardiological Sciences, St. George’s Hospital Medical School, London; Departments of Biochemistry and ‘Medicine, University of Cambridge

Congenital long QT syndromes (LQTS) are associated with sudden cardiac death and result from mutations in genes encoding ion channels involved in repolarisation. The relationship between modified function of these channels and the integrated electrophysiology of LQTS has not been defined. Early fractionation of paced endocardial electrograms is associated with risk in hypertrophic cardiomyopathy (HCM) and primary ventricular fibrillation (VF). The same methods for assessing intraventricular conduction and electrogram fractionation in response to a decremental pacing sequence have been applied to patients with LQTS. Fractionation has been measured in terms of the S,S interval at which delay increases (S,S,D) and the increase in electrogram duration (IED) between an S,S of 150 ms and just below VERB.

<table>
<thead>
<tr>
<th>Group</th>
<th>S,S,D (ms)</th>
<th>IED (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human control</td>
<td>251-287</td>
<td>1.5-11</td>
</tr>
<tr>
<td>Human LQTS</td>
<td>311-363</td>
<td>18-30</td>
</tr>
<tr>
<td>Ferret control</td>
<td>189-208</td>
<td>5.5-14</td>
</tr>
<tr>
<td>Ferret AP-A</td>
<td>238-285</td>
<td>1.5-34</td>
</tr>
</tbody>
</table>

The results [see table] showing large increase in S,S,D and IED (expressed as ranges) in patients with LQTS and documented VF compared to controls are similar to those obtained in HCM VF survivors. The relationship between these clinical manifestations and the functional consequences of LQTS mutations have been investigated by applying the same protocols to 8 endocardial sites in the perfused ferret heart. LQT1, has been modelled using antiarrhythmic agents (AP-L) to inhibit inactivation of SCN5A-encoded I Na. In this case [see table] and in a similar model of LQT, there are concentration-dependent increases in S,S,D and IED with patterns that entirely reproduce the clinical data. The results provide a link between the electrophysiological consequences arising from ion channel mutations and clinical risk in LQTS.

β-ADRENOCEPTOR STIMULATION INCREASES DISPERSION OF CARDIAC REPOLARISATION

MD Lowe, FP Ludman, SA Newell, E Rowland, AA Grace. Department of Cardiology, Papworth Hospital; Department of Cardiological Sciences, St. George’s Hospital Medical School

β-adrenoceptor blockers reduce risk in some patients with cardiac disease, but the optimal use of β-selective versus non-selective agents is not established. β1 receptor stimulation has functional effects in human atrium but β2-mediated effects on human ventricle. The effects in vivo have not been described. The aim of this study was to examine the effects of β- adrenoceptor stimulation on ventricular repolarisation. 22 patients with coronary artery disease (CAD) and 16 patients without CAD were compared to 12 patients with normal coronary arteries (NCA: 9 males, mean age 58). Patients were appropriately stratified for e.g. LV function, previous myocardial infarction etc. QT dispersion (QTD) was calculated using standard protocols. Incremental doses of salbutamol (S, 10-30 µg min-1) or isoprenaline (I, 1.25-3.75 µg min-1) were infused through a central vein. Heart rate was maintained constant with atrial pacing. Increases in QTD were significant in both CAD (p<0.001; ANOVA) and NCA (p=0.002) patients with both salbutamol and isoprenaline but occurred at lower doses in CAD patients. In a separate group of patients intra-coronary injection of isoprenaline resulted in shortening of right ventricular monophasic action potential duration indicating a direct action on cardiac repolarisation.

Increases in QTD with both salbutamol and isoprenaline are consistent with β1-adrenoceptor stimulation having important electrophysiological effects in human ventricle.
PERMANENT ENDOCARDIAL PACING ACHIEVED BY A PERCUTANEOUS APPROACH IN PATIENTS WITH MECHANICAL TRICUSPID VALVE REPLACEMENT - LONG TERM FOLLOW UP

CL Bray, Y Steen
Regional Cardiothoracic Centre Wythenshawe Hospital
Manchester

The presence of a mechanical tricuspid valve prosthesis prevents safe conventional access to the right ventricle to achieve permanent endocardial pacing. Previous experience with percutaneous right ventricular and left ventricular catheterisation and angiography in patients with prosthetic valves has been associated with low morbidity and no problems with cardiac tamponade. We have developed a new approach to accomplish permanent endocardial pacing in patients with previous pericardiectomy using direct venricular puncture and insertion of a standard passive fixation endocardial pacing electrode. We report the long term follow up of 6 patients treated using this new approach; four patients with mechanical tricuspid valve prosthesis and two patients with superior vena caval occlusion who had had previous pericardiectomy but in whom epicardial electrodes were exhibiting exit block. In the study group follow up measurement of stimulation threshold, sensing threshold and chronic lead impedance are comparable to those measured in a control group of patients with the same model of electrode implanted via the conventional transvenous approach. There have been no early or late complications associated with the percutaneous approach. The data confirm satisfactory long term pacing for up to 5 years. We conclude that this new technique is a satisfactory minimally invasive alternative to established techniques for achieving long term permanent cardiac pacing in patients with mechanical tricuspid valve prosthesis or vena caval occlusion with previous pericardiectomy.

SHOULD MODE SWITCHING DDDR PACEMAKERS BE USED IN ALL PATIENTS WITH A HISTORY OF ATRIAL TACHYARRHYTHMIAS?

K Kamalvand, A Ketokasik, K Tan, G Lloyd, H Birdi, C Bucknall, N Sulke, Guy's & St Thomas' Hospital Trust, London

Previous studies have shown that a history of atrial fibrillation (AF) is the strongest predictor for the development of chronic AF following pacemaker implantation. DDDR pacemakers with mode switching (MS) cost significantly more than VVIR devices. Identifying patients who will develop chronic AF will thus result in considerable cost savings without adversely affecting management. 62 patients with DDDR pacemakers (52 MS) and a history of AF or atrial flutter (AFL) (34 male, mean age 63 (SD 123) were followed up for a median duration of 14 months (range 3-40). The indications for pacing were radiofrequency ablation of the AV node for drug resistant AF/AFL in 28 (45%) and Tachy-brady syndrome and/or heart block in 34 (55%). 16 (26%) developed chronic persistent AF/AFL. The programmed pacemaker mode was dual chamber in 52 patients (84%) (DDDR 46, DDDR 6), and VVIR in 10 (16%). 6 patients with chronic AF/AFL were still programmed to dual chamber modes (4 DDDR with MS, 2 DDDR). Overall, 11 patients (17%) were on class III antiarrhythmic drugs. The following variables were analysed in a multivariate model to predict the development of chronic persistent AF/AFL age, sex, indication for pacing, pacemaker type, duration of symptoms, and history of previous DC cardioversions (DC). The only independent predictor for the development of persistent AF/AFL was a pre-implantation history of DC. 71% of patients with a history of DC developed persistent AF/AFL as compared to 13% with no previous history of DC (p=0.001). The duration of symptoms of AF/AFL prior to pacemaker implantation tended to be longer in patients who developed chronic AF/AFL (mean 71 months) compared to those who remained in sinus rhythm (mean 54 months), but this was not statistically significant. In conclusion, in the medium term, the majority of patients with a history of AF/AFL and DDDR pacemakers remain in sinus rhythm and benefit from the advantages of dual chamber pacing. A history of previous DC cardioversions is a strong independent risk factor for the development of chronic persistent AF/AFL. VVIR pacing in this patient subgroup may therefore be more appropriate with considerably financial savings.

SUBPECTORAL ICD IMPLANTATION: COMPARISON OF PATIENT ACCEPTABILITY UNDER LOCAL AND GENERAL ANAESTHESIA

KJ Lipscomb, NJ Linker, AM Zaidi, A Fitpatrick, University Department of Cardiology, Manchester Heart Centre, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL

Background. Local anaesthesia with conscious sedation has been reported for the prepercutaneous implantation of permanent pacemakers. This technique has not yet gained acceptance for the implantation of cardioverter defibrillators (ICDs) as these devices are bulkier, are often implanted submuscularly and require testing of defibrillation thresholds at implant. We report the acceptability of local anaesthesia (LA) with conscious sedation in 14 patients undergoing submuscular implants compared with 12 in whom general anaesthesia (GA) was employed using the same implant technique.

Methods. 26 patients (19 male, 7 female, mean age 56 years) underwent subpectoral ICD implant between August 1995 and November 1996. 13 (50%) had experienced aborted sudden death, 13 (50%) had haemodynamically unstable ventricular tachycardia. 17 patients (65%) had established CAD, mean ejection fraction was 43% (SD 19). 12 procedures were performed under GA. 14 patients were sedated with Midazolam and diamorphine and local anaesthesia was achieved with 0.5% Bupivicaine. Ventricular fibrillation was induced by AC current (8), T-Wave shock (10) or programmed burst pacing (7). Mean number of inductions was 2.1 (SD 0.9). Patients were contacted after the procedure to enquire about acceptability. Results. 8 patients undergoing implant under LA had no recollection of the procedure or test shock. 6 described the procedure as painfree but recalled the test shock describing it as mildly uncomfortable. All subjects stated that they would be willing to undergo a second implant under LA and 10 patients who had a GA would be willing to undergo implant under LA. The cosmetic result was acceptable in all patients. Conclusions. Subpectoral implantation of ICDs produces a cosmetically satisfactory result and is well tolerated under local anaesthesia with conscious sedation.

BAROREFLEX SENSITIVITY MAY BE ESTIMATED USING SPECTRAL ANALYSIS

SW Lord, RH Clayton, MCS Hall, J Bishop, A Murray, JM McComb, RA Kenzy. Royal Victoria Infirmary and Freeman Hospital, Newcastle upon Tyne.

Baroreflex sensitivity (c) is a useful predictor of prognosis after myocardial infarction, but has traditionally required invasive techniques (intravenous phenylephrine) to measure it. We have compared two non-invasive techniques (Valsalva and spectral analysis) with intravenous phenylephrine to measure c.27 normal volunteers (16 male, age 22-62) were studied on 3 separate occasions at the same time of day at least one week apart. ECG and finger arterial blood pressure (Finapres) were sampled at 250 Hz. An intravenous cannula was inserted, and the subject rested for 30 minutes. 3 Valsalva manoeuvres and a further 15 minutes of supine rest were recorded in random order. Phenylephrine (PE) was then infused at up to 200μg/min for two separate periods. c(PE) was estimated from each Valsalva manoeuvre using the standard algorithm. Two values of c were estimated from the ratio of spectra from resampled systolic blood pressure (SBP) and RR interval series over medium and high frequency ranges (c(mf), 0.05-0.15 Hz, c(hf), 0.15-0.35 Hz). Classical baroreflex sensitivity, c, was estimated from the relationship between mean cycle length and SBP only when the rise in SBP was >20mmHg/min. Agreement between methods was assessed using the method of Bland and Altman. Measurements of c(mf) agreed with measurements of c(mf) (mean difference 1.06 ms/mmHg 95% Cl -7.4 to 9.6 ms/mmHg) and with those of c(PE) (mean difference -0.5 ms/mmHg 95% Cl -15.4 to 14.4 ms/mmHg) but not with those of c(hf). There was no order effect. Thus c may be reliably estimated using spectral analysis and the Valsalva manoeuvre. The variability of the estimation is less for spectral analysis, suggesting that it is the better non invasive method.
MIDODRINE: A ROLE IN THE MANAGEMENT OF NEUROCARDIOGENIC SYNCOPE

C Ward, J Gray, J Gilroy, R A Kenny.
Cardiovascular Investigation Unit, Royal Victoria Infirmary, Newcastle Upon Tyne.

PURPOSE: The management and mechanism of neurocardiogenic syncope remains controversial, however venous pooling in the lower extremities during orthostatic stress has been postulated to play a role. The purpose of this study was to evaluate the role of midodrine as a venoconstrictor in influencing symptom frequency and haemodynamic responses during head-up tilt in a series of patients with neurocardiogenic syncope.

PATIENTS AND METHODS: Sixteen outpatients (mean age 56 ± 18 years; 5 male) with frequent hypotensive symptoms (>2 syncope episodes and >20 symptoms of syncope in 6 months) and reproducible syncope during head-up tilt were studied in a double blind placebo controlled study. Patients were randomised to placebo for one month and midodrine for one month with a one week wash out period in between. During each study month symptom events were recorded and at the end of each study month the patient had a quality of life assessment (Short Form 36), a global assessment of therapeutic response and GTN-head-up tilt with heart rate (electrocardiogram), phasic blood pressure (digital photoplethysmography) and thoracic fluid index (transstracheal impedance plethysmography) measurements.

RESULTS: Patients had an average of 7.3 more symptom free days on midodrine than on placebo (95% CI: 4.6 to 9; p<0.0001). Eleven patients reported a positive therapeutic response on midodrine (p=0.0002) and all domains of quality of life showed improvement during midodrine treatment, in particular physical function (8.1; 95% CI: 3.7 to 12.2), energy and vitality (14.6; 95% CI: 2.1 to 7.3) and change in health (22.2; 95% CI: 11 to 33.4).

Fourteen patients who induced syncope on placebo compared to 6 on midodrine (p<0.01). Time to syncope was longer on midodrine (6.3 ± 3 mins versus 8.8 ± 2 mins; p<0.05). Baseline supine systolic blood pressure, was higher and heart rate lower on midodrine compared to placebo. Lower thoracic fluid index measurements on midodrine indicated increased venous return both when supine and during head-up tilt.

CONCLUSIONS: Midodrine had a marked beneficial effect on all parameters measured: symptoms during head-up tilt, symptom frequency and quality of life. Midodrine could be a useful treatment with low adverse effect profile for patients with frequent symptoms attributable to neurocardiogenic syncope.
COST OF MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION IN THE THROMBOLYTIC ERA

Mahon NG, O Rahallaigh P, Brennan J, Codd MB, McCann HA, Segrue DB

Department of Clinical Cardiology, Epidemiology and Biostatistics, Mater Hospital, Dublin

In an era of rapid advances in therapeutic options for acute myocardial infarction (AMI), cost considerations have become an integral part of the provision of medical care. Accurate audit of activities and costs thereof have become vital to health planning and resource allocation.

Aims: to evaluate the cost of management of acute myocardial infarction per patient in a tertiary referral center; to identify proportional contribution of different elements of the total cost.

Methods: Data were collected on 850 consecutive patients with AMI admitted to the one center from Jan 1992 to Dec 1994. For each patient 78 variables of interest were recorded including number of days spent on ward/CCU/ITU, treatments given, and investigations and procedures performed. Detailed costing of investigative and therapeutic procedures was carried within the department of clinical cardiology. Information on the cost of hospital days in general ward/CCU/ITU was obtained from the finance department.

Results: Using data obtained as described above the cost per patient per hospital admission for AMI was £5513. The total cost to the hospital of AMI for the time studied was £4,685,730 or approximately £1.5 million per year. The cost of hospital accommodation accounted for more than 90% of the total cost, with cardiac investigations and interventions accounting for less than 10% of the total. Thrombolysis contributed under 1% to the total cost. Management costs in the very old (>75 yrs) did not differ from those of the remaining population despite considerably lower rates of intervention. We conclude that AMI places a considerable burden on health care resources, the bulk of which arises from the need for hospitalization rather than from expensive investigations and treatments.

ONE-YEAR OUTCOME AND HEALTH SERVICE USE OF A NATIONAL SAMPLE OF PATIENTS HOSPITALISED FOR ACUTE MYOCARDIAL INFARCTION (AMI) IN IRELAND

HMG McGee, A Montgomery, JH O'Hora

Department of Cardiology, Beaumont Hospital, Dublin, Ireland

Population-specific information on the natural history of AMI, including mortality rates and health service use, is important for service planning and evaluation and for individual patient care. This study evaluated one-year clinical outcomes and health service use of a national sample of patients admitted to Irish hospitals for AMI.

METHOD

All Irish hospitals admitting >25 patients annually for AMI (n=38) recorded details on 25 consecutive admissions for suspected AMI. Of 950 patients, 795 (70%) were confirmed as having an AMI. At one year post-AMI, hospital records and GP data was obtained regarding clinical outcome and hospital and GP service use.

RESULTS

Of 425 medical charts sought, 91% were available for consultation. The GP survey had a 56% response rate. 79 (8%) of patients died in hospital and a further 1% within 30 days of admission. A further 1% died over the subsequent year (overall one-year mortality: 10%). 58% of patients received thrombolysis. Length of hospital stay was 12.7 days (mean) 9.8) with an average 8.0 (6.2) GP visits over the subsequent year. 7.5% of patients underwent revascularisation (3.5% CABG; 4% PTCA) while 3% of patients had a repeat AMI in this year. At the end of the year, 78% were being prescribed aspirin, 12% anticoagulants, 34% ace inhibitors and 31% beta blockers. GPs reported that 8% of patients had undertaken a formal cardiac rehabilitation programme but for a further 21% of patients, GPs reported only knowing what patients had done a programme. These data provide a first national profile on the aftermath of AMI in Ireland and identify areas for further improvement in service delivery.

INVESTIGATION AND INTERVENTION POST MYOCARDIAL INFARCTION IN SCOTLAND 1989-94

Multivariate analysis of the Influence of Age, Sex, Deprivation, Health Authority and Year of admission.

J.N. Findlay, Royal Alexandra Hospital, Paisley Scotland M. McLeod, E. Juszczak, Information and Statistics Division, N.H.S. Scotland, A.D. Cunningham, C.R.I. University of Glasgow.

There has been publication of conflicting evidence regarding gender and social class bias in cardiological practice. Part of this may be due to using a clinical diagnosis of angina or death certification of myocardial infarction as the marker for “need” as these are not synonymous with coronary heart disease (CHD). To overcome this we used an objective marker of CHD - discharge from hospital with the primary diagnosis of acute myocardial infarction (AMI) -ICD code 410 as the basis of “need” and from the Scottish linked database 1989-1995 examined the rates of coronary angiography (CA), angioplasty (PTCA) and bypass surgery (CABG) in the year following discharge with AMI. In 1988-93 there were 34609 males (mean age 68) and 25486 females (mean age 72) first emergency admissions with AMI. Female admisions exceeded males after the age of 74 which was the upper limit of age used in analysis. The odds ratios (OR) for the crude rates of CA and CABG but not PTCA were higher in men than women for each year (1.5 and 1.8 respectively). But in those aged <55 crude rates of all CA and PTCA but not CABG were higher in women than in men. In multivariate analysis, in comparison with the Scottish average, the 4 Health Authorities with access to CA showed rates of CA ranging from 1.4-3.0 vs the remainder 0.6-1.5 and for PTCA 0.9-3.0 vs 0.6-1.5 and for CABG 0.8-1.5 vs 0.6-1.4. When comparing rates for male group, multivariate analysis showed an increase in men in CA of 1.3 (1.2-1.4 95%CI) and CABG 1.6 (1.3-1.9 95%CI) but not PTCA 0.8 (P=NS). The lowest deprivation group showed an increase rate of CA (1.5) and CABG (1.9) but not PTCA (1.1) compared with the most deprived group. The most significant effect was seen with age. When comparing age group 35-44 vs 65-74 the O.R. for CA, PTCA and CABG was 9.3, 9.8 and 3.2 respectively. From 1989 to 1993 the increase in CA, PTCA and CABG was 1.7, 2.1 and 1.9 respectively. In conclusion even post AMI there remains an unaccounted difference in intervention related to sex and social class though PTCA was not affected by this.

ACE INHIBITOR USE AFTER MYOCARDIAL INFARCTION: DOES AUDIT CHANGE CLINICAL PRACTICE?

SJ Walters, R Lowe, MS Norritt, GC Kaye and JL Caplin

Department of Cardiology, Royal Infirmary, Hull

The publication of several landmark studies (SAVE, AIR, GISSI 3 and ISIS 4) confirming a beneficial effect of Angiotensin Converting Enzyme Inhibitors (ACEI) after myocardial infarction (MI), has led to the development of guidelines for ACEI use in this setting. In light of this trial evidence do we now identify and treat all eligible patients?

We initially conducted a retrospective note review of consecutive MI patients admitted to CCU only (1st audit). The results of the first audit were discussed widely with all admitting physicians, and agreement was reached on areas to be targeted for improved clinical practice. Twelve months later the audit was repeated, this time reviewing consecutive MI patients admitted to any hospital department (2nd audit).

<table>
<thead>
<tr>
<th>Heart Failure</th>
<th>LVEF&lt;40%</th>
<th>All Eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=31)</td>
<td>(n=21)</td>
<td>(n=39)</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
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<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>First Audit:</td>
<td>(n=100)</td>
<td></td>
</tr>
<tr>
<td>ACEI +</td>
<td>20 (62.5%)</td>
<td>18 (85.7%)</td>
</tr>
<tr>
<td>ACEI -</td>
<td>11 (37.5%)</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.097 (ns)</td>
<td>0.75 (ns)</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Second Audit:</td>
<td>(n=73)</td>
<td></td>
</tr>
<tr>
<td>ACEI +</td>
<td>13 (43%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>ACEI -</td>
<td>17 (57%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.099 (ns)</td>
<td></td>
</tr>
</tbody>
</table>

(+ means ACEI given, - means no ACEI given)

Despite initial audit highlighting significant deficiencies in ACEI use post MI, there does not appear to have been any subsequent improvement in clinical practice. These results have implications for the effectiveness of ‘educational audit’ when written guidelines are not subsequently produced.
THE POTENTIAL FOR POST-IMPACT RISK REDUCTION WITH LIPID THERAPY IN THE UK: THE ASPIRE SURVEY

TJ Bowker, MD, B Thompson, MD, M Thompson, MD, & D A Wood, for the ASPIRE Investigators. Cardiac Medicine, National Heart & Lung Institute, University of London, England.

To measure the potential for secondary coronary prevention in the UK, the British Cardiac Society undertook a national survey (ASPIRE). A random sample of 12 district general hospitals identified 25 consecutive patients, <70 yrs of each sex, admitted for AMI >6 months prior to the survey, who were then invited for prospective interview & examination. 346 male and 369 female AMI patients (respectively median ages 61.4 & 63 yrs) were studied. 121 (51 male) had died by the time of interview and were replaced in the sample. 247 (84%) male & 225 (80%) female AMI survivors attended for interview. Of these, 156 males (63%) had a total cholesterol (TC) >5.5 mmol/L, only 7 of whom were on hypolipidaemic medication. The respective values for females were 190 (81%), with 18 on hypolipidaemic medication. (The number of patients on medication with TC <5.5 was 7 (34) in males & 5 (24) in females. The TC in 63% of male and 81% of female UK AMI survivors <70 yrs, further improvement in lipid management was indicated to bring their TC <5.5 mmol/L. The 4S study showed a reduction of 37% over 5 yrs in the relative risk (RR) of coronary events (death & non-fatal MI) for both sexes on lipid therapy. Assuming 95% compliance, an improvement of 36% in the RR (compared to that of current practice) should be achievable, if appropriate lipid management is adopted in the UK. In UK AMI survivors <70 yrs from any one year, this would lead to the prevention of about 1100 male and 400 female coronary events in that one-year cohort over 5 yrs. In this study, 63% of male and 71% of female AMI’s were the patient’s first ever manifestation of coronary disease. This implies that if appropriate lipid management was applied for 5 consecutive years, in UK AMI survivors <70 yrs, the cumulative number coronary events prevented would be of the order of 2500 in males and 1000 in females.

UNCHANGING IN-HOSPITAL FATALITY FROM ACUTE MYOCARDIAL INFARCTION 1982-1992

N Brown, T Young, D Gray, JR Hampton, AM Skene
Division of Cardiovascular Medicine, University Hospital, Nottingham.

We have examined trends in all admissions with acute myocardial infarction (AMI) to two District General Hospitals serving a population of 600,000 in the two time periods 1982-1984 and 1989-1992, that is a period before and after the widespread introduction of aspirin, B blockers and thrombolysis in management. An increase in patients hospitalised with AMI occurred from 719 cases in 1982 to 960 in 1992. There was a 20% rise in admissions of patients aged over 75 yrs with AMI. The mean age rose from 62.1 to 66.6 years (p<0.001) and the mean duration of stay fell from 8.74 to 7.24 days (p<0.001). The number of patients managed on a coronary care unit rose from 569 (79.4%) in 1982 to 692 (72.2%) in 1992. Significant improvements were seen in the proportion of patients arriving within 6, 12 and 24 hours of onset of symptoms over the 10 years (p<0.05 for the trend), but 3 in 20 still arrived outside the 12 hour time frame for thrombolysis in 1992. Use of proven drug treatment increased, B blockers from 14% of patients in 1982 to 37% in 1992, aspirin was used in over 70% of patients from 1989 and thrombolytic use rose 1.3 fold from 36% to 48% of patients between 1989 and 1992. Age and sex standardised case fatality remained unchanged over the study period.

Population Screening with Natriuretic Peptides to Detect a Wall Motion Score Index of ≤1.2

T McDonald, CE Morrison, H Tunstall-Pedoe, JJ McMurray and HJ Dargie.
Cardiology Department, Western Infirmary, *Scotish MONICA Project Glasgow.

A Wall Motion Index (WMI) ≤1.2 usefully defines significant left ventricular systolic dysfunction (LVD). However, using echocardiography to detect LVD in the general population would not be cost effective. We have tested the usefulness of the natriuretic peptides, N-terminal atrial natriuretic peptide (N-ANP) and brain natriuretic peptide (BNP) for detecting subjects with a WMI≤1.2 in the general population. We studied 4000, 1098 men and women, randomly sampled from North Glasgow. All had a WMI derived by the ASE 20 segment method and plasma available for N-ANP and BNP determination. Standard 12 lead ECGs were coded as abnormal if they contained a Q wave, left bundle branch block or an ST/T wave abnormality. The prevalence of a WMI ≤1.2 was 5% (50), of whom 76% were asymptomatic (i.e. free of cardiac dyspnoea and/or not on a loop diuretic). N-ANP and BNP concentrations in subjects are shown below:

<table>
<thead>
<tr>
<th>Category</th>
<th>WMIS1.2</th>
<th>Asymptomatic WMI≤1.2</th>
<th>Symptomatic P WMI≤1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-ANP (pg/ml)</td>
<td>1.5</td>
<td>3.2</td>
<td>4.5</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>7.1</td>
<td>14.1</td>
<td>24.4</td>
</tr>
</tbody>
</table>

Receiver Operator Characteristic analysis to detect a WMI≤1.2 resulted in a BNP concentration of 8.8pg/ml giving a sensitivity of 80% and a specificity of 57% for detecting a WMI≤1.2; an N-ANP conc. of 1.23ng/ml gave a sensitivity of 74% and specificity of 52%. Restricting the analysis to detect a WMI≤1.2 in subjects with an abnormal ECG resulted in an improvement of the accuracy: BNP: 81% sensitive, 70% specific and N-ANP; 82% sensitive, 73% specific.

Natriuretic peptides are useful screening tools for the detection of a WMI≤1.2 in the population. Targeting screening to individuals with an abnormal ECG improves their accuracy.
A COMPARISON OF METHODS FOR TARGETING CHD RISK FOR PRIMARY PREVENTION

IU Haq, PR Jackson, WW Yen, LE Ramsay
University Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF

The Sheffield table is a simple method for targeting a specified level of CHD risk, and indicates the total cholesterol (TC) level conferring that risk in an individual. We have examined the inclusion of the TC:HDL ratio rather than TC alone improves prediction. The sensitivity and specificity of the TC and the TC:HDL tables, targeted at a CHD event rate of 3% per year, were compared to the full Framingham equation in 216 men and women aged 35-70 years with TC 25.5 mmol/l who were studied prospectively. The 'treat' and 'no treat' decisions from the table for men and women yielded groups with a mean CHD risk by the Framingham equation of 4.1% per year and 1.8% per year respectively for the TC table, and 3.6% per year and 1.5% per year respectively for the TC:HDL table. The TC table had sensitivity of 45% and specificity 98%, and the TC:HDL table had sensitivity of 100% and specificity 94%. The TC:HDL table thus improved sensitivity with no significant loss in specificity. In men only (n=126), both tables were then compared to Joint European Task Force Guidelines and to the targeting of patients with TC ≥ 6 mmol/l using the PROCAM normal standard. The sensitivity and specificity of the various methods is shown in the table.

<table>
<thead>
<tr>
<th>Method</th>
<th>CHD risk targeted</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>CHD risk treated</th>
<th>CHD risk predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheffield TC</td>
<td>3</td>
<td>53</td>
<td>96</td>
<td>4.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Sheffield TC:HDL</td>
<td>3</td>
<td>97</td>
<td>82</td>
<td>3.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Joint Euro Task Force</td>
<td>3</td>
<td>100</td>
<td>26</td>
<td>2.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Joint Euro Task Force</td>
<td>4</td>
<td>68</td>
<td>37</td>
<td>2.6</td>
<td>0.6</td>
</tr>
<tr>
<td>TC 56%Snared</td>
<td>3</td>
<td>51</td>
<td>51</td>
<td>2.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

The TC:HDL table is highly sensitive and specific when compared to the complete Framingham equation and to the independently derived PROCAM equation, and identifies accurately individuals at high and low CHD risk. It is as sensitive but significantly more specific than Joint European Task Force recommendations. Targeting patients by cholesterol threshold alone is unacceptably inaccurate. It remains to be shown whether use of the TC:HDL ratio is accepted readily by ordinary doctors.

The atrial septum in fetal Hypoplastic Left Heart Syndrome

Andrew C. Cook, Gurdeep K. Sharland
Department of Fetal Cardiology, Guy's Hospital, London, U.K.

Premature closure of the foramen ovale has long been implicated in the etiology of the Hypoplastic Left Heart Syndrome (HLHS). A restrictive atrial septum is also an indication for early intervention in HLHS after birth and has recently been cited as the cause of pulmonary vascular disease resulting in early death after stage I of the Norwood operation. In order to establish the state of the foramen ovale in the developing human fetus with HLHS, the atrial septum of 177 fetuses with this syndrome were examined. The size and patency of the foramen ovale together with the attachments and thickness of the flap valve were documented. The same parameters were measured in 21 fetuses with normal atrial septum. A progression of this condition to HLHS during fetal life has been documented. 246 fetuses with structurally normal hearts were used as age matched controls. In fetuses with atrial and aortic atresia (group 1:72 of 117) the morphology of the foramen ovale showed wide variation. Premature closure was rarely encountered (4/72). The size of the foramen ovale ranged from severe hypoplasia (2W72) to a normal (12/72) or dilated foramen ovale (17/72). Deviation of the flap valve towards the left atrium and hypoplasia of the limbus were also commonly observed. In contrast those hearts with severe aortic stenosis (group 3: n=27) had a normally sized foramen, no deviation of the flap valve attachments and a normally formed limbus. In this group premature closure of the flap valve was common (16/27). Fetuses with aortic atresia and a patent, hypoplastic mitral valve (group 2:45 of 117) showed a combination of the features found in groups 1 & 2. In all groups, the lungs of fetuses with a prematurely closed foramen showed evidence of pulmonary vascular disease. These findings indicate that a closed atrial septum and pulmonary vascular abnormalities should be expected in 14% of fetuses with HLHS. The atrial septum will be restrictive in a further 45% and may well become closed by term. Inter-atrial flow patterns should be documented when diagnosis of HLHS is made in the fetus. Premature closure of the foramen ovale is therefore more likely to be a result of HLHS whereas severe hypoplasia of the foramen cannot be excluded as a cause for reduced flow into the left heart leading to the syndrome in some fetuses.

LV Systolic Dysfunction After Open Repair of Simple Defects in Infants and Children: Quantification With a Conduccate Catheter After By-pass

Royal Brompton Hospital, London, U.K.

Difficulty in quantifying post-operative LV dysfunction has hampered its investigation and therapy. Optimal measurement of LV function during the perioperative period, with its dramatic changes in loading conditions, requires the use of load-independent indices of systolic and diastolic function e.g. end-systolic (Ees) and end-diastolic (Eed) elastance. In 13 patients (11ASD, 1 double-chambered RV, 1 supravalvar AS, age0:25-14.4 years, weight 3.1-46 kg) LV function was measured from real-time pressure-volume loops using conductance and microtip catheters placed in the long-axis via the LV apex. Basal dp/dtmax normalised to maximal developed pressure ([dp/dtmax]Fmax) and end-diastolic pressure ([pdi(min)]Fmax) time constant of isovolumic relaxation(r) and Ees and Eed during IVC snaring were measured before and 10 min post-bypass. Mean bypass time was 41±14 min, mean crossclamp time 27±11 min.

Results:

<table>
<thead>
<tr>
<th>Event</th>
<th>Pre-bypass</th>
<th>Post-bypass</th>
<th>%change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ees(mmHg/ml/kg)</td>
<td>0.34±0.17</td>
<td>0.21±0.15</td>
<td>-40.7(p&lt;0.001)</td>
</tr>
<tr>
<td>Eed(mmHg/ml/kg)</td>
<td>0.06±0.11</td>
<td>0.12±0.19</td>
<td>78.3±0.57</td>
</tr>
<tr>
<td>[dp/dtmax]Fmax(1/sec)</td>
<td>8.35±1.42</td>
<td>8.92±1.29</td>
<td>7.7(p&lt;0.17)</td>
</tr>
<tr>
<td>[pdi(min)]Fmax/100 (sec)</td>
<td>11.75±3.19</td>
<td>10.92±2.3</td>
<td>-7.1(p&lt;0.24)</td>
</tr>
<tr>
<td>t(1/sec)</td>
<td>4.5±1.66</td>
<td>4.4±1.34</td>
<td>12.3-3.0(p&lt;0.76)</td>
</tr>
</tbody>
</table>

Conclusion: This is the first study to demonstrate the utility of a conductance catheter technique, in children, for the assessment of perioperative LV pressure-volume relationships. Incomplete myocardial protection was demonstrated by a deterioration in systolic function after even short bypass and crossclamp times.

REVERSIBLE ISCHAEMIA CONTRIBUTING TO RIGHT VENTRICULAR DYSFUNCTION UP TO TWENTY YEARS AFTER THE MUSTARD OPERATION FOR TRANSPOSITION OF THE GREAT ARTERIES

TA Mills, TJ Bernard, RD Hoole, RB Homa-Giles, RF Uren, TB Cartmill, RE Hawker, JS C Caldermar, Royal Alexandra Hospital for Children and Royal Prince Alfred Hospital, Sydney NSW, Australia.

The median term survival of intra-atrial baffle repair (Mustard procedure) for transposition of the great arteries (TGA) is good, seeing many patients into adult life, but prognosis is limited by progressive right ventricular (RV) dysfunction. We suggest that ongoing myocardial ischaemia is an important factor that may potentially be reversible. Using 99mTc-nicodim myocardial single photon emission computed tomography (SPECT) in 35 patients (median 30 months age) who had undergone Mustard operation for simple TGA at median 20 (range 1-4) months of age. The patients were aged 10-21 (median 13.8) years; 11 in NYHA class I, and 2 in class II. All were in a regular cardiac rhythm during the studies which were performed in each patient after dipyridamole stress and at rest (sinus in 11, nodal in 1, atrial flutter with 3:1 block in 1). The RV tomographic images were examined in 3 parallel and 2 orthogonal planes, analysed in 12 segments. Stress perfusion defects were present in 12/13 patients, in 35/53 (22%) of cardiac segments analysed; median 3 (range 1-7) segments per patient. The stress defects were fully reversible at rest in 5 of the 12 patients, and partly reversible in three others. RV wall motion and/or thickness was normal at rest in only 2 pts. Rest wall motion abnormalities generally occurred in the same segments as the observed fixed perfusion defects, and was similarly abnormal in all those with fully reversible defects. Wall motion was normal in the patient with no perfusion deficit. The number of stress defects correlated with increasing age (R=0.56). Median RV ejection fraction was 46% (range 15-68%)

We have demonstrated reversible and fixed perfusion defects with concordant regional wall motion in the right (sincteric) ventricle ten to twenty years after Mustard repair for TGA. Potentially reversible ischaemia resulting in infarction may therefore be important in the pathogenesis of late RV dysfunction in this group.
SPONTANEOUS RESOLUTION AND COLOUR DOPPLER CHARACTERISTICS OF RESIDUAL AND RECURRENT SHUNTS AFTER IMPLANTATION OF COOK DIRECT OCCLUDER CLOTS: O Unal, M Blackburn, G Veldman, J G Gibbs. Department of Paediatric Cardiology, Killingbeck Hospital, Leeds.

80 duct occlusion procedures were performed in 76 patients. Single coils were used in 58 cases, two coils in 18 and three coils in 4. Results were assessed by echocardiography 10 minutes after the procedure, again the following morning and at 1, 3, 6 and 12 month intervals where possible. In 27 cases (34%) there were small residual shunts on immediate echo; 15 (56%) of these had resolved by 24 hours, 70% by 1 month and 74% by 3 months with no further spontaneous resolution in the remaining 8 cases. However in the 53 cases where the duct appeared completely occluded on immediate echo, 11 recurrent shunts were detected at 24 hours and in 2 cases a recurrent shunt appeared at 1 month. Of these recurrent shunts, 2 were due to coil embolisation but in 11 there was no evidence of device movement. Of these 11 recurrent shunts, 6 resolved on later follow up but persisted. Overall, residual or recurrent shunts were found in 23 (29%) cases at 24 hours, falling to 13 (16%) at 3 months. 4 patients have had repeat procedures producing complete occlusion and at last follow up 67 (85%) patients have complete occlusion. Analysis of the characteristics of residual or recurrent shunt jets showed single jets in all patients who had a single coil but in 4 patients who had more than 1 coil there were 2 separate jets in 1 and 3 jets in the other. The latter required 3 further coils to achieve occlusion. Small shunts may reappear up to one month after apparent complete duct occlusion using detachable coils. When any residual shunt is present at 3 months follow up it is unlikely to resolve spontaneously. When multiple coils have been implanted initially, residual shunting may take some months to appear in which, even if the shunt is very small, may require multiple further coils to achieve total occlusion.


Primary balloon valvoplasty was attempted in 23 consecutive neonates presenting to our institution with severe aortic stenosis, using a retrograde approach via the axillary (20) or femoral arteries (2) or antegrade via the right ventricle and aortic valve defect (1). Median age 4 days (range 1-30), median weight 3.6 kg (range 1.1-4.5). In all but 1 case, which subsequently underwent surgical valvotomy, the valve was successfully dilated. Balloon/aortic annulus ratio was 1.01 ± 0.12. Valvoplasty significantly reduced the peak systolic pressure gradient from 60±31 to 20±15mmHg (mean reduction 67±23%), whilst increasing aortic regurgitation by a mean of 2.2±1.2 grades. Overall mortality was 39% (5 early and 4 late deaths after 30 days), but was higher in the subgroup of 15 neonates undergoing valvoplasty in the first week of life than later (55% vs 12%) and highest in those with ductal dependent systemic circulations (73%). Mortality was not related to the degree of residual aortic obstruction. Arterial complications occurred in 3 patients (femoral avulsion, femoral thoraxis, axillary thoraxis). 7 children have required 1 or more reinterventions; Ross procedure (3 and 43 months), homograft valve replacement (6 months), open valvotomy (1 and 3 months) and repeat balloon valvoplasty (1, 1, and 8 months). Of 10 children requiring treatment in the first week of life and surviving 1 month, 40% required reintervention as compared to 25% after the first week. Of 14 patients alive at a median follow up of 48 months (range 8-69), 9 are on no treatment whilst 5 require diuretics ± hydralazine. The median Doppler estimated gradient at follow up was 30mmHg (range 10-80). In conclusion, whilst neonatal aortic balloon valvoplasty is successful in terms of gradient reduction, the mortality in those requiring treatment in the first week of life appears to exceed the mortality rate for alternative therapies such as the Norwood procedure, with reintervention being common in the 47% surviving. The high mortality in this group is contrasted with a much better prognosis in those treated after the first week of life, who have a survival rate of 88% and a reintervention rate of 25% at a median follow up of 57 months (range 8-69).

GROWTH RETARDED FETUSES SHOW DIFFERENT BIOPHYSICAL PROPERTIES OF THE AORTA: SUPPORTIVE EVIDENCE FOR FETAL PROGRAMMING? H M Gardiner, K Jepson, J M Quinlivan, Dept Obstetrics, Malmo, University of Lund, Sweden * Centre for Fetal Care, RPLMS, London UK

Hypertension in adults who were small for gestational age (SGA) has been attributed to early programming but supportive evidence from fetal cardiovascular studies is lacking. Aims: To examine the hypothesis that abnormal arterial flow patterns in SGA fetuses influence early vascular development which may result in later hypertension.

Methods: Arterial pulse wave velocity (PWV) and waveform characteristics were examined longitudinally in the descending aorta of 20 normally growing (N) and 12 SGA fetuses using an ultrasonic phase-locked echo-tracking system. Group N were examined at 4-weekly intervals from 20 weeks' gestation. The SGA fetuses were defined as showing weight deviation of 28% from the mean at 32 weeks' gestation compared with their initial biometric scan. A comparison of the descending thoracic aortic pulse wave characteristics at the last scan before delivery in each patient is considered here.

Results: The relative pulse amplitude (change in diameter /diastolic diameter) was significantly reduced in the SGA fetuses (14.6% vs 21.7%, p<0.0001). The augmentation index, a measure of the pulse wave amplitude (the "elastic recoil") was slower (3.38±0.74 vs 4.32±0.83 mmHg, p=0.0058). There were no differences in PWV and PWVd. These differences in intrauterine waveform characteristics support the hypothesis that growth retardation is associated with abnormal programming of the origin of which may be either increased arterial wall stiffness, or may reflect the increased afterload of the fetoplacental circulation. Longer surveillance of these infants may determine whether these observations are true indicators of persistent cardiovascular abnormality in the growth retarded individuals.

TOWARDS TRANSPLANTATION TOLERANCE: DONOR-ANTIGEN SPECIFIC HYPORESPONSIVENESS FOLLOWING CARDIAC TRANSPLANTATION IN HUMANS, P Hornick, K Taylor, JR Bachelor, M Rose, M Yacoub, R Lechler, Royal Postgraduate Medical School, and Harefield Hospital, UK

Background: Strategies to induce allograft tolerance can be employed in small laboratory mammals. Objective: To assess at a cellular and molecular level whether tolerance occurs to the cardiac allograft in man by quantifying the direct anti-donor alloresponse. Methods: 10 patients (A-J) with progressive chronic rejection (transplant associated coronary artery disease) were investigated using 7T MRI following routine orthotopic cardiac transplantation. Limiting dilution analysis is the most sensitive and quantitative technique for measuring the frequency of alloreactive T cells. Frequencies of recipient T helper and cytotoxic cells with direct anti-donor alloreactivity were determined following transplantation. Limiting numbers of recipient T cells were cultured with fixed numbers of irradiated donor derived splenic antigen presenting cells (APC's). Plates were irradiated prior to the addition of an IL-2 sensitive indicator cell line (CTLL) or 51Cr labelled targets. Frequencies were calculated from the proportion of wells negative for IL-2 (HTL) or 51Cr release (CTL) at each recipient cell dilution utilizing a standard mathematical model. Frequencies were compared to those generated between the recipient T cells and third party spleen cells. Results: Following transplantation the T helper direct anti-donor alloresponse is substantially reduced, by a log order of magnitude, in 5 of the 10 patients studied to 3rd party controls. Tolerance demonstrated by HTL was paralleled by CTL frequencies in 4 of these 5 patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>HTL</th>
<th>CTL</th>
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<tbody>
<tr>
<td>P (106)</td>
<td>1/10218</td>
<td>1/10445</td>
</tr>
<tr>
<td>P (101)</td>
<td>1/1007</td>
<td>1/1007</td>
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<td>P (103)</td>
<td>1/1007</td>
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<tr>
<td>P (102)</td>
<td>1/1007</td>
<td>1/1007</td>
</tr>
<tr>
<td>P (104)</td>
<td>1/1007</td>
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</table>

Conclusions: These data are the first demonstration in man as in the rodent model, prolonged residence of an allograft can be accompanied by tolerance in T cells with direct alloreactivity which is to both donor HLA class I and II molecular determinants. These data have implications for graft outcome, adjustment of immunosuppression, and patient monitoring.
P 38

‘EARLY’ TRANSPLANT ASSOCIATED CORONARY ARTERY DISEASE: ITS RELATIONSHIP TO ACUTE REJECTION, HLA MISMATCH, AND DONOR RECIPIENT PHENOTYPE
P. Hornick, J. Smith, A. Pomerance, N. Banner, A. Mitchell, M. Rose, M. Yacoub
Department of Cardiothoracic Surgery, Harefield Hospital, Middlesex

Transplant associated coronary artery disease (TxCAD) is the manifestation of chronic rejection in the cardiac allograft. Both immunological and non-immunological factors are thought to contribute to its development. TxCAD which develops early may have a different pathogenesis to TxCAD which develops later, i.e., that immunological factors are predominantly important. Between 1980-1994, 534 consecutive heart transplant patients with yearly angiograms, serological HLA typing, and biopsy data were reviewed. Patients were divided into 3 groups: early (1-2yrs), late (3-14yrs), none (clear angio-0yrs). There was a significant association between the number of histologically proven acute rejection episodes within 3 months and at 1 year and the development of early TxCAD. Early Vs late p<0.05, Early Vs None p<0.05. Furthermore, for 16 patients who died prior to their first year angiogram but who were diagnosed as having TxCAD on post-mortem examination (Very Early group), there was a significant association with acute rejection episodes: Very Early Vs Early p<0.05, Very Early Vs Late p<0.05, Very Early Vs None p<0.001. There was no statistical difference between the number of acute rejection episodes in the late and disease-free groups within 3 months or 1 year of transplantation and the development of TxCAD. The number of acute rejection episodes within 3 months and 1 year is also significantly related to freedom of development of TxCAD: p<0.005 at 3 months and p=0.0018 at 1 year. We were also able to show the early development of TxCAD portrayed a significantly worse prognosis compared to the other groups p<0.0001, but that once TxCAD has been detected the rate of death is equivalent between early and late groups. There was no significant association between the mean number of HLA mismatch score for class I or class II antigens nor could any particular class I/II phenotype for recipient or donor be identified which exerted a protective or deleterious effect upon the development of early TxCAD. These data indicate differences in pathogenesis between early and late TxCAD and defines the relative importance of acute rejection in the multifactorial antilogous of late and early TxCAD.

PHYSIOLOGICAL CARDIAC RESERVE IN MAN: RELATIONSHIP WITH EXERCISE CAPACITY AND IMPLICATION FOR TRANSPLANT SELECTION

Physiological cardiac reserve can be defined as the extent to which the cardiac pump can augment its rate of hydraulic energy (power) output from baseline resting states to that required to maintain maximal exercise. We hypothesized that this reserve is a major determinant of exercise capacity. Seven subjects with a wide range of cardiac function (from heart failure patients to athletes) underwent treadmill stress limited cardiopulmonary exercise tests to measure their aerobic exercise capacity (represented by VO2max) and cardiac reserve. Cardiac output was measured non-invasively using the CO2 rebreathing technique. Using standard formula, cardiac power output (CPOmax) at peak exercise was calculated and significantly related to aerobic capacity, CPOmax(watts) = 0.0015*VO2max(mls/min) + 0.35, r=0.87, p<0.001. It also correlated well with exercise duration (r=0.62, p<0.001), suggesting that cardiac reserve, as an indicator of overall cardiac function, is a major determinant of exercise capacity. In the study, cardiac reserve ranged from 0.27 to 5.62 W, indicating a 20-fold difference between the most impaired function and that of the fittest subject. The recommended cardiac transplant criterion of VO2max ≤ 14 mls/min·kg-1 corresponds to CPOmax ≤ (1.3 - 2.7) W, implying that this criterion would include patients with a wide range of cardiac dysfunction, some of whom, with relatively preserved cardiac function, may not require immediate cardiac transplantation. Direct evaluation of cardiac reserve may therefore contribute to a more precise identification of patients with true end-stage cardiac pump failure.

A TWELVE YEAR EXPERIENCE OF HEART-LUNG TRANSPLANTATION IN CHILDREN: A COMPARISON OF RESULTS BEFORE AND AFTER 1990
R Radley-Smith, A Khaghani, M Yacoub
Harefield Hospital, Middlesex, UK.

Since 1984, 91 children under the age of 16 years have undergone heart-lung transplantation at our unit. Prior to 1990, 61 children (Group A) aged between 10 weeks and 15.7 (mean 9.3) years underwent heart-lung transplantation for pulmonary vascular disease (PVD) in 50 and parenchymal lung disease in 11. Since 1990, 30 children (Group B) aged between 2.9 and 15.6 (mean 11.1) years were transplanted for PVD in 19 and PLD in 11. There were 24 (39%) in-hospital deaths in Group A predominantly due to bleeding or multiorgan failure, and 6 (20%) in Group B which were multifactorial. Both groups were maintained on Cyclosporin and Azathioprine alone. Routine steroids were only given for persistent rejection or deteriorating lung function. Rejection was diagnosed on clinical grounds, changes in lung function and transbronchial biopsy. Obliterative bronchiolitis (OB) defined as severe, unremitting deterioration in lung function leading to consideration for re-transplantation or death and confirmed by histology, was more common in younger children (p<0.05). With a follow-up of 9-150 months in Group A, 21 (34%) children developed OB 9-79 (mean 28) months after transplant, 12 were retransplanted and all have subsequently died. In Group B, with a follow-up of 5-78 months, 6 children (20%) have thus far developed OB 15-44 (mean 32) months after transplant, 2 were retransplanted and 5 patients have died. OB accounts for 2630 late deaths. Actuarial survival at one and five years was 59% and 26% in Group A and 77% and 60% in Group B. It is concluded that results have improved since 1990, possibly due to improved techniques and to operating on older children, but the incidence of OB in this age group remains a concern.

A COMPARISON OF TACROLIMUS AND CYCLOSPORIN AS IMMUNOSUPPRESSION AFTER HEART TRANSPLANTATION
N Banner, M Yacoub, A Khaghani, M Burke, J Davis, M Rinaldi, M Vignos, M Hammel, R Hetzer, R Devrient, J Gaedjekakshak, B Meiser, B Reichert. Harefield Hospital, Harefield UB9 6JH and the European Multicenter Tacrolimus Heart Study Group.

A 5 centre pilot study was conducted to compare oral tacrolimus (TRL) with oral cyclosporin (CSN) as immunosuppression after heart transplantation. 82 primary heart transplant recipients (aged > 18 years) were randomized to receive TRL or CSN (2:1 ratio) in conjunction with steroids and azathioprine. Induction therapy with ATG was administered as per local standard practice and 43 patients received ATG. Demographic and baseline characteristics for the two treatment groups were comparable. Median daily doses of TRL were 0.08mg/kg at month 1 (whole blood trough concentration 13.0mg/ml) and 0.09mg/kg at month 12 (13.9mg/ml) whereas CSN doses were 4mg/kg (205mg/ml) and 4.0mg/kg (167mg/ml) respectively. Acute Rejection was diagnosed clinically or by biopsy. Results are 12-month Kaplan-Meier estimates:

<table>
<thead>
<tr>
<th></th>
<th>Treated Rejection</th>
<th>Treated Rejection</th>
<th>Patient Survival</th>
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<tbody>
<tr>
<td></td>
<td>(all patients)</td>
<td>(with ATG induction)</td>
<td></td>
</tr>
<tr>
<td>TRL</td>
<td>54</td>
<td>74%</td>
<td>53%</td>
</tr>
<tr>
<td>CSN</td>
<td>28</td>
<td>82%</td>
<td>73%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.44</td>
<td>0.13</td>
<td>0.13</td>
</tr>
</tbody>
</table>
| Abnormal kidney function (TRL: 61% vs CSN 39%) and hyperglycaemia (54% vs 39%) tended to be more frequent in the TRL group. Hypertension was more common (74% vs 86%). Hypercholesterolaemia (9% vs 25%) and gum hyperplasia (0% vs 11%) were less evident in patients receiving TRL. The lowest incidence of rejection occurred in those who received both TRL and ATG induction. This study did not have the statistical power to assess survival after transplantation and there were no significant differences in rejection rates or patient survival. This data will be used to plan a phase 3 trial comparing tacrolimus and cyclosporin in heart transplantation.
INITIAL EXPERIENCE WITH MINIMALLY INVASIVE AORTIC VALVE REPLACEMENT VIA TRANSVERSE STERNOTOMY

Bridgewater BJM, Ray SG, Hooper TL
Departments of Cardiothoracic Surgery and Cardiology, Wythenshawe Hospital, Manchester

We have performed minimally invasive aortic valve replacement on 8 patients with symptomatic aortic stenosis. Seven were women, the median age was 78 years (range 60 to 89 years) and they were high risk cases as shown by a median Parsonnet score of 20 (range 9 to 26). All patients had a gradient of greater than 80 mmHg across the aortic valve confirmed by cardiac catheterisation or echocardiography. At surgery an 8 cm incision was made at the 2nd interspace and the sternum was divided transversely along with both internal mammary arteries. Cardiopulmonary bypass was established by cannulating the aorta with venous drainage from the right atrium and IVC. Satisfactory access was obtained in all cases. The aorta was cross clamped and cardiopulmonary arrest achieved by inflating warm blood cardioplegia into the aortic root or coronary arteries. After opening the aorta the diseased valve was removed and replaced in the usual way. Intraoperative transoesophageal echocardiography was used in all patients to aid de-airing, assess left ventricular contraction and confirm satisfactory prosthetic valve function. Seven patients received tissue valves and one a mechanical valve. The median aortic cross-clamp time was 56 minutes (range 45 to 96 minutes) and bypass time was 80 minutes (range 60 to 125 minutes). There was one death from major gastro-intestinal haemorrhage, on the 19th post-operative day, and one patient was re-explored for bleeding in the early post-operative period. The remainder of the patients did well with little post-operative pain. Overall the median post-operative ventilation time was 12 hours (range 3 to 24 hours), median ITU stay was 1 day (range 1 to 5 days) and median post-operative in-hospital stay was 9 days (range 6 to 19 days).

Our early experience would cautiously lead us to recommend the use of minimally invasive aortic valve replacement, particularly in frail elderly patients.

SERUM S100B AFTER COMPLEX AORTIC SURGERY: THE EFFECTS OF HYPOThERMIC CIRCULATORY ARREST

K Bhattacharya, DP Taggart, JDS Kay*, S Westaby, R Pillai
Oxford Heart Centre and *Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford

Background: Neuropsychological morbidity has persistently clouded the success of complex aortic surgery. Hypothermic total circulatory arrest (TCA) may expose patients to a greater cerebral insult than that of cardiopulmonary bypass (CPB) alone. This study characterises serum S100B, present in high concentrations in astroglial cells, levels in patients undergoing aortic surgery with or without TCA, using S100B as a marker for cerebral injury.

Methods: 26 patients underwent aortic surgery with or without TCA. Serial blood samples were taken and the resultant serum stored for batch analysis. S100B was measured, in duplicate, using a radioimmunoassay.

Results: There were significant elevations in serum S100B concentrations in all patients compared to preoperative levels, reaching peak levels at skin closure. S100B rises were greater in the TCA group at all time points and persisted for longer. Significant correlations between TCA time and S100B concentrations were present at 5 hours (r = 0.59, p = 0.035) and 24 hours (r = 0.66, p = 0.015) postoperatively.

Conclusions: (i) S100B elevations were significantly higher in patients who had TCA. (ii) TCA time correlates with S100B levels 5 hours and 24 hours after surgery. (iii) This study raises the suspicion that greater cerebral injury occurs in patients undergoing TCA than without.

CONTROLLED WARM BLOOD CARDIOPLEGIA REPERFUSION PREVENTS SUBSTRATE DERANGEMENT IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

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Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, Bristol

Reperfusion, following myocardial ischaemic arrest with cold blood cardioplegic solution, is associated with substrate derangement (e.g. ATP, taurine, glutamine, glutamate and aspartate) in patients undergoing coronary artery bypass surgery. Administration of warm blood cardioplegia reperfusion at the end of the ischaemic period has been reported to improve myocardial recovery. A total of 37 consecutive patients (mean age 60.7 ± 6.7 years) with a left ventricular ejection fraction greater than 50%, undergoing primary elective coronary revascularization were recruited in this prospective, randomized trial comparing cold blood St Thomas’ I cardioplegic solution (n=19) and cold blood St Thomas’ 1 cardioplegic solution with terminal warm blood cardioplegia (n=18). In order to assess the effect of warm reperfusion on myocardial substrates, the intracellular concentrations of amino acids and ATP were measured in apical left ventricular biopsies collected prior to the ischaemic period and after 20 minutes of reperfusion.

The data show that controlled warm reperfusion with blood cardioplegic solution at the end of ischaemic arrest prevents substrate derangement seen early after reperfusion. Preservation of these important metabolites is likely to improve cellular recovery following coronary surgery.

S-100 PROTEIN RELEASE IN A RANGE OF CARDIOTHORACIC SURGICAL PROCEDURES

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Department of a Cardiothoracic Surgery, St George’s Hospital, Blackshaw Road, London, SW17 0QT

Introduction: Measurement of cerebral injury in cardiac surgery by neuropsychological tests is time consuming and prone to many sources of inconsistency. The neuropsychiatric S-100 protein is released into the circulation following neuronal injury in proportion to the magnitude of damage. Is it sufficiently sensitive to detect differences in patients undergoing cardiac surgery?

Methods: Four groups of patients with increasing cerebral hazard were selected: I = lung resection; II = coronary surgery; III = aortic root replacement and IV = aortic surgery with deep hypothermic circulatory arrest. Serum S-100 levels were measured before the procedure and 1/2hr, 1hr, 2hrs, 4hrs and 24hrs post-operatively.

Results: All patients survived the procedure.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>CPB time</th>
<th>S-100 peak mg/L</th>
<th>AUC mg/Lh</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4</td>
<td>66</td>
<td>0.02</td>
<td>0.2</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>58</td>
<td>0.20</td>
<td>0.30</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>56</td>
<td>1.09</td>
<td>5.92</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>64</td>
<td>2.5</td>
<td>26.06</td>
</tr>
</tbody>
</table>

AUC S-100: Circulatory arrest (n=60, P<0.04)

Conclusions: Post operative S-100 levels were within normal limits for thoracotomy patients and were progressively elevated with CABG, AR and circulatory groups. The AUC S-100 correlated significantly with the duration of circulatory arrest. S-100 levels may be a useful tool in the investigation of neuroprotective strategies.


**PERSISTENT RIGHT VENTRICULAR DYSFUNCTION FOLLOWING CORONARY BYPASS GRAFTING.**

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Royal Brompton Hospital, London

The right ventricle is susceptible to injury during ischaemic arrest for CABG but has not been widely studied due to the lack of an index of RV function that is quantitative, non-invasive and widely available. Ischaemic injury has been shown to affect movement of the ventricle in its long axis and can be assessed quantitatively using echocardiography. Method: Echocardiographic measurements of the longitudinal movement of the right (RV) and left (LV) ventricular free walls were made using an off-line digitizing system and computer analysis software, in 45 pts age (59.2±7) yrs with 3 vessel disease and ejection fraction >50% who had complete revascularisation, pre, 5 days and 6 weeks post CABG. 21 normal controls were also studied.

Results: Pre vs Control. RV systolic excursion (SE), LV shortening rate (SR), lengthening rate (LR) and SE were reduced compared to control. Tricuspid and mitral E/A ratio were both reduced. Pre vs Postop. At 5 days, all RV parameters SE, LR, SR became depressed (2.2±0.5 vs 0.8±0.2 cm, 10±2.6 vs 4.7±1.3 cm, 9.3±2.8 vs 3.7±1.5 cm, p<0.001) while at the LV free wall, SR and LR increased (61±4 vs 7±2.2 cm/s, 6±2.0 vs 7±1.9 cm/s, p<0.05) and SE remained unchanged. Tricuspid E/A ratio remained depressed (1.9±0.4 vs 3.1±0.6, p<0.05) but mitral E/A ratio increased. At 6 weeks all RV parameters remained depressed while for the LV, they were maintained.

Conclusion: Abnormalities of RV long axis become more extensive, those present preoperatively deteriorate, and remain at 6 weeks after CABG, whereas LV long axis function had not only recovered by 5 days but had improved compared to before operation. Therefore despite effective myocardial protection of the LV, the RV remains susceptible to injury during CABG, particularly when the long axis, which reflects subendocardial fibre function is assessed.

**ACCURACY OF ULTRAFAST MAGNETIC RESONANCE IMAGING FOR ASSESSMENT OF RIGHT AND LEFT VENTRICULAR VOLUMES AND MASS.**

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Magnetic Resonance Unit, Royal Brompton Hospital, London

In this study we investigated the accuracy and feasibility of 3 ultrafast imaging breath-hold cine sequences in the assessment of the right (RV) and left ventricular (LV) volumes and LV mass in comparison with conventional cine gradients echo imaging and electron beam tomography (EBT).

We investigated 15 healthy volunteers (8 male, 7 female) with mean age 33 yrs (range 21-59 yrs). Imaging was performed on a 0.5T using echo planar imaging (EPI), fast spiral imaging (SPI), fast gradient echo imaging (FLASH), all with k-space segmentation, and conventional gradient echo imaging (GRE). For all imaging methods, cine images were obtained in contiguous ventricular short axis slices to cover the entire RV and LV. Acquisition of EPI, SPI and FLASH cine took 16 cardiac cycles per slice and was performed during breath-holds. Scan time of the conventional gradient echo imaging sequence (single average) was 128 cardiac cycles per slice. Comparison of LV stroke volume of GRE versus FLASH, EPI and SPI showed good agreement of methods and revealed a mean difference (Sd) of 1.72±13.8, 0.74±13.2 and 0.30±13.8 [ml]. RV stroke volume comparison showed a mean difference (Sd) of 0.12±13.9, 3.3±13.1 and 3.0±13.9 respectively. There was also good agreement of LV enddiastolic (LVEDV) and endystolic volume (LYESV). RVEDV showed slightly higher variation of values than LVEDV, which represents the fact that clear identification of RV anterior wall is often more difficult than LV wall delineation. The level of agreement in assessing ejection fraction (EF) was high in all three ultrafast imaging sequences for both LV and RV. LV mass was in general underestimated by all three ultrafast breath-hold sequences and showed in comparison with GRE mean differences (Sd) of 11.5±23.7, 14.5±21.8 and 15.5±25.6 [g] for FLASH, EPI and SPI. The degree of agreement with GRE was also shown no significant differences between the three ultrafast methods. The average total scan time of each ultrafast imaging scheme was less than 8 mins, whilst the total average acquisition time per EPI was 23 mins, with the particularity SPI images were highly susceptible to incorrect shimming. FLASH images appeared much better and usually revealed better contrast between blood and myocardium. Ultrafast imaging techniques like echo-planar, fast spiral and fast gradient echo imaging with k-space segmentation showed good accuracy and good agreement with conventional gradient echo imaging in assessing ventricular volumes and mass. We demonstrated the feasibility of these techniques: 0.5 T and found an equally high degree of accuracy for all three methods.

**A SUPERIOR TECHNIQUE TO ASSESS RIGHT VENTRICULAR (RV) VOLUMES IN HUMANS UNDERGOING CARDIAC SURGERY.**

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Conductance catheters (CC) have been widely used to assess left ventricular volumes but their use in the RV has not been fully explored. Experimental studies have suggested that the accuracy of volume estimation can be improved if the CC lies along the RV long axis i.e. apex to pulmonary valve. We compared volume signals in humans obtained from a CC interrogating both axes within the RV cavity. Ten patients having routine coronary artery surgery were studied. Following sternotomy, a 7F conductance catheter and 2 SP microcatheter were inserted into the RV, firstly through the RV outflow tract (OT) and then through the right atrium (RA) with the catheter tip positioned in the ventricular apex. Duplicate measurements of A (the gain constant) measured against thermodilution, parallel conductance (VC) estimated using the hypertonic saline technique, and corrected RV volumes were obtained from both catheter positions in each patient. Absolute values and their repeatability were compared. The mean ±S.D Vc from the OT was 73.8 (±31.5)ml compared with 99.1 (±25.8)ml from the RA; p = 0.025. The mean % difference between duplicate measurements of Vc was 14.1 (±15.9) from the OT vs 42.5 (±40.0) from the RA; p = 0.023. The mean % A from the OT was 0.52 (±0.2) vs 0.39 (±0.17) from the RA; p = 0.01. The mean % difference between duplicate measurements of A was not significantly different, OT = 5.9 (±4.1) and RA = 5.45 (±6.0); p = 0.439. The corrected end-diastolic volumes were similar: OT = 112.5 (±44.1)ml and RA = 118.2 (±50.1)ml; p = 0.34. Values for stroke work, stroke volume and ejection fraction did not differ significantly between the two routes. Insertion of the catheter through the OT was technically much easier. CCs can be used to provide a beat-to-beat assessment of RV volume in humans. The higher values of A and smaller Vc volumes obtained from the OT indicate that more of the RV cavity is interrogated by this route. These findings combined with the superior repeatability of these measurements suggest that conductance RVCCs provide a more accurate assessment of true RV volume in patients undergoing cardiac surgery.

**CORRELATION OF MYOCARDIAL HISTOLOGICAL FINDINGS IN HIBERNATING MYOCARDIUM WITH DOBITAMINE STRESS ECHOCAROGRAMY AND NITRATE INFUSION/TECHNETIUM-99m SCINTIGRAPHY.**

Departments of Cardiology, Pathology, Cardiac Surgery & Diagnostic Imaging, Mater Misericordiae Hospital, D7.

Available data suggests that dobutamine stress echocardiography (DSE) is useful for the detection of “hibernating” myocardium. The diagnostic value of Technetium-99m tetrofosmin scintigraphy (99mTc) remains controversial. There are no published data which correlate the histological findings of hibernating myocardium (e.g. interstitial fibrosis) with DSE or 99mTc studies. In this study patients with anterior regional wall abnormalities and significant LAD disease undergoing CABG had pre operative DSE and nitrate enhanced 99mTc performed. During CABG, 1 transmural biopsy (Tunet) was taken from the anterior wall of the left ventricle between the distal LAD and the last diagonal branch, and 1 from the watershed area. Follow up echocardiography was performed 3 months post operatively. A total of 8 patients were studied yielding 56 segments for analysis. Use of 99mTc was found to be useful in detecting hibernating myocardium segments with a sensitivity of 100%. We did not find a strong inverse correlation between percent fibrosis and percent nucleated cells (r = 0.78). DSE is far superior to 99mTc for detecting hibernating myocardial segments, and an isotopic response correlates with histological findings.
ENHANCED DETECTION OF REVERSIBLE ISCHAEMIA WITH INOTROPIC AS COMPARED TO VASODILATOR STRESS MYOCARDIAL PERFUSION IMAGING.

P Seman, R Khattar, U Raval B Senior, A Lahiri. Department of Cardiology, Northwick Park Hospital, Harrow, UK.

There is a conspicuous lack of data comparing inotropic and vasodilator stress myocardial perfusion imaging for the detection of reversible ischaemia which is an important prognostic determinant in patients with coronary artery disease. It is also unclear to what extent reversible perfusion defects represent myocardial ischaemia. Accordingly, 21 patients with angiographically documented coronary artery disease underwent adenosine (inotropic) and dipyridamole (vasodilator) Tc-99m sestamibi SPECT on separate days. The stress tests were performed within 3 months after angiography, and patients were clinically stable during this period. Simultaneous echocardiography was performed to assess reductions in systolic wall thickening as an indicator of reversible ischaemia with both stress tests. For both Tc-99m sestamibi and echocardiography the left ventricle was divided into 12 identical segments which were then graded according to perfusion and wall thickening respectively (1 = normal to 4 = absent). The extent and severity of reversible defects was calculated by subtracting the sum of individual segment scores at rest from that at peak stress (Δ PS). The Δ PS was significantly higher for adenosine compared to dipyridamole (mean Δ PS = 8.8 ± 5.5 versus 3.2 ± 4.4 for adenosine and dipyridamole, respectively, p < 0.001). Similarly, a significantly larger proportion of reversible perfusion defects with adenosine stress was accompanied by reversible wall thickening abnormality compared to dipyridamole (88% versus 24% respectively, p < 0.001). Therefore inotropic stress in conjunction with myocardial perfusion imaging is superior to vasodilator stress for the detection of reversible ischaemia in patients with coronary artery disease. This finding may be associated with a prognostic advantage for adenosine compared to dipyridamole stress imaging.

POSITRON EMISSION TOMOGRAPHY AND DOBUTAMINE ECHOCARDIOGRAPHY FOR ASSESSING VIABILITY IN PATIENTS WITH MODERATE VENTRICULAR DYSFUNCTION

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Both low-dose dobutamine echocardiography (DE) and 18F-flurodeoxy-glucose (FDG) positron emission tomography (PET) are used for the assessment of myocardial viability in patients (pts) with hibernating myocardium. Since the accuracy of these two methods could vary according to the severity of left ventricular (LV) dysfunction, in the present study we aimed to compare their predictive value (PV) only in pts with moderate impairment of LV function. DE (5 and 10 μg/kg/min) and FDG PET during euglycaemic hyperinsulinaemic clamp (EHC) was performed in 18 pts (age: 60±11, ejection fraction 42±10%) before coronary angioplasty (PTCA). Repeat resting echocardiography was performed 4 months after PTCA. DE viability in dysfunctional (D) segments (S) was defined as improvement in regional WMSI by ≥1 grade during DE. S were defined as PET viability, if the mean metabolic rate of glucose (MRG, μmol/mg) was >20±25. Out of 114 D-S, 70 (60%) were PET-viable and 54 (46%) DE-viable (concordance of 77%). A total of 53 D-S were revascularised. After PTCA 25 (47%) S improved, of which, 24 (96%) were PET viable and 24 (96%) DE viable and 26 S did not improve of which 21 (81%) were PET non-viable and 13 (50%) were DE non-viable. PET and DE had similar sensitivity, 96% vs 96%, negative PV: 95% vs 95% and positive PV: 83% vs 65% (p=NS). However, specificity of PET was greater than DE, 81% vs 50% (p=0.02).

In conclusion: In pts with moderate LV dysfunction both quantitative FDG PET during EHC and DE have high accuracy in identifying myocardial viability although the specificity of PET is greater than DE.

VALUE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN DETECTION OF ISCHAEMIA AT A DISTANCE FROM THE INFARCT RELATED ARTERY FOLLOWING ACUTE MYOCARDIAL INFARCTION

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The purpose of this study was to evaluate the usefulness of DE in the detection of disease remote from the infarcted vessel territory early post acute myocardial infarction. DE was performed on 125 patients post acute myocardial infarction. Overall, DE was positive for ischaemia in 109 of 121 patients with significant CAD (sensitivity = 90%). Disease in 1 vessel remote to the infarct site was correctly identified by dobutamine stress induced wall motion abnormalities in 37% (14 of 38) of the remaining 24 patients, 20 were identified by DE as having ischaemic heart disease but misclassified as having infarct vessel only or multivessel disease. Multivessel disease was correctly identified by DE in 15 of 33 patients, while 36 were falsely classified as having double or infarct vessel only disease. Sensitivity, specificity, positive and negative predictive accuracy of DE for detecting remote disease (in 1 or 2 vessels) were 62%, 91%, 95% and 47% respectively. Thus DE, whilst sensitive in the detection of ischaemia post acute myocardial infarction (90%), is not sensitive in the detection of vessel disease in addition to disease of the infarct related artery (62%).

QUANTIFICATION OF MYOCARDIAL PERFUSION WITH CONTRAST ECHOCARDIOGRAPHY DURING VENOUS INJECTION OF CONTRAST

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Quantification of changes in myocardial blood flow (MBF) and myocardial blood volume (MBV) with myocardial contrast echocardiography (MCE) depends critically upon identifying the linear portion of the relationship between microbubble concentration and measured videointensity. MBV and MBF are closely coupled during infusion of inotropes and with normal coronary arteries any increase in epicardial flow results in an increase in MBF. Increasing amounts of a contrast agent MRX-115 (12.5-250μl) was injected intravenously (IV) at baseline and during IV infusion of increasing amounts of adrenaline in 6 dogs with a flow probe around the left anterior descending (LAD) coronary artery. Intermittent harmonic MCE was performed gated to end-systole and peak videointensity measured over the LAD bed. Microbubble dose was plotted against peak background subtracted videointensity at baseline and during hyperaemia. From the linear ranges of these plots a dose of 0.1 ml of contrast was selected for injection and kept constant for the remainder of the experiment. An excellent correlation was found between the peak myocardial background-subtracted video intensities in the LAD bed and the LAD flow rate (r=0.9, n=23 P<0.001) following identical injections of contrast. It is concluded that quantification of myocardial blood flow with MCE depends on a linear relation between microbubble concentration and videointensity. Due to differences in post processing, each echocardiographic system will need calibration to identify this linear range.
CINE MAGNETIC RESONANCE FOURIER VELOCIMETRY OF BLOOD FLOW THROUGH CARDIAC VALVES: COMPARISON WITH DOPPLER ECHOCARDIOGRAPHY
RH Mohiddin, PD Gatehouse, H Renier, DN Firmin, DJ Pennell.
Royal Brompton Hospital, London, UK.
Non-invasive measurement of blood flow velocity through the cardiac valves has important clinical applications. A wide variety of magnetic resonance (MR) methods are available for flow measurement. The aim of this study was to investigate the ability of cine MR Fourier velocimetry to measure flow through healthy cardiac valves and to compare MR and Doppler peak velocity measurements. Ten healthy volunteers (age mean ± SD, 24 ± 4 years) without history of valvular disease were studied. Four of the subjects were females. In each subject, aortic, pulmonary, mitral and tricuspid valves were evaluated with MR and Doppler. The heart rate during magnetic resonance and Doppler studies was not significantly different. The mean difference between the two studies was 2 beats/minute, with a 95% confidence interval of (-22 beats/minute, +25 beats/minute). Peak systolic flow velocity in the aortic and pulmonary valves, and peak diastolic flow velocity in the mitral and tricuspid valves measured with MRI and Doppler echocardiography correlated well. The mean difference between the two measurements (MR - Doppler) was 63 mm/sec, with a 95% confidence interval of (-180 mm/sec, +310 mm/sec). The agreement between the two observers interpreting the same magnetic resonance velocity maps was close. The mean difference between the two measurements was 23 mm/sec, with a 95% confidence interval of (-20 mm/sec, +60 mm/sec). There was no significant difference between MR and Doppler, or between the two MR observers. Magnetic resonance Fourier velocimetry has the necessary ease, reliability and speed to measure blood flow through the cardiac valves. Measurement of peak blood velocity through the cardiac valves by this method showed satisfactory agreement with Doppler but its clinical application for assessing diseased cardiac valves needs to be established.

<table>
<thead>
<tr>
<th>Infarct</th>
<th>Infarct 2</th>
<th>5 post</th>
<th>10 post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IBS</td>
<td>19.2 ± 1.85 (NS)</td>
<td>19.8 ± 1.85 (NS)</td>
<td>20.7 ± 1.86 (NS)</td>
</tr>
<tr>
<td>Cyclic IBS</td>
<td>6.5 ± 0.95 (p &lt; 0.01)</td>
<td>5.1 ± 0.95 (NS)</td>
<td>5.9 ± 0.95 (NS)</td>
</tr>
</tbody>
</table>

Conclusion: Reversible changes in the cyclic variation in integrated backscatter occur during balloon angioplasty and reflect acute ischaemia and changes in microvascular flow. Therefore, this methodology may be useful in acute myocardial infarction to determine whether or not thrombolysis has been successful.

A NOVEL METHOD TO FACILITATE THREE-DIMENSIONAL ECHOCARDIOGRAPHIC JET VOLUME CALCULATIONS
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*Physiological Flow Studies Group, Imperial College London*

The advent of three-dimensional echocardiography (3DE) has provided several new techniques for the assessment of cardiac flow events; these may permit more accurate quantification of regurgitant flow. The relationship of 3D-derived colour Doppler jet volume to regurgitant flow rate is currently one area under study. To perform jet volume calculations using the commercially available 3DE system (TomTec Imaging Systems), a segmentation process must be performed which involves manual tracing of the jet border in multiple orthogonal slices down its length. This process can be time-consuming. This study was designed to assess whether segmentation could be facilitated using the 3D system’s existing thresholding software to trace the jet border. We studied a series of 17 simple jets generated by steady flows through circular orifices in a purpose-built flow model. Three orifice diameters were used (2.6, 6.0 and 10.0 mm) at continuous flow rates of 0.2-2.5 l/min. The resulting jets were imaged in an orthogonal axis to the orifice plane with colour Doppler settings remaining unchanged throughout. Multiple 2D images were obtained by 180° rotational acquisition and transferred to a TomTec Echoscan Workstation for generation of a 3D dataset. For each orifice diameter, the volume of each jet was calculated using the standard segmentation procedure (V1) and the new thresholding technique (V2). Correlation with actual flow rate was excellent for both methods, with r values >0.95 for all orifice diameters. The mean difference between V1 and V2 was small (2.3 l/min, SD 1.5 l/min). Calculation times were significantly shorter for the threshold method (2.6 ± 5 mins, p<0.001). In conclusion this study demonstrates that the threshold method facilitates quicker jet volume calculations without loss of accuracy. This improvement in off-line computation time may enhance the clinical application of 3D flow quantification.

BENIGN CLINICAL COURSE OF PARAPROSTHETIC REGURGITATION DETECTED AT EARLY POSTOPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHY
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Department of Cardiology, University Hospital of Wales, Cardiff.

Transesophageal echocardiography (TOE) with colour flow mapping is a very sensitive method of detecting paraprosthetic regurgitation, but the natural history of such jets is unknown. To assess the prevalence, echocardiographic features and clinical outcome of paravalvar jets, we performed TOE prospectively in 161 patients (88 male, 93 female, mean age 60 ± 10 yrs) within 2 hours after aortic valve replacement (n103), mitral valve replacement (n48), or both mitral and aortic valve replacement (DVR, n10). All patients were studied in the ITU, using a biplane or multplane probe. Results: 24 patients had paravalvar regurgitant jets (PVJ); 5% after AVR (n3; mean jet length 2.3 (sd1.6) cm and mean width at origin 0.4 (0.4) cm); 37% after DVR alone (n18; jet 1.7 (1.1) by 0.2 (0.4) cm); and 33% had mitral PVJ after DVR (n3; 3.3 (3.0) by 0.2 (0.1) cm). 18 of the 21 jets involving the mitral valve arose from the medial aspect of the valve ring, and all but one were free jets. 2 of 3 jets arising laterally were adherent to the lateral wall of the left atrium. Paravalvar jets arising from AVRs did not demonstrate any specific pattern of origin. None of the patients had a cardiac murmur, and none developed haemodynamically significant regurgitation during follow-up of between 6 and 12 months. Thirty patients had repeat TOE six months after surgery. None had new PVJ. In 5 patients with mitral PVJ initially, this had disappeared in 2, increased in 2, and remained unchanged in one. Conclusion: Small paravalvar regurgitant jets are common after mitral valve replacement but they are associated with a favourable clinical outcome in the first year after surgery.
PHASE II STUDIES WITH FS069 ULSATRSOND CONTRAST AGENT FOR ECHOCARDIOGRAPHIC PERFUSION IMAGING
J Hancock, H Dittrich, D E Jewitt, M J Monaghan
Department of Cardiology, King's College Hospital, London

FS069 is a transpulmonary ultrasound contrast agent consisting of Albumin shell microspheres (1-6um diameter) filled with perfluoropropane gas. It has excellent ultrasound backscatter properties and long in-vivo persistence. It therefore has the potential to facilitate ultrasound evaluation of organ perfusion following intravenous injection. Recent small studies have demonstrated that increased echocardiographic sensitivity and signal to tissue backscatter ratio may be obtained by analysis of the backscattered 2nd harmonic of the contrast agent resonant frequency. Therefore, a Phase II study consisting of 490 intravenous doses (0.1ml - 4.0ml) of FS069 administered to 5 normal subjects and 20 patients with left ventricular dysfunction (EF<40%) and/or pulmonary hypertension (>40mmHg) was performed. Fundamental and 2nd harmonic continuous and intermittent real time images of myocardium, kidney and liver were recorded on SVHS video and Optical Disc. Video densitometry and qualitative scoring (0 = no enhancement, 1 = faint, 2 = moderate, 3 = good, 4 = attenuation) was performed using a tissue region of interest before, during and after contrast injection.

<table>
<thead>
<tr>
<th>Mean 2nd harmonic densitometry (grey level units)</th>
<th>Baseline</th>
<th>Continuous</th>
<th>Intermittent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart 49</td>
<td>60 (p&lt;0.03)</td>
<td>82 (p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Kidney 48</td>
<td>55 (NS)</td>
<td>72 (p&lt;0.0002)</td>
<td></td>
</tr>
<tr>
<td>Liver 55</td>
<td>69 (p&lt;0.05)</td>
<td>71 (p&lt;0.001)</td>
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</tbody>
</table>

Qualitative evaluation by two observers demonstrated a mean enhancement score of 1.07, 1.32, 2.23 for fundamental, continuous harmonic and intermittent harmonic imaging modes respectively.

Conclusion: Intravenous injections of FS069 ultrasound contrast agent can be used successfully to demonstrate organ perfusion, particularly in combination with advanced echocardiographic techniques such as intermittent 2nd Harmonic imaging. This has important clinical implications.

ROTATIONAL CORONARY ANGIOGRAPHY: EARLY RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
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Rotational coronary angiography allows multiple views of a coronary artery during a single rotational sweep. It may therefore reduce radiation exposure and procedure time. The study evaluated conventional and rotational angiography in 32 patients investigated for coronary artery disease. Rotational angiography was performed using a Phillips Integris HM3000 system and a ceiling suspended C arm. 3 sweeps were performed for the left coronary artery (LCA): (1) Lateral to RAO, (2) LAO caudal (Cd) to RAO Cd, (3) LAO cranial (Cr) to RAO Cr. 1 sweep was performed for the right coronary artery (RCA), Lateral to RAO. In the conventional group images were acquired in RAO, RAO Cd, RAO Cr, Lateral, LAO Cr and LAO Cd for the LCA. RAO and LAO views were used for the RCA. Angiography was performed by a sole operator using 4 Fr catheters and a femoral approach. Image quality was assessed from selected stills by a radiologist blinded to the imaging modality.

<table>
<thead>
<tr>
<th>Rotational</th>
<th>Conventional</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast use: mL</td>
<td>106 (10)</td>
<td>111 (14)</td>
</tr>
<tr>
<td>Engagement time: secs</td>
<td>253 (55)</td>
<td>210 (49)</td>
</tr>
<tr>
<td>Procedure time: secs</td>
<td>861 (127)</td>
<td>841 (231)</td>
</tr>
<tr>
<td>Screening time: secs</td>
<td>120 (29)</td>
<td>148 (109)</td>
</tr>
<tr>
<td>Fluoroscopy dose: μSv</td>
<td>2.6 (1.2)</td>
<td>3.1 (3.5)</td>
</tr>
<tr>
<td>Scattered dose: μSv/μr2</td>
<td>88 (62)</td>
<td>79 (33)</td>
</tr>
<tr>
<td>Exposure dose: μSv</td>
<td>9.8 (5.1)</td>
<td>19.0 (7.3)</td>
</tr>
<tr>
<td>Total dose: μSv</td>
<td>12.4 (6.1)</td>
<td>22.1 (10.2)</td>
</tr>
<tr>
<td>Image quality score</td>
<td>17.1 (1.8)</td>
<td>16.1 (1.9)</td>
</tr>
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</table>

N=16 each group. Figures = Mean (SD), P calculated by t test.

Rotational angiography reduces the patient total radiation dose and produces images of comparable quality to conventional angiography without prolonging the investigation time. The advantages in terms of radiation safety mean this technique should be considered for all cardiac catheter laboratories with appropriate equipment.
IN-PATIENT OUTCOME AND CLINICAL RESTENOSIS IN BENESTENT AND NON-BENESTENT LESIONS.

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King's College Hospital, London

The Benestent (BS) trial demonstrated a reduction in clinical and angiographic restenosis with the use of coronary stents compared with balloon angioplasty. However, "BS-type" lesions (native vessel with stable angina, single lesion, <15 mm, vessel >3 mm diameter, non-ostial, non-bifurcational, non-stenotic lesion with no thrombus) represent a highly selected group of the general angioplasty population. We have assessed the stenting rate in "BS-type" lesions and compared the in-patient outcome and target vessel revascularisation (TLRs) rates in BS and non-BS lesions treated with coronary stents. Between 1 Jan 1995 and 31 Oct 1996 angioplasty was performed on 1500 vessels in 1173 patients. In the total group, 693/1500 (46%) vessels had a stent implanted, but only 178/1500 (12%) met the BS criteria. Of these 178 BS lesions only 68 (38%) received an intracoronary stent (BS-stenting in 68/693 [9.8%] of total stented population), the remaining achieving a good intimal angiographic result by balloon angioplasty alone. Primary success, major adverse cardiac events (MACE = in-patient death, Q-wave myocardial infarction and CABG) and target lesion revascularisation (TLR) rates at 6 months are shown below:

<table>
<thead>
<tr>
<th></th>
<th>Benestent (n=68)</th>
<th>Non-Benestent (n=587)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary success</td>
<td>65 (96%)</td>
<td>52 (90%)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>MACE</td>
<td>3 (4%)</td>
<td>58 (10%)</td>
</tr>
<tr>
<td>CAGB</td>
<td>1 (1.5%)</td>
<td>21 (3.6%)</td>
</tr>
<tr>
<td>TLR</td>
<td>1 (1.5%)</td>
<td>50 (8.5%)</td>
</tr>
</tbody>
</table>

In conclusion, only a small proportion of a general angioplasty population undergo stenting for a BS-type lesion but these patients have an excellent outcome. Patients stented for non-BS lesions have a higher in-patient complication rate, but the 6 month TLR rate remains encouragingly low.

THE EFFICACY OF STENTING IN LAD AND NON-LAD CORONARY CIRCULATION: INSIGHTS FROM TRIAL OF ANGIOPLASTY AND STENTS IN CANADA (TASC I)


TASC I was a multicentre trans-Canada study that randomized 270 patients to receive either conventional balloon angioplasty (PTCA) or a Palmaz-Schatz coronary stent in the setting of elective angioplasty. This provides us with the opportunity to compare the effect of stent versus PTCA on clinical outcome (procedure to end of study) in the left anterior descending coronary artery (LAD) versus non-LAD subgroups to determine any difference which may be important in clinical decision making. The mean follow up was 6.6 ± 2.6 months.

<table>
<thead>
<tr>
<th>Stent</th>
<th>No Stent</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>61</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>(4.9)</td>
</tr>
<tr>
<td>CAGB</td>
<td>(2.3)</td>
</tr>
<tr>
<td>Rpt PTCA</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Any Event</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>Any Event incl. bailout</td>
<td>6 (9.8)</td>
</tr>
</tbody>
</table>

*p=0.029; **p=0.09; ***p=0.009; 1P = 0.06. CABG, coronary artery bypass surgery; MI, myocardial infarction.

A strategy of stenting as compared to PTCA in the LAD subgroup was associated with a lower event rate. Stenting in the non-LAD territories conferred no clinical benefit over PTCA. This has implications on the current use and "over-use" of stents.

The majority of acute myocardial infarction (AMI) in the UK present to the District General Hospital (DGH). If, as a result of publications demonstrating the superiority of primary angioplasty (PTCA) over thrombolyis, PTCA is selected as the reperfusion strategy of choice, it would necessitate the provision of PTCA in the DGH. This feasibility study is designed to see if PTCA can be performed safely and effectively in a DGH and to make some preliminary assessment of the resource implications. In 64 days to date 33 consecutive patients (pts), 36 male, aged 34-77 (mean 62) with suspected AMI have undergone immediate angiography (door to lab time 15-245 mins mean 44) and if the infarct related artery (IRA) was identified, proceeded to PTCA (door to balloon time 48-296 mins mean 90). Aspirin 300mg and heparin 150iu/kg were given on admission achieving mean activated clotting time at start of PTCA of 264secs. 11(21%) pts did not proceed to PTCA, 3 (5.7%) not AMI, 2 (3.8%) had normal arteries; 47.5% had TIMI 3 flow in IRA and 2(3.8%) unsuitable anatomy. Of 42 attempted PTCA (9.5%) were for repeat events. Left ventricular ejection fraction (EF) was <45% in 18(43%) and <30% in 5(12%). Intra-arterial balloon pump was used in 2 pts with cardiogenic shock (BP<90mmHg). There were 5(12%) failures and 38(88%) successes (TIMI 3 flow in IRA). There were 4 (9.5%) sub acute recurrences, 2 with stents, all were successfully recanalised. Of 53 pts there were: 23(8%) in hospital deaths (1 from stroke at day 4 and 1 from pericardial tamponade day 1); 2(8%) strokes (1 fatal, 1 minor); 47(5%) transfusions for blood loss; and 4 late transfers for urgent revascularisation for non IRA ischaemia. There were no emergency surgical requirements for coronary or femoral complications of PTCA. The experience to date suggests that PTCA in the DGH is feasible, effective and safe.

ANGIOPLASTY PILOT PPTCA

To determine whether PTCA on the coronary arteries of domestic pigs at a balloon/artery ratio of 1:1.1. Vessels were harvested at 3 days, in glycol methacrylate, serially sectioned (10 mm) and quantitative morphometry was performed at proximal, mid and distal stent. Cross-sectional areas (CSAs) of vessel lumen and wall and maximum thickness of neointima in 81 sections and related to strut number and maximum strut separation.

Results.

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strut number vs. lumen CSA</td>
<td>+0.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Strut number vs. neointima CSA</td>
<td>-0.16</td>
<td>ns</td>
</tr>
<tr>
<td>Maximum strut separation vs. neointima thickness</td>
<td>+0.32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maximum strut separation vs. neointima CSA</td>
<td>+0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum strut separation vs. lumen CSA</td>
<td>-0.17</td>
<td>ns</td>
</tr>
</tbody>
</table>

Conclusion. Closely spaced and even stent struts produce little neointima or late lumen loss. Asymmetry of deployment encourages neointimal growth where inter-stent distances are greatest. Closely spaced struts may act as a barrier to cell migration and proliferation, or widely separated struts lead to local wall stretch. In-stent restenosis may be reduced by developing designs with more metal coverage and uniform strut expansion.

IN-STENT RESTENOSIS: MORE METAL AND MORE SYMMETRY REQUIRED?

J Guna, N Mallik, L Shepherd, CM Holt, SE Francis, CMH Newman, DC Crossman, DC Cumberland. Sections of Cardiology and Interventional Cardiology, University of Sheffield

Introduction. Intravascular ultrasound has shown that in-stent restenosis is a consequence of excessive neointimal growth rather than recoil. The cause remains unclear, its occurrence limits stent use in smaller vessels and the optimal treatment has not been defined. Aim. To explore the relationship between in-stent restenosis and strut geometry. Method. 30 stainless steel balloon expandable stents were implanted at 8 atm in the coronary arteries of domestic pigs at a balloon/artery ratio of 1:1.1. Vessels were harvested at 28 days, in glycol methacrylate, serially sectioned (10 mm) and quantitative morphometry was performed at proximal, mid and distal stent. Cross-sectional areas (CSAs) of vessel lumen and wall and maximum thickness of neointima in 81 sections and related to strut number and maximum strut separation.
MULTILINK™ STENTING WITH ASPIRIN ALONE - NO Ticlopidine, Warfarin, IVUS, OR QCA.

AL Calver, KD Dawkins, GA Haywood, HH Gray, JM Morgan, IA Simpson. Wessex Cardiothoracic Unit, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD.

In order to determine the outcome of a minimalist approach to intra-coronary stenting, we have studied prospectively 121 patients who received 166 Multilink™ stents to 152 coronary artery lesions. Patients were pre-treated with aspirin 300mg, given heparin (10,000-15,000iu) during the procedure, and aspirin alone (150-300mg) post procedure. Moderate high pressure inflation was used in all patients for stent deployment and post implantation dilatation. Maximum pressure was 14 (SD±1.8) atmospheres. Neither IVUS nor QCA were used. Patients average age was 60 (range 37-82) yrs, 95 (78%) were male, and 27 (22%) had unstable angina. Vessels treated were: LAD 69, RCA 50, Cs 22, diagonal 2, intermediate 1, vein grafts 8. Lesion types were: A: 47, B1 67, B2 30, C 8. Indications for stenting were: elective 119 (78%), sub-optimal result 28 (18%), bail-out 4 (3%), restenosis 1 (1%). The post procedure length of hospital stay was 2 days (SD±2.3) days. In hospital complications were: Death 0, sub-acute occlusion 2 (1.6%), acute MI (post-Q) 2 (1.6%). Both cases of sub-acute occlusion occurred in patients with complex pathology and multiple stents. Both were successfully treated with emergency CABG. Follow up has been obtained in all 121 patients (mean follow-up 84 (SD±40) days). During this period there were no major cardiac events (death, CABG, acute MI), 5 patients (4%) were re-studied because of recurrent angina (re-study at 86 (SD±36) days of follow-up). Of these, 4 had restenosis within their stent (3 were treated with further PTCA and 1 was refered for elective CABG), and I was referred for elective CABG due to native disease progression (the stent was widely patent). Thus coronary intervention with Multilink™ stents is safe and effective using a simple and cost effective minimalist approach with aspirin alone. With this approach, in this group of patients, the rate of stent occlusion remained low (1.6%).

PHOSPHORYLCHOLINE STENT COATING AS A METHOD OF LOCAL DRUG DELIVERY: PRELIMINARY DATA FROM AN EX VIVO MODEL.

J Armstrong, CM Elist, P Stratford*, DC Cumberlaid.
Section of Cardio Sciences, University of Sheffield, Sheffield and *Biocompatible Ltd, Farsham.

Coronary stents can maintain vessel patency and reduce restenosis, but have thrombogenic potential. A polymer matrix incorporating phosphorylcholine mimics the cell membrane, and when coated onto stents enhances its haemocompatibility. Drug incorporation into phosphorylcholine could allow controlled local delivery of anti-proliferative or anti-platelet agents. We have used an ex vivo flow model to investigate the release of dipyrindamole (fluorescent) from phosphorylcholine coated stents implanted into human saphenous vein with a 3.5mm balloon at 8atm. The stented vein was washed for 10 seconds in culture medium and secured into a flow chamber. Culture medium was circulated at 70ml/min, at 95mmHg, 37°C and 5% CO₂. After 24 hours the vein was removed, cut longitudinally to remove the stent, map frozen and sectioned for examination by fluorescence microscopy. Sections were examined proximal, distal and at the stent site. Dipyrindamole was seen throughout the vessel wall in all sections, and maximum fluorescence was at the stent site. Samples from the culture medium were analysed by fluorescence. This showed that the circulating level of dipyrindamole at 24 hours was 2-3% of total dipyrindamole loaded onto the stent. The culture medium used to wash the stented vein immediately after implantation contained slightly higher levels of dipyrindamole (4% of total loaded onto stent). We are currently looking at circulating levels of dipyrindamole between 0 and 24 hours. Conclusion: The perfused organ culture model of saphenous vein may be used in studies to investigate drug release from coronary stents. Dipyrindamole is taken up into the vessel wall and released in small amounts into fluid surrounding the stent.

ISCHAEMIC PRECONDITIONING MAY ABOLISH THE PROTECTION AFFORDED BY ATP-SENSITIVE POTASSIUM CHANNEL OPENERS IN ISOLATED HUMAN ATRIUM

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The Hatter Institute, Department of Academic Cardiology, University College London Hospitals, London.*Cardiothoracic Surgery, The Middlesex Hospital, London.

The ATP-sensitive potassium channel (KATP) has been implicated in the mechanism of ischaemic preconditioning. This study compared the protective effects of pre-operative nicardipine, a KATP channel opener, to ischaemic preconditioning. We also investigated the combination of a preconditioning protocol and nicardipine exposure. Methods: human atrial trabeculae obtained from patients undergoing routine coronary revascularisation, were divided on the basis of pre-operative nicardipine status. Trabeculae were superfused with oxygenated Tyrode's solution in an organ bath and paced at 1Hz. 4 groups were studied (n = 6 per group). 1) Control - 90 min hypoxic substrate-free perfusion at 37°C (simulated ischaemia), followed by 120 mins of reoxygenation with substrate at 1Hz (reoxygenation). 2) Preconditioning (PC) - 3 mins simulated ischaemia and 7 mins reoxygenation, followed by 90 mins simulated ischaemia and 120 mins reoxygenation. 3) Nicardipine - preoperative exposure, 90 mins simulated ischaemia and 120 mins reoxygenation. 4) Nicardipine + Preconditioning - preoperative exposure, 3 mins simulated ischaemia and 7 mins reoxygenation, followed by the 90 mins simulated ischaemia and 120 mins reoxygenation. The endpoint was the average recovery of contractile function (%R) measured at the end of 120 mins reoxygenation. Results: mean ± standard error of mean.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (PC)</th>
<th>Nicardipine (Nic) + Prec</th>
<th>Nicardipine + Prec</th>
<th>Nicardipine (Nic) + Prec</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>27.2 ± 1.1</td>
<td>50.5 ± 3.6*</td>
<td>55.3 ± 5.3*</td>
<td>29.7 ± 3.1</td>
</tr>
</tbody>
</table>

Nicardipine exposure and preconditioning both resulted in a similar degree of protection, which was significantly different to controls (*p<0.05, ANOVA). This protection was abolished by the addition of a normally protective preconditioning protocol. Further work with other KATP channel openers has produced the same effect. These data show that oral nicardipine affords ischaemic protection of human atrium. This protection is lost when an ischaemic preconditioning protocol is added to nicardipine exposure.

Cardioprotective effect of nicardipine is not modified by ischaemia preconditioning in the rabbit

J Imagawa, GF Baxter, JM Yellon.
The Hatter Institute, Department of Academic & Clinical Cardiology, University College London Hospitals, London.

Nicardipine (NIC), a hybrid of potassium channel opener and nitrates, has cardioprotective effects in human and various animal models of ischaemia. We previously showed that ischaemia preconditioning (IP) abolishes the protection afforded by preoperative NIC in an isolated human aortal muscle preparation, using functional recovery, a surrogate endpoint. Infarct size is a more precise measure of ischaemic injury. In view of this paradoxical result, the present study was undertaken to assess i) the effects of NIC in a rabbit model of myocardial infarction, and ii) if IP influences any protective effect of NIC using the infarct size endpoint. Methods: Rabbits underwent a midline sternotomy under Hypnor/Injeneobidone anesthesia. Left coronary branch was occluded for 30 min followed by 120 min of reperfusion. Animals were randomised into four groups; 1) Saline infused i.v. before and during 30-min ischaemia; 2) NIC (10ng/kg bolus + 10ng/kg/min) was infused i.v. before and during 30-min ischaemia; 3) Preconditioned with a 5-min ischaemia followed by 10-min reperfusion before 30-min ischaemia under saline infusion; 4) Preconditioned under NIC infusion. Risk volume (R) and infarct volume (I) were determined by fluorescent microscopes and tetrodotoxin staining, respectively. Results: NIC conferred a 41% decrease in I/R. IP resulted in more pronounced protection than NIC. The combination of IP with NIC showed the intermediate protective efficacy between NIC alone and IP alone group. There were no differences in R or haemodynamic changes between groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>R (cm3)</th>
<th>I (cm3)</th>
<th>I/R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>8</td>
<td>1.05±0.07</td>
<td>0.42±0.05</td>
<td>42.1±15.7</td>
</tr>
<tr>
<td>NIC</td>
<td>8</td>
<td>0.99±0.07</td>
<td>0.25±0.06</td>
<td>24.9±6.9***</td>
</tr>
<tr>
<td>IP</td>
<td>8</td>
<td>1.15±0.06</td>
<td>0.15±0.05</td>
<td>13.4±4.3**</td>
</tr>
<tr>
<td>NIC + IP</td>
<td>8</td>
<td>1.18±0.07</td>
<td>0.21±0.05</td>
<td>18.0±4.2**</td>
</tr>
</tbody>
</table>

Mean ± SEM. *P<0.05, **P<0.01 vs. Saline (ANOVA).
A ROLE FOR BOTH ADENOSINE A1 AND A3 RECEPTORS IN ISCHAEMIC PRECONDITIONING OF HUMAN ATRIUM

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Adenosine A1 receptors have been shown to play a role in ischaemic preconditioning of human myocardium. The aim of this study was to investigate whether the adenosine A3 receptor may be involved as well. Human atrial trabeculae were suspended in an organ bath, superfused with oxygenated Tyrode's solution and paced at 1 Hz. They were randomized into 7 groups (n=6 per group) each of which was subjected to 90 min simulated ischaemia (hypoxic substrate-free superfusion and rapid pacing at 3Hz), followed by 120 min reoxygenation (unpaced Tyrode's solution and pacing at 1Hz) after the following treatments: 1) Control (C) - no treatment; 2) Preconditioning (PC) - 3 min simulated ischaemia and 7 min reoxygenation; 3) CPA (A1 agonist) - 5nM superfused for 5 min, followed by a 5 min washout; 4) DPCPX (A1 antagonist) - 200nM superfused for 15 min; 5) CPA + DPCPX - DPCPX superfused for 5 min, CPA + DPCPX superfused for 5 min, followed by DPCPX superfused for 5 min; 6) IBMECa (A3 agonist) - 30nM superfused for 5 min, followed by a 5 min washout; 7) IBMECa + DPCPX - DPCPX superfused for 5 min, IBMECa + DPCPX superfused for 5 min, followed by DPCPX superfused for 5 min. Compounds were evaluated at A1 or A3 selective concentrations based on their Ki values for cloned human receptors. The endpoint was percentage recovery of contractile function (R%) measured at the end of 120 min. reoxygenation. Results: mean ± standard error of mean (*p<0.05 vs controls, TOWAY ANOVA).

<table>
<thead>
<tr>
<th>Group</th>
<th>CPA</th>
<th>DPCPX</th>
<th>IBMECa</th>
<th>IBMECa + DPCPX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>27.7±1.0</td>
<td>55.3±2.5*</td>
<td>52.2±3.1*</td>
<td>31.8±0.9</td>
</tr>
</tbody>
</table>

Blockade of A1 receptors completely abolished the protection provided by CPA. Blockade of A1 receptor stimulation failed to completely abolish the adenosine A3 agonist IBMECa. Thus activation of A3 receptors may play a role in ischaemic protection of human atrium.

ABNORMAL MICROVASCULAR RESPONSES IN CARDIAC SYNDROME X CANNOT BE EXPLAINED SOLELY BY THE PRESENCE OF EPICARDIAL SUBANGIOGRAPHIC ATEROMA

I D Cox, J R Clague, J P Bagger, MA Burrows, C M Hann, D E Ward, J C Kaski
Department of Cardiological Sciences, St George's Hospital Medical School, London

Aim: To study the relationship between coronary microvascular inhomogeneity and epicardial subangiographic atheroma (SAA) in syndrome X.

Patients: We studied 9 patients (8 women; median age 55, range 43-72) with syndrome X (anginal pain, positive exercise ECG and normal coronary angiogram) who were undergoing repeat coronary angiography due to persistent disabling anginal pain despite anti-anginal therapy. None had documented coronary spasm, blood pressure >150/95 mmHg, left ventricular hypertrophy or cholesterol >6.5 mmol/l, and all were non-smokers.

Methods: Vasodilatory drugs were stopped 24 half-lives prior to catheterisation. Repeat angiography was completely normal in all cases. Coronary flow velocity responses during intracoronary infusion of acetylcholine (ACH - 0, 107 and 10-6M) and during an intracoronary bolus of 300g/k glyceryl trinitrate (GTN) were assessed using a Doppler ultrasound guide-wire deployed in the proximal LAD artery. Simultaneous quantitative angiography was performed to enable calculation of coronary flow volume reserve i.e. the ratio of baseline to peak flow volume for each dilator (CFR-ACH/GTN). Intimal thickening due to SAA was measured by intravascular ultrasound at 1mm intervals through the LAD.

Results: The mean CFR-ACH was 1.76 (range 1.3-4.5) and was classified as abnormal (<2) in 5 patients; CFR-GTN was >2 in all cases. Six patients had significant intimal thickening (>0.3 mm) and the maximal median intimal thickness was 1.0 mm (range 0.7-1.2 mm). Two of the five patients with CFR-ACH <2 had no significant SAA and there was no significant correlation between the severity of SAA and CFR-ACH (r=0.054, p=NS; Spearman's Rank Correlation Coefficient).

Conclusions: Abnormal endothelium-dependent microvascular responses in syndrome X patients cannot be explained simply by the presence of SAA.

INSULIN, HDL AND CORONARY HEART DISEASE: 11.3 YEAR EVALUATION OF THE FIRST FOLLOW-UP COHORT OF THE RISC STUDY (RISC-I)

IF Goldstein, R Bruce, C Walton, F Levy, M Worthington, JC Stevenson, WJ Division of Metabolic Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, London.

Hyperinsulinemia has been identified as a predictor of CHD in some but not all prospective studies. High density lipoprotein (HDL) concentration is inversely related to hyperinsulinemia, but the two have rarely been evaluated together as CHD predictors. The Risk Indicators in a Screened Cohort (RISC) Study has enabled further investigation of their relative importance. 770 male executives (age 26-70y) initially free from vascular disease were followed for an average of 11.3 years. Metabolic (including oral glucose tolerance test glucose and insulin, and serum cholesterol and triglycerides), haematological, anthropometric and lifestyle variables were measured. HDL cholesterol was measured in 522 participants. 23 potential predictors of the development of CHD were considered. Significant predictors were identified by stepwise entry into the Cox model. Relative risks were estimated according to quintile cut-offs for each significant predictor. Results: 44 new cases of CHD were detected (31 in the subgroup with HDL measured). In the entire group the order of Cox model entry (HDL excluded) was high serum cholesterol (relative risk 4.2, 95% confidence interval 2.1-7.5), elevated mean arterial pressure (3.5, 1.6-5.8), current heavy cigarette smoking (2.8, 1.4-7.4), age in the range 49-54 years (3.1, 1.5-5.2), family history of heart disease (1.8, 0.9-3.4), and high systolic/MDUHRHs blood pressure (life 1.9, 1.0-3.6). In the subgroup with HDL measurements, low HDL (2.7, 1.2-6.4) was an additional predictor and age was no longer significant. Neither fasting nor glucose tolerance test insulin emerged as significant. Conclusions: Hyperinsulinemia was not a risk factor in this group of mainly social class 1 and 2 males, either in the presence or absence of HDL measurements. Future studies will need to consider insulin resistance, or groups with prevalent hyperinsulinemia.

INCREASED QT DISPERSION DURING ISCHAEMIA IS UNAFFECTED BY β-ADRENOCEPTOR ANTAGONISTS

M D Lowe, SA Newell, E Bowland, AA Grace
Department of Cardiology, Papworth Hospital; Department of Cardiological Sciences, St George's Hospital Medical School

Recent studies suggest that myocardial ischaemia results in increased dispersion of ventricular repolarisation, but whether this is a direct cellular effect or receptor-mediated is unknown. β-blockers attenuate the effects of ischaemia and decrease arrhythmia risk but mechanisms are uncertain. The purpose of this investigation was to study the influence of ischaemia on a measure of repolarisation inhomogeneity, QT dispersion (QTd), and examine contributing factors. Three groups were studied: 34 patients with coronary artery disease who had no overt ischaemia during atrial pacing (CAD); 22 patients with CAD who developed ischaemia (CAD/isch); and 19 patients with normal coronary arteries (NCA). Mean age and male/female ratio was not significantly different between groups. Other potential influences e.g. LV function, previous myocardial infarction, extent of CAD, drug therapy etc. were also examined. Patients taking β-adrenoceptor antagonists were equally distributed between the three groups. QTd (mean ± SD) was determined from 12 lead ECGs (50mm/s paper speed) at rest and during atrial pacing at 400-700ms cycle length. Bazett's formula is not applicable during atrial pacing so QTd was not corrected for heart rate. CAD and CAD/isch had higher QTd at rest than NCA (69.3 ± 40.4 ms vs. 52.6 ± 19.0 ms, p<0.02; ANOVA). Increased paced heart rate reduced QTd in NCA and CAD; in patients who developed myocardial ischaemia QTd increased significantly (p<0.001) with:

<table>
<thead>
<tr>
<th>QTd (ms; mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
</tr>
<tr>
<td>NCA</td>
</tr>
<tr>
<td>CAD</td>
</tr>
<tr>
<td>CAD/isch</td>
</tr>
</tbody>
</table>

Increases in QTd were not influenced by treatment with β-blockers or other potential modulating influences suggesting that β-mediated effects are not responsible for the increase in dispersion during ischaemia. Patients with CAD therefore have increased resting QTd, with those developing ischaemia during atrial pacing demonstrating further increases in QTd not attenuated by β-adrenoceptor antagonists.
CORONARY ANGIOGRAPHY, CARDIAC FUNCTION AND EARLY INTERVENTION IN PATIENTS WITH SUSPECTED INFARCTS AND ST DEPRESSION
HS Lee, CL Bray, R Levy, S Ray, C Ward, DH Bennett, MI Brooks
Department of Cardiology, Wythenshawe Hospital, Manchester

Patients with suspected myocardial infarction (MI) who present with predominant ST segment depression in the electrocardiogram have a poor prognosis. Few data are available on the relationship between left ventricular function and outcome of early intervention in these patients. Fifty-one patients (age 47 to 84 years, mean (SD) 67 (9) with 22% ST depression admitted to the coronary care unit in a one month period were included. The mean ST depression was 3 (1) mm. MI was diagnosed in 27 (53%) patients with 21 (41%) having a history of previous infarcts. There were eight (16%) in-hospital death. Coronary angiography was performed in 42 (82%) patients (age 47 to 84 years, mean 67 (10) months, 33 male, 6 female) and had either triple (TVD) or double vessel disease (DVD). Five patients had left main stem stenosis (LMS). Patients with more severe ST depression are likely to have more severe disease (see Table). LV function (see Table) was assessed in 38 patients with mean ejection fraction (EF) of 54% (13%). Coronary angioplasty was performed in six and bypass surgery in 16 patients (median waiting time 10 days). There were less in-hospital death (2/22 patients (9%) and those with revascularisation than those without (6/29 (21%). Table: N = number of patients, ALL = all patients, ≤3 mm = patients with ST depression of ≤3 mm, ≤1 = hypokinesia.

<table>
<thead>
<tr>
<th>N</th>
<th>DVD</th>
<th>TVD</th>
<th>DVD</th>
<th>IMH</th>
<th>GLOBAL</th>
<th>NORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>42</td>
<td>14 (33%)</td>
<td>26 (62%)</td>
<td>5 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3mm</td>
<td>22</td>
<td>5 (23%)</td>
<td>17 (77%)</td>
<td>4 (18%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Patients with severe and predominant ST segment depression have a high incidence of extensive coronary artery disease, justifying the left main stem. A significant number of patients have a good LV function and are suitable for revascularisation with good outcome.

RISK STRATIFICATION FOLLOWING MYOCARDIAL INFARCTION IN SCOTLAND.
GS Hillis, IR Mahy, KP Jeannings. Department of Cardiology, Aberdeen Royal Infirmary, Aberdeen.

Controversy remains concerning the optimal algorithm for identifying patients requiring invasive investigation after myocardial infarction. This study surveyed current practice in Scotland, and assessed the degree to which resource limitations are perceived to influence this practice. With the support of the Scottish Cardiac Society, all consultant cardiologists and physicians with a specialist interest in cardiology in Scotland (n = 61) were asked to complete a postal questionnaire detailing their current approach to risk stratification in a series of brief clinical scenarios (varying according to patient age, electrocardiographic findings, use of thrombolysis and early complications) and to indicate whether additional resources would influence their practice. Responses were received from 46 (75%) of those surveyed. Exercise testing was the most commonly used non-invasive investigation and was little influenced by clinical factors other than age. Early submaximal exercise testing was favoured by a minority of respondents (35 out of 184 potential cases: 19%). When selected, maximal exercise testing would be undertaken within 2 weeks of infarction in 13% of cases, but after 4 weeks in 39%. Only 41% of cardiologists would routinely undertake further risk stratification (beyond ecocardiography) in an otherwise fit 77 year old lady, while 39% believe coronary angiography is indicated in a 45 year old patient with a non-Q wave infarct, independently of non-invasive investigation. Radionuclide perfusion imaging is rarely used in routine practice (6 out of 184 potential cases: 4%). Only 43% of respondents felt constrained by limited resources. The results indicate that there is considerable heterogeneity in the methods used to select patients for coronary angiography after myocardial infarction, but suggest that the preferences of physicians, rather than external factors, may be responsible for much of the variation.

GENETIC RISK FACTORS FOR CORONARY ARTERY DISEASE IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY
GK Davis*, B Mackness, DH Roberts*, PN Durrington, MI Mackness, AM Haegerty
Regional Cardiac Centre, Victoria Hospital, Blackpool* and University Department of Medicine, Manchester Royal Infirmary, Manchester

The angiotensin converting enzyme (ACE) gene DD genotype and the human paraoxonase/arylesterase (HUMPONa) BB gene have been reported to be associated with coronary artery disease (CAD). We determined the prevalence of both polymorphisms in patients with ischemic cardiomyopathy (ISC) compared to a normal population and sought associations with coronary atherosclerosis and left ventricular dysfunction.

Methods: 100 patients were genotyped for the ACE polymorphism including 50 for the Humpona gene polymorphism. All patients had either ECG evidence of myocardial infarction and/or CAD demonstrated by coronary angiography. Left ventricular (LV) function and dimensions were obtained by echocardiography. Patients were genotyped for both gene polymorphisms by the polymerase chain reaction (PCR) technique using genomic DNA obtained from white cells and specific flanking primers. The PCR products were resolved (after digestion with the restriction enzyme AlwI for Humpona genotyping) by agarose gel electrophoresis.

Results: The HUMPONa BB genotype was present in 11% of patients and controls (n=100, p=NS). The ACE DD genotype was more common in patients (40% vs 26%, p<0.01). The angiographic Humpona subgroups (39/50) showed more 3 vessel CAD in HUMPONa AA patients compared with AB/BB group (78% vs 42%, p<0.05, independent of total cholesterol, smoking and diabetes). The mean left ventricular end diastolic dimensions were larger with IL vs DD ACE genotypes were similar.

Conclusions: Both the ACE and Humpona genotypes are important markers in patients with ISC. The ACE DD genotype is more common in these patients but does not influence the degree of ventricular dilatation. The HUMPONa AA genotype is independent associated with more severe CAD in ISC patients.

THE EFFECT OF AN ACUTE CHEST PAIN NURSE (ACPn) ON DOOR TO NEEDLE TIMES AT AN INNER CITY TEACHING HOSPITAL
C Hughes, K Scott, Dr S Saltissi, Dr P Mullins
Royal Liverpool University Hospitals

British Heart Foundation guidelines state that patients with acute myocardial infarction (AMI) should receive thrombolysis within 30 minutes of admission. An audit at this hospital revealed that 'door to needle' (DTN) times were unacceptable and local purchasers specified that times should improve by 10%. An ACPn was appointed in November 1995 to improve current practice. The role of the ACPn involves triage and management of patients with acute chest pain, initiating training for medical and nursing personnel in Accident & Emergency (A&E) and implementing an Integrated Care Pathway which includes thrombolysis protocol. To assess the impact of the ACPn we audited the DTN times of patients attending the A&E Department between June and November 1996, of which the ACPn saw 25%. 83% of patients are now thrombolysed within 90 minutes and 46% within 30 minutes. All times are mean values.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Time Pre ACPn</th>
<th>Time Post ACPn</th>
<th>Time if seen by ACPn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysed</td>
<td>65 of 90</td>
<td>88 of 149</td>
<td>NA</td>
</tr>
<tr>
<td>Pain to Needle (minutes)</td>
<td>393 (90-1872)</td>
<td>295 (35-2610)</td>
<td>NA</td>
</tr>
<tr>
<td>DTN (minutes)</td>
<td>101 (30-208)</td>
<td>65 (5-350)</td>
<td>38 (9-216)</td>
</tr>
<tr>
<td>Improvement (minutes)</td>
<td>NA</td>
<td>36 (36%)</td>
<td>63 (42%)</td>
</tr>
</tbody>
</table>

Conclusion: The employment of an ACPn has significantly improved DTN times but if the 30 minute target is to be achieved in more patients a 24 hour ACPn service should be provided.
THE EFFECT OF REPETITIVE EPISODES OF EXERCISE-INDUCED MYOCARDIAL ISCHAEMIA ON LEFT VENTRICULAR (LV) FUNCTION IN PATIENTS WITH CHRONIC STABLE ANGINA: CUMULATIVE STUNNING OR ISCHAEMIC PRECONDITIONING?
C A Rinaldi, AZ Linhart, ND Masani, RJ Hall
University Hospital of Wales, Cardiff, U.K.

The pathophysiology of chronic LV dysfunction in patients with coronary artery disease (CAD) may involve the phenomenon of myocardial stunning (MS). We have previously shown that MS follows a single episode of exercise-induced ischemia, we examined the effects on LV function of 2 episodes of ischemia at 3 different time intervals. In 42 patients with an angiographically proven CAD, stable angina and normal LV function we performed an exercise test (Ex1) followed by a repeated test (Ex2) at either: 30 minutes (Grp 1, n=14), 60 minutes (Grp 2, n=14) or 4 hours (Grp 3, n=14). Quantitative echocardiographic assessment of systolic and diastolic LV function (ECHO) was performed at baseline and at each test after each test. Results: In all groups heart rate BP and ST changes normalised within 10 minutes of exercise in all cases. In Grp 1 despite similar indices of ischemia there was less systolic and diastolic dysfunction following Ex2. In Group 2 these indices were more severe and prolonged following Ex2. In group 3 the LV abnormalities were similar between tests. Echo data are shown (means±sd).

Group 1 (30 minutes)

<table>
<thead>
<tr>
<th>Pre</th>
<th>Ex1</th>
<th>Ex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF 3.8±2.5</td>
<td>3.1±2.4*</td>
<td>3.2±2.5</td>
</tr>
<tr>
<td>IRP 88±10115</td>
<td>94±11</td>
<td>92±115</td>
</tr>
</tbody>
</table>

Group 2 (60 minutes)

<table>
<thead>
<tr>
<th>Pre</th>
<th>Ex1</th>
<th>Ex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF 3.5±2.6</td>
<td>3.8±2.6</td>
<td>3.8±2.6</td>
</tr>
<tr>
<td>IRP 98±115115</td>
<td>115115</td>
<td>115115</td>
</tr>
</tbody>
</table>

Group 3 (4 hours)

<table>
<thead>
<tr>
<th>Pre</th>
<th>Ex1</th>
<th>Ex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF 4.2±2.6</td>
<td>3.9±2.6*</td>
<td>3.8±2.6</td>
</tr>
<tr>
<td>IRP 115115</td>
<td>115115</td>
<td>115115</td>
</tr>
</tbody>
</table>

Group 3 shortening fraction(%), IRP=isovolumic relaxation period (msecs)

Conclusion: The improvement in Grp 1 would be consistent with the phenomenon of ischemic preconditioning, whereas Grp 2 results suggest that repeated episodes of MS may cause cumulative and prolonged LV dysfunction. Grp 3 results suggest that MS is no longer cumulative if the LV is allowed sufficient time to recover.

BETA BLOCKERS PRESERVE CARDIAC VAGAL TONE UNDER CONDITIONS OF STRESS
JC Vaill, M Al-Ani, J Hammond, WA Littler, JH Coote*, JN Townsend
Departments of Cardiovascular Medicine and Physiology, University of Birmingham, Birmingham.

Conditions of stress are associated with profound impairment in cardiac vagal control and increased risk of sudden death. Animal studies suggest that lipophilic beta blockers act centrally to restore vagal activity, preventing ventricular fibrillation during stress. Our aim was to establish whether beta-blockers are effective in preserving normal vagal tone in stress in humans, and to compare lipophilic (high CNS penetrance) with hydrophilic agents. In a double blind, randomised cross-over study, we studied 15 healthy male subjects (age 18-21) after 72 hours treatment with placebo, atenolol (50mg od) or metoprolol (50mg bd) in 3 study visits at least a week apart. Effective and equivalent beta-blockade was confirmed with sub-maximal bicycle exercise testing. On each visit, the 3 minute periods of ECG were recorded at rest, during mental arithmetic (MA) and during head-up passive tiltting (TILT). ECG data were subjected to power spectral analysis using autoregressive modelling. Vagal activity was determined using the power of the high frequency (HF) peak in normalised units. In each group, there were significant reductions in mean R-R interval during MA and TILT. Results for cardiac vagal activity:

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Atenolol</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF (ms)</td>
<td>MF (ms)</td>
<td>HF (ms)</td>
</tr>
<tr>
<td>50.5±4.2</td>
<td>17.6±2.4</td>
<td>12.7±3.2</td>
</tr>
<tr>
<td>60.5±4.7</td>
<td>24.6±2.1</td>
<td>21.5±5.2</td>
</tr>
</tbody>
</table>

Values are mean±sd

RESULTS

The findings suggest that beta blockers preserve normal vagal tone in states of central stress. This may be an important mode of their action in reducing sudden death in cardiac disease.

EPIDEMIC HYPOTENSION DURING DAILY ACTIVITY IN HYPERTROPHIC CARDIOMYOPATHY AND PROPENSITY TO SUDDEN DEATH; UTILITY OF BEAT TO BEAT BLOOD PRESSURE MONITORING.
K Prasad, JP Stevenson, M Gould, WJ McKenna. Cardiothoracic Sciences, St. George’s Hospital Medical School, London, UK

BACKGROUND & METHODS: Identification of high risk patients with hypertrophic cardiomyopathy is a major management problem. Abnormal blood pressure response (ABPR) during exercise is an independent marker for sudden death in the young but treadmill exercise does not simulate normal activity. To determine the relation between ABPR during exercise and normal activity we performed beat to beat BP monitoring in 29 patients with HCM (mean age 25±4 yrs). The monitoring was performed with a novel portable apparatus (Portapress) using alternative finger cuff inflation (Plethysmography) powered by a lithium battery. 4 patients had experienced an episode of VF arrest prior to this study. 7 patients with vasovagal syncope(VVS) and 6 normal subjects formed the control group.

RESULTS: A sudden drop in SBP >30 mmHg or MAP >20 mmHg was defined as abnormal and all such episodes in each recording were coded (n=38). 8 patients (7 with ABPR) demonstrated such episodes. Episodic hypotension was common in those with ABPR (p<0.02), those with history of VF arrest or died during follow up (p<0.01) but infrequent in others. Only 60% of the episodes were associated with symptoms of syncope or pre-syncope. Majority of the episodes occurred during moderate daily activity and had relative bradycardia (HR 40-50). Hypotensive episodes were not seen in patients with VVS or normal controls. There were 2 deaths during 18 month follow-up in patients with ABPR and episodic hypotension but none in those without.

CONCLUSION: 40% of patients with HCM and ABPR have episodic hypotension during normal often moderate, daily activity. Episodic hypotension is associated with history of VF arrest and higher incidence of sudden death.

PREVALENCE OF CARDIOINHIBITORY CAROTID SINUS HYPERSENSITIVITY (CICSH) IN ACCIDENT AND EMERGENCY ATTENDANCES WITH FALLS OR SYNCOPE
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Cardiovascular Investigation Unit and Regional Cardiological Unit, Nev castle upon Tyne

A fall is defined as "coming to rest at a lower level with or without loss of consciousness". In previous studies up to 30% of patients with CICSH present with a history of unexplained or recurrent falls and deny syncope - possibly attributable to amnesia for loss of consciousness. The aim of this study was to determine the prevalence of CICSH in patients attending the Accident and Emergency (A&E) Department with an unexplained fall or recurrent falls (defined as >3 or more falls in preceding last year). 18542 consecutive A&E attendances aged 50 years or over were screened of whom 37% attended because of a fall. Fallers were excluded from further study if their falls were readily explained by medical attributable cause (myocardial infarction, dysrhythmia, stroke, etc., 22%), patients had cognitive impairment (18%) or falls were accidental (i.e slip, trip, etc., 40%). 16% (1092) of falls remained unexplained or were recurrent. Of these 34% declined further study. Carotid sinus massage (CSM; supine and tilted upright with simultaneous ECG and phasic BP measurement) was carried out in 495 patients; 91 had CICSH defined as "greater than 3 mV in systole of asystole supine or upright."

% CICSH 50 - 64yrs 10%
64yrs 22%
Overall Mean Age 72.8yrs
Falls with syncope 74%
Unexplained fallers 63%
Recurrent fallers 37%
Possible drug associated CICSH 18%

Such patients should be referred for further investigation of neurovascular instability. These figures will aid in establishing guidelines for use by staff in the Accident and Emergency department.
A COMPARISON OF THE IMPACT ON BLOOD PRESSURE OF MEDICAL AND SURGICAL PROCEDURES AT THE CAROTID SINUS
R Steedsa, A Sivagurub, P Galinesc, J Beard, G Venables, K Channerb
Departments of Cardiology, Neurology, and Vascular Surgery, Royal Hallamshire Hospital, and Department of Radiology, Northern General Hospital, Sheffield

We studied 30 patients with symptomatic carotid artery stenoses greater than 70% luminal diameter enrolled in a multicentre study comparing carotid endarterectomy (CEA) and carotid angioplasty (PTA). Blood pressure (BP) was measured 46 hours prior to the index procedure and 1 month afterwards using 24 hour ambulatory monitoring (Spacelabs). 12 patients underwent CEA and 18 patients had PTA. Baseline BP was higher in the CEA group (mean BP 115.5 mmHg ± 10.1 cf. 104.9 mmHg ± 11.7) but this difference was not significant. We calculated the changes in BP from baseline for each patient, then compared the overall changes between the two groups using parametric analysis of covariance methods. In patients who underwent CEA, there was a significant mean fall in systolic BP (-12.3 mmHg, 95% CI -21.4 to -3.3, p=0.01), diastolic BP (-6.1 mmHg, 95% CI -10.7 to -1.5, p=0.02), and mean BP (-9.2 mmHg, 95% CI -18.7 to -2.7, p=0.01). In patients following PTA, there were no significant changes-systolic BP (2.8 mmHg, 95% CI -7.2 to 1.5, p=0.19), diastolic BP (-0.5 mmHg, 95% CI -3.6 to 2.6, p=0.70), mean BP (-1.7 mmHg, 95% CI -5.3 to 1.9, p=0.54). These data suggest that CEA may contribute to the long term reduction in risk of stroke following this procedure. Temporary disruption of the carotid sinus during PTA does not lead to alteration of BP at 1 month. This may reduce the efficacy of the procedure in treatment of carotid stenosis.

AMBULATORY BLOOD PRESSURE IS SUPERIOR TO CLINIC MEASUREMENT FOR THE LONG TERM PREDICTION OF LEFT VENTRICULAR HYPERTROPHY AND CAROTID ATHEROSCLEROSIS IN HYPERTENSION
RS Khattar, C Kinsey, R Senior, A Lahiri. Department of Cardiovascular Medicine, Northwick Park Hospital, Harrow.

Cross-sectional studies have generally shown ambulatory blood pressure to be a better indicator of target organ damage than clinic measurement, but longitudinal data are lacking. This study compared clinic versus ambulatory blood pressure monitoring (ABPM) for the long term prediction of left ventricular hypertrophy (LVH) and carotid atherosclerosis. We randomly followed-up 266 treated hypertensives (148 males, 118 females; mean age 58±11 years) who underwent 24 hour ABPM based on an elevated clinic BP, a mean of 9.9±3.5 years ago. ABPM variables included mean systolic BP, diastolic BP and pulse pressure. At follow-up, echocardiography and carotid ultrasonography were performed to derive LV mass index (LVMI) and maximal carotid intima-media-thickness (IMTmax), an index of carotid atherosclerosis severity. LVMI ≥130g/m² for men and ≥110g/m² for women was considered to represent LVH. Body mass index (BMI), pack years of smoking and serum cholesterol were also determined. Correlation coefficients for the factors most strongly associated with LVMI and IMTmax are shown below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>LVMI</th>
<th>IMTmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.36</td>
<td>0.48</td>
</tr>
<tr>
<td>Ambulatory pulse pressure</td>
<td>0.36</td>
<td>0.47</td>
</tr>
<tr>
<td>Ambulatory systolic BP</td>
<td>0.30</td>
<td>0.32</td>
</tr>
<tr>
<td>Pack years of smoking</td>
<td>-0.03</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Age, BMI and ambulatory systolic BP were independent predictors of LVH (R²=16%), whereas age, pack years and ambulatory pulse pressure, were independent predictors of IMTmax (R²=34%). Notably, clinic BP did not feature in the model. These findings promote a role for ABPM in guiding aggressiveness of anti-hypertensive therapy in an attempt to limit potential target organ damage.

Tissue Inhibitors of Metalloproteinases as Markers of Atherosclerosis Related Myocardial Fibrosis in Hypertension
P M Timms, V Sirkovskia, F Maxwelld, A Wright, G D Gunn
Dept of Biochemistry, Dept of Cardiology, Stobhill Hospital, Glasgow

Introduction: Atherosclerosis (Aldo) and Angiotensin I1 have been shown as mediators of myocardial fibrosis in hypertensive left ventricular hypertrophy. Elevated levels of procollagens 11 peptides have been found in patients with hypertensive left ventricular hypertrophy (LVH). Tissue inhibitors of metalloproteinases (TIMP) inhibit matrix metalloproteinases (MMP) which are responsible for breakdown of collagen. MMP levels have been found to be low in fibrosis associated liver disease with a corresponding rise in TIMP levels. Aim: to analyse a relationship between aldosterone, P111P, TIMP and echo determined LV mass in hypertensive patients. Patients: Previously untreated hypertensive patients (n=15, group 1) with no other chronic medical illness or previous surgical procedure and good echo for analysis and a matched population of normotensive controls (n=16, group 2) with no previous chronic medical illness or surgical procedure. Results: The mean age of group 1 was 51.8 years and that of group 2 was 44.7 years. The levels of TIMP, Aldo, P111P and LV mass are shown in table:

<table>
<thead>
<tr>
<th>TIMP ng/ml</th>
<th>Aldo ng/ml</th>
<th>P111P U/ml</th>
<th>LV Mass g/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP (Gr 1)</td>
<td>493</td>
<td>0.358</td>
<td>0.68</td>
</tr>
<tr>
<td>Control (Gr 2)</td>
<td>187</td>
<td>0.349</td>
<td>0.54</td>
</tr>
</tbody>
</table>

P111P levels were significantly elevated in group 1 as compared to group2. TIMP levels correlated well with Aldo levels and LV mass in hypertensive patients (r=0.63) but not in the normotensive controls. There was no correlation between the P111P and TIMP levels in either group. Conclusion: Elevated TIMP levels in hypertensive patients is a useful marker of aldosterone driven myocardial fibrosis and hypertrophy.
Tissue Inhibitors of Metalloproteinases as Markers of Left Ventricular Hypertrophy and Myocardial Fibrosis in Hypertension.

P S Srikantham, P Timms, A Wright, P Maxwell, P G Dunn.
Dept of Cardiology, Dept of Biochemistry, Stobhill Hospital, Glasgow.

Introduction: Raised levels of serum procollagen-1 peptides have been found in hypertensive left ventricular (LVH) suggesting increased collagen deposition. Matrix metalloproteinases (MMP) are responsible for the breakdown of collagen. Tissue inhibitors of metalloproteinases (TIMP) inhibit MMP. Low levels of MMP with elevated TIMP levels have been seen in tissues with increased deposition of collagen.

Aim: To analyse the relationship between TIMP and degree of LVH as assessed by echocardiography in untreated hypertensives.

Patients: Previously untreated hypertensive patients (n=16, group1) with no other chronic medical illness or previous surgical procedure and suitable echo for analysis. Matched population of normotensive controls (n=16, group2) with no previous chronic medical illness or surgical procedure.

Results: The mean age in group 1 was 51.8 years. The mean LV mass index in group 1 was 129.9±4g/m² (vs 96.9±g/m² in group 2, p<0.01). Mean TIMP in group 1 was 40.9±6ng/ml in group 2 (p<0.001). TIMP levels correlated well with LV mass index in the hypertensive group (r=0.72). TIMP levels also correlated well with LV posterior wall thickness (r=0.65). However, there was no correlation between TIMP and blood pressure in these patients. The levels of TIMP in the normotensive control group did not show any correlation with LV mass or LV wall thickness.

Conclusion: TIMP is a useful quantitative marker of LVH in hypertension and may reflect the degree of myocardial fibrosis providing potential for a better understanding of the regressive process.

WHITE COAT HYPERTENSION IS ASSOCIATED WITH LESS LONG TERM CARDIOVASCULAR COMPLICATIONS COMPARED TO ESSENTIAL HYPERTENSION.

RS Khattar, R Senior, A Lahiri. Department of Cardiovascular Medicine, Northwick Park Hospital, Harrow.

The prognostic significance of white coat hypertension remains unclear and longitudinal data are lacking. This study aimed to assess the long term prevalence of left ventricular hypertrophy (LVH) and degree of cardiac artery thickening in white coat compared to overt hypertension.

We randomly followed-up 262 patients (146 males, 116 females; mean age 58±11 years) with elevated baseline clinic blood pressure, who underwent 24 hour ambulatory blood pressure monitoring (ABPM) and had LV mass index (LVMi) and carotid intima-media thickness (IMT) assessed. LVMI ≥130g/m² for men and ≥110g/m² for women was considered to represent LVH. Body mass index (BMI), pack years and cholesterol were determined. Comparison of the two groups is summarized below:

<table>
<thead>
<tr>
<th></th>
<th>White coat (n=70)</th>
<th>Overt (n=192)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 11</td>
<td>60 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 ± 4.5</td>
<td>26.8 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pack years</td>
<td>3.9 ± 7.5</td>
<td>8.7 ± 15.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVH (%)</td>
<td>27</td>
<td>55</td>
<td>0.006</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.55 ± 0.15</td>
<td>0.63 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multiple regression analysis after adjustment for clinical variables, showed IMT (p=0.02) and LVH (p=0.05) to be significantly lower in the white coat compared to overt hypertension group. These findings suggest a more benign outcome in those with white coat hypertension as identified by ABPM.

FIRST LINE TREATMENT IN CHRONIC HEART FAILURE: COMPARISON OF A LOOP DIURETIC WITH A DOPAMINE RECEPTOR ANTAGONIST.

R Andrews, A Charlesworth*, A Evans, AJ Cowley. Department of Cardiovascular Medicine, University Hospital, Nottingham and *Nottingham Clinical Trial Data Centre, Nottingham.

Loop diuretics remain a cornerstone in the first line treatment of chronic heart failure (CHF) despite concerns about their adverse metabolic and neurohormonal effects. Dopamine agonists have natriuretic and vasodilator properties with a favourable metabolic and neurohormonal profile and are a potential alternative to loop diuretics in CHF.

Methods: We compared the effects of the orally active dopamine agonist ibopamine with frusemide as first line therapy in 14 patients with NYHA II CHF in a double-blind, cross-over study. After baseline measurements of modified Bruce exercise time, corridor walk time, 24 hour urine volume and sodium excretion and neurohumoral factors, patients were randomly allocated to receive either frusemide 40mg od or ibopamine 100mg tds for 8 weeks. Assessments were performed at 2 weekly intervals. After 8 weeks patients crossed over into the alternate treatment arm for a further 8 weeks. Results. There were 4 exacerbations of CHF during ibopamine treatment and none during frusemide treatment. After 8 weeks treatment treadmill exercise time was 90±73 seconds with frusemide and 646±134 with ibopamine (P=0.05). 24 hour urinary sodium excretion at weeks 2 and 4 (P<0.05) and 24 hour urine volume at week 2 (P=0.001) were lower during ibopamine treatment. At week 8 supine (P=0.076) and erect renal (P=0.05) were lower with ibopamine treatment. Conclusions: Ibopamine is ineffective as first line therapy in CHF, probably because of a lesser natriuretic potency than frusemide. Diuretics therefore remain the first-line therapy of choice in patients with CHF.
WHAT DOSE ACE INHIBITION IN HEART FAILURE THERAPY?

GA Cooke, J Al-Timman, P Marshall, DJ Wright, LB Tan. Leeds University and Killingbeck Hospital, Leeds, UK.

ACE inhibitors are accepted as standard therapy for heart failure, but there is uncertainty as to which doses should be used in clinical practice. Cardiac power output and exercise capacity are zero at the extremes of inulin and zero peripheral vascular resistance, and maximum at an intermediate point between the extremes. We tested the hypothesis that at high doses of ACE inhibition there is a tendency towards over vasodilatation such that cardiovascular function and exercise capacity are relatively compromised. We conducted a cross-over randomised, placebo-controlled trial comparing the effects of 3-month treatment each with 20 and 5 mg od of lisinopril (L20 and L30) in 12 patients with moderate heart failure (NYHA II-III, LVEF<45%). Standard haemodynamic and gas exchange data were collected non-invasively during symptom-limited treadmill exercise and dobutamine stress tests. Comparing the L20 with the L30 treatment phases, during equivalent peak dobutamine stress and maximal exercise tests, the haemodynamic data showed trends toward higher cardiac performance with L30 therapy.

Dobutamine: BR CO CPO Ex:BR CO CPO

L20 123 10.1 2.0 W 139 12.2 2.7 W
L30 111 8.9 1.7 W 134 11.9 2.6 W

p values: 0.35 0.32 0.15 0.11 0.12 0.24

The primary end-point of aerobic exercise capacity was significantly higher during L30, with peak oxygen uptake of 21.2 (L20) vs 19.6 ml/min.1kg -1, p=0.012. Twenty-four adverse reactions were reported during L20 compared to 18 during L30 treatment periods. Conclusion: The aerobic exercise capacity of patients is shown in this study to be higher with the lower dose lisinopril. The answer to whether the high or low dose of lisinopril will confer greater longevity will be available when the ATLAS mortality study has been analysed.

EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON 24 HOUR BAROREFLEX SENSITIVITY IN HEART FAILURE

JC Vaile, TJ Stallard, PJ Jordan, JH Coote1, JN Townsend, WA Little. Departments of Cardiovascular Medicine and Physiologically, University of Birmingham, Birmingham.

In chronic heart failure (CHF), baroreflex sensitivity (BRS) is impaired. Studies using single laboratory estimates have suggested that BRS may be increased by treatment with ACE inhibitors. We have examined the 24 hour pattern of BRS in heart failure and its modulation by ACE inhibitor treatment. We studied 12 patients with chronic heart failure (NYHA class III-IV, mean ejection fraction 24%) due to coronary artery disease (n=9) or dilated cardiomyopathy (n=3). All were in sinus rhythm. Patients underwent 24 hour ambulatory intra-arterial blood pressure (IABP) recordings (OMRON method), before and after 16 weeks of treatment with captopril (Q) incremented to 20mg 2d. Concurrent therapy included only diuretics (n=12), digoxin (n=3) and amiodarone (n=1). Control IABP recordings from patients without heart failure, matched for age and waking IABP, were selected from a departmental database. BRS was assessed throughout each 24 hour period by off-line computer analysis of 25 consecutive beats where both IABP and pulse interval (PI) progressively increased (baroreceptor loading) or decreased (baroreceptor unloading). For each sequence, the slope of the linear relationship (r ≥ 0.8) between IABP and PI was taken as a measure of BRS. Statistical analysis was by paired t test (log BRS).

BRS values are mean ±SD:

<table>
<thead>
<tr>
<th></th>
<th>Awake BRS</th>
<th>Asleep BRS</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(24 hour mean±SD) (mmHg/mL) (wake vs sleep)</td>
<td>(BR)</td>
<td>(C)</td>
<td>(P)</td>
</tr>
<tr>
<td>Control</td>
<td>60 ±2.9</td>
<td>89 ±4.2</td>
<td>0.001</td>
</tr>
<tr>
<td>CHF pre-Q</td>
<td>5.4 ±0.9</td>
<td>6.4 ±1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>CHF post-Q</td>
<td>5.4 ±1.3</td>
<td>7.7 ±2.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*p<0.05 compared to control (log BRS).

In heart failure as in health, BRS increases significantly during sleep.

Compared to controls, this nocturnal rise in BRS is significantly blunted but increases significantly* after treatment with captopril. ACE inhibition did not produce any detectable increase in BRS during waking hours which we suggest was due to BRS inhibition by exercise and the altering renal function. In heart failure ACE inhibition increases BRS and restores the normal diurnal variation.

THE IMPORTANCE OF RIGHT VENTRICULAR FUNCTION FOR MAINTAINING EXERCISE TOLERANCE IN PATIENTS WITH LEFT VENTRICULAR DISEASE

KM Webb-Peploe, MY Henela, AJS Coats, DG Gibson Royal Brompton Hospital, London.

No measure of cardiac function, as assessed by echo has been shown to predict exercise tolerance in patients with dilated left ventricles. Cardiopulmonary exercise testing and 2-D guided M-mode echocardiography were performed in 22 male patients in sinus rhythm with LV EDD>6.4cm and fractional shortening (FS)<25% and in 11 normal controls (10 male). 11 patients (mean age 55±6 years) had coronary artery disease (HJD) and 11 (mean age 49±5 years) had angiographically normal coronaries (DCM). The two patient groups did not differ significantly in age or traditional values of left ventricular function; EDD, ESD or FS. They did however differ significantly in longitudinal right ventricular function, exercise tolerance and mV02. The group with DCM had greater right ventricular RV excursion (2.4±0.5 vs 1.5±0.5cm, p<0.001) and peak shortening velocity (0.52±0.7 vs 3.7±3.1cm/s, p<0.05). This compared with the 11 normal controls (mean age 51±7 years) in whom RV excursion was 2.6±0.3cm and peak lengthening velocity 10.4±2.0cm/s. The DCM group exercised for longer on the treadmill compared to those with IHD (79±14 vs 48±8 sec, p<0.001). They also achieved a higher mV02 (26.0±7.5 vs 18.5±3.9ml/kg/min, p<0.01) with a lower VE-VCO2 slope (30.9±6.4 vs 16.3±5.6±5.1, p<0.05). The 11 normal controls achieved a mean exercise time of 95±106 sec, an mV02 of 31.5±4.6ml/kg/min and a VE-VCO2 slope of 25.4±8.3. Within the patient group as a whole RV systolic excursion correlated with mV02 (R=0.59, p<0.01). Conclusion: In patients with dilated, impaired left ventricles, preserved right ventricular function predicts a better exercise time and mV02.

SERUM URIC ACID AS A MARKER OF IMPAIRED OXIDATIVE METABOLISM IN CHRONIC HEART FAILURE

F Leyva, SD Anker, TP Chua, IF Godland, JC Stevenson, AJS Coats. Wyna Division of Metabolic Medicine and Department of Cardiac Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, London.

Elevated serum uric acid concentrations have been observed in clinical conditions associated with hypoxia. Since chronic heart failure (CHF) is a state of impaired oxidative metabolism, we sought to determine whether serum uric acid concentrations relate to measures of functional capacity and disease severity. Methods: Patients with CHF (n=59) and healthy controls (n=20) underwent assessment of maximal oxygen consumption (MVO2) and regression slope relating to minute ventilation to carbon dioxide output (VE-VCO2) during a maximal treadmill exercise test. A metabolic assessment included measurement of serum uric acid and insulin sensitivity (obtained by minimal modelling analysis of glucose and insulin responses during an intravenous glucose tolerance test). Results: Compared to controls, patients with CHF had a 52% lower MVO2, 56.8% higher serum uric acid concentrations, and a 60.5% lower insulin sensitivity (all p<0.01). In the CHF group, serum uric acid correlated with exercise time (r=-0.53), MVO2 (r=-0.50) (both p<0.001), VE-VCO2 (r=-0.45) and NYHA class (r=-0.36) (both p<0.01). In multiple regression analysis, serum uric acid concentrations emerged as a significant predictor of MVO2 exercise time (both p<0.01), VE-VCO2 and NYHA class (both p<0.02), independently of diuretic dose, age, body mass index, serum creatinine, alcohol intake, plasma insulin levels, and insulin sensitivity. Conclusions: There is inverse relationship between serum uric acid concentrations and measures of functional capacity in patients with CHF. The strong inverse relationship between serum uric acid and MVO2 suggests that in CHF, serum uric acid concentrations can provide an index of an impairment of oxidative metabolism.
QT INTERVAL PARAMETERS ON A 12 LEAD ECG AS PREDICTORS OF MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE
Brookhart S, Basis PD*, Nolan J*, Andrews R, Lindsay HSJP, Mullon M', Baig W, Prescott R', Cowley AJ', Fox KAA*, University Hospital, Nottingham, *Yorkshire Heart Centre, Leeds, Doncaster Royal Infirmary, Doncaster, University of Edinburgh, Edinburgh

The QT interval has been shown to be a marker of poor prognosis in patients with ischaemic heart disease. Recently, a few small studies have indicated that QT dispersion can be used to identify patients with congentive heart failure (CHF) who have a higher mortality. Methods: We have prospectively investigated the relationship between QT interval and QT dispersion and mortality in a large cohort of patients with CHF. QT parameters were measured on 12-lead ECGs from 519 patients with mild to moderate CHF by a single operator. The principle end-point was all-cause mortality. Results: The mean follow-up period was 470 ± 170 days (mean ± standard deviation), age was 62.8 ± 9.7 years, NYHA class was 2.4 ± 0.6, ejection fraction was 41.5 ± 17% and cardio-thoracic ratio (CTR) was 53 ± 6.8. The mean maximum rate corrected QT interval (QTcmax) was 492 ± 74.8 ms and rate corrected QT dispersion (QTcd) was 80.6 ± 42.1 ms. During the follow-up period of at least 1 year, 76 (14.6%) patients died. Univariate analysis revealed the following factors to be significantly related to all-cause mortality: NYHA class (p < 0.001), urea (p < 0.001), CTR (p < 0.001), QTcmax (p < 0.001), sodium (p < 0.001), albumin (p < 0.001), heart rate (p < 0.0003), ejection fraction (p < 0.0009), bundle branch block (p < 0.005), and QTcd (p < 0.001). Multivariate analysis was carried out using forward stepwise Cox’s proportional hazards, with this procedure the QT parameters quickly fell out of the model leaving urea (p < 0.0001), CTR (p < 0.001), sodium (p = 0.008) and ejection fraction (p = 0.015) as the only independent predictors of all-cause mortality. Of these, a strong QTcd and a weak univariate predictor of all-cause mortality in patients with mild to moderate heart failure. However, none of the QT parameters were significant independent predictors of heart failure mortality.
A GENE LOCUS FOR ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY MAPS TO CHROMOSOME 17p1-q3

AS Coenraet, T Moraen,1 A. Tounoepoulou,1 EWA Needham, VA Murray, RJ Heslewood, S Cliff, MI Oster, RK Mattr, WJ McKenna

St George's Hospital Medical School, London, & 1Yannis Protonotarios Medical Centre, Naxos, Greece

Arrhythmogenic right ventricular cardiomyopathy (ARVC) causes sudden death, arrhythmias, and heart failure. Familial disease is common and three loci have been reported for autosomal dominant forms of the disease. Identification of the genetic basis of ARVC is dependent on the accurate determination of disease status. This is difficult because of the unknown nature of early disease, the high rate of non-penetrence and variable expression, and phenotypic copies due to other causes.

Protonotarios identified the phenotype of Naxos syndrome (ARVC + palmoplantar keratodema + wavy hair) which recently has been denoted as a distinct clinical entity (McKusick # 601214)*. We evaluated the population of Naxos, Greece. From a total population of approximately 20,000, eleven families of 148 persons were identified. 21 had Naxos syndrome. Segregation analysis identified autosomal recessive inheritance. The disease had high penetrance and expression, thus improving diagnostic accuracy, and therefore represented an excellent model to investigate the genetic basis of ARVC.

In 40 family members molecular genetic analysis was performed. Radio-labelled short-sequence repeat markers were resolved on denaturing polyacrylamide gels. The loci for the autosomal dominant forms of the disease were excluded. Subsequently, following a candidate gene search strategy, a marker which co-segregated with the disease in a recessive manner exclusively and mapped to 17p1-q3 was identified. The peak 2 point lod score was 4.07 at 8 = 0. A recessively inherited disease haplotype has also been identified around this locus. A cluster of cardiac and skin genes map to this interval and are currently under evaluation.

DEATH, SUDDEN DEATH AND SUDDEN CARDIAC DEATH IN A YOUNG POPULATION

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Sudden death (SD) in the young may be due to unsuspected structural cardiac abnormality. SD may also be due to arrhythmia but retrospective diagnosis is rarely possible and there are no reliable population data on the incidence and relative importance of underlying causes. This study examines the incidence and causes of SD in a population of children and adolescents.

Details of all deaths at age 1-20y in a population of 3.1m in 1985-92 were obtained from OPCS. Coroners' and hospital records provided extra information. Deaths after hospital admission and unnatural deaths were not analysed further.

In a population of 806,900 children and adolescents age 1-20y there were 2145 deaths in eight years (26.6/100,000/y). 825 (38%) were due to chronic diseases, 1094 (51%) were unnatural and 226 (11%) were sudden. Of 111 SD with a previous diagnosis the commonest causes were epilepsy (29%), asthma (22%) and cardiac disease (25%). SD from known cardiac disease included aortic stenosis (3), un paced AV block (3), long QT syndrome (LQTS) (1) and atrial repair of transposition (5) but no cases of hypertrophic cardiomyopathy (HCM). Of 76 unexpected SD with a cause at necropsy 14 had cardiac abnormalities, including HCM (5) and other left ventricular outflow obstruction (6). There were 39 cases of unexpected SD with no cause at necropsy. A retrospective diagnosis of LQTS was made in 2.

Most SD due to heart disease occurs in children with a diagnosis made in life. In the absence of a previous diagnosis only structural defects can be identified post mortem and in this group HCM is rare. Arrhythmias are a probable cause of unexplained SD but firm retrospective diagnosis is usually impossible. The unexplained SD in our population probably underestimates total arrhythmic deaths.

ENALAPRIL DOES NOT IMPROVE CONDUIT ARTERY ENDOTHELIAL FUNCTION IN YOUNG SUBJECTS WITH INSULIN-DEPENDENT DIABETES MELLITUS (IDDM).


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IDDM is a major risk factor for premature large vessel atherosclerosis. Endothelial dysfunction occurs in young subjects with IDDM and may be a marker of early vascular damage. Angiotensin converting enzyme inhibitors retard the progression of renal microvascular complications but their effect on large vessel physiology in IDDM is unknown. In a randomised double blind parallel group trial we studied the effects of 6 months treatment with enalapril (treated to 20mg od) or placebo on endothelial function in 91 subjects with IDDM (56 males, mean age 30.9 yrs, range 18-44). Subjects were normotensive, normocholesterolaeic, non-smokers and had no overt vascular disease. Using high resolution external ultrasound, brachial artery reactivity in response to reactive hyperaemia (endothelium-dependent flow mediated dilation) (FMD) was compared to that of GTN (endothelium-independent dilation) (GTN-MD) at baseline, and after 6 months of treatment. The results (mean SD) are summarized in the table.

<table>
<thead>
<tr>
<th>Vessel Size (mm)</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.55 (0.61)</td>
<td>3.52 (0.62)</td>
<td>3.48 (0.58)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>3.59 (0.57)</td>
<td>3.56 (0.57)</td>
<td>3.56 (0.48)</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>2.3 (2.7)</td>
<td>2.9 (3.4)</td>
<td>3.0 (2.6)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.6 (2.4)</td>
<td>2.6 (2.7)</td>
<td>2.8 (2.9)</td>
</tr>
<tr>
<td>GTN-MD (%)</td>
<td>18.3 (7.6)</td>
<td>18.7 (9.4)</td>
<td>19.6 (7.5)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>17.5 (8.0)</td>
<td>16.9 (8.1)</td>
<td>18.4 (8.3)</td>
</tr>
</tbody>
</table>

Young IDDM subjects have impaired large vessel endothelial function even in the absence of microvascular disease, hypercholesterolaemia or hypertension. This was not significantly improved despite treatment with the enalapril for 6 months.

DIFFERENTIAL PLASMA ENDOTHELIN LEVELS IN SUBGROUPS OF PATIENTS WITH ANGINA AND ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES

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Introduction. This study investigated whether plasma endothelin (ET) levels differ in clinically distinct subgroups of patients with angina and normal coronary angiograms.

Method. We prospectively studied 63 patients (mean 57 ± 10 years, 54 female) with exercise-induced angina pectoris and normal coronary angiograms. Twenty one age and gender matched healthy volunteers constituted the control group. Patients with coronary spasm, left ventricular hypertrophy, valvular abnormalities, renal failure and reduced left ventricular function (ejection fraction < 50%) were excluded. ET was assessed by radioimmunoassay.

Results. Of the patient group, 7 had left bundle branch block (LBBB) at rest or induced by exercise (group A), 7 had previous myocardial infarction (group B), 24 had positive exercise tests (group C), 16 had negative exercise tests (group D) and 9 had systemic hypertension (group E). The mean plasma ET concentration (pg/ml ± SD) was significantly higher in patients compared to controls (3.6 ± 1.1 vs. 2.9 ± 0.7, p = 0.001). Mean plasma ET was higher in patients of group A (4.3 ± 1.1), group B (4.3 ± 0.7) and group C (3.6 ± 1.2) compared to normal controls (2.9 ± 0.7) (p = 0.001 and p = 0.001 respectively). Patients with LBBB or previous MI had higher ET levels than those with negative exercise tests (p = 0.002) and those with hypertension (p = 0.01).

Conclusions. Plasma ET is elevated in patients with angina pectoris and angiographically normal coronary arteries, particularly in those patients with a history of previous myocardial infarction and those with left bundle branch block. In these patients, elevated plasma ET may reflect a primary disturbance of microvascular function or may be a marker of secondary endothelial damage.
### CLOSING THE AUDIT LOOP: NURSE LED THROMBOLYTIC THERAPY.

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An initial 12 month prospective audit of thrombolytic therapy in acute myocardial infarction (AMI) was undertaken to determine the "door to needle" time in patients eligible for immediate thrombolysis (positive history and 1st ECG confirmation). Of 488 patients (mean age 67 years) admitted with AMI 214 (44%) were given thrombolysis of whom 185 were eligible for immediate thrombolysis. The median "door to needle" time was 75 min (range 10 to 121 min). In view of this unacceptable delay in treatment Clinical Nurse Specialists were appointed to triage all patients presenting with chest pain in the A&E Department and start thrombolytic therapy as indicated.

In the subsequent 12 month period, 420 patients (mean age 66 years) were admitted with AMI, 224 (53%) were given thrombolysis of which 134 were eligible for immediate thrombolysis. The median "door to needle" time was reduced to 18 min (range 5 to 145 min; p<0.001). Nurse Specialists thrombolysed 86 patients (median "door to needle" time 15 min; range 5 to 30 min) and doctors thrombolysed 48 patients (median "door to needle" time 26 min; range 5 to 145 min; p<0.001).

These data emphasise the value of dedicated staff in reducing the "door to needle" time for thrombolysis to a minimum and confirm the central role played by the Clinical Nurse Specialist.

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### INTRAVENOUS L-ARGININE IMPROVES ENDOTHELIAL FUNCTION IN CIGARETTE SMOKERS.


**Introduction:** Endothelial dysfunction is an important early event in atherogenesis; we have previously demonstrated impaired endothelial dependent dilation in cigarette smokers which may be due to decreased production or increased breakdown of nitric oxide (NO). L-arginine, the precursor of NO has been shown to improve endothelial function in subjects with hypercholesterolaemia though its effect in cigarette smokers is not known. Aim: To determine the effect of intravenous L-arginine on endothelial function in young current cigarette smokers without other risk factors for atherosclerosis.

**Methods:** Eight current smokers were studied (mean age 32, range 25-35; mean pack years 11, range 4-20). Subjects were not diabetic or hypertensive, normocholesterolaemic and had no clinical evidence of vascular disease. Using high resolution ultrasound, we measured brachial or radial artery diameter at rest and following a brief period of reactive hyperaemia in the distal limb. Flow mediated dilation (FMD) was determined (endothelium-dependent) on two separate occasion, before and after intravenous infusion of L-arginine (0.1 g/Kg body weight), or 0.9% saline (placebo) in a randomised double blind fashion. Response to glyceryl trinitrate (GTN) (endothelium-independent dilation) was measured at the end of each study. Results: FMD improved significantly from 0.57±1.18 to 2.63±2.23 per cent (p=0.02) following L-arginine, there being no significant change following placebo. L-arginine had no effect on blood pressure, heart rate, degree of reactive hyperaemia. Response to GTN was not influenced by L-arginine but correlated with total pack years smoked (r=0.74, p=0.01), which may represent smooth muscle cell sensitisation to chronically decreased NO bioavailability in the heaviest smokers. Conclusion: Acute administration of L-arginine improves endothelial function in healthy young cigarette smokers. This may indicate a novel method of vascular protection.
ENDOTHELIAL FUNCTION IN CORONARY ARTERY DISEASE: EFFECTS OF SYMPATHETIC AND CONVERTING ENZYME INHIBITION ON HAEMOSTATIC VARIABLES
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The normal endothelium subserves numerous regulatory functions, including production of fibrinolytic and plasminogen substances. Considerable evidence points to the renin-angiotensin system (RAS) as a modulator of endothelial function and we have hypothesised that it may interact with the sympathetic system to drive diurnal fluctuations in haemostatic balance and contribute to the diurnal rhythm of ischaemic events in coronary artery disease. To test this hypothesis we 20 patients with stable coronary disease were treated first with placebo, then a β-blocker (bisoprolol 20mg daily) and finally an ACE-inhibitor (quinapril 20mg od), each for 4 weeks. At the end of each treatment period patients underwent 24h Holter monitoring for heart rate variability (HRV) and 6 hourly measurements of tissue plasminogen activator antigen (tPA-Ag), plasminogen activator inhibitor-1 antigen (PAI-1-Ag), and plasma renin. Baseline fibrinolytic activity showed a circadian pattern with morning peaks of PAI-1-Ag and tPA-Ag (p<0.001). ACE-inhibition produced a huge increase in circulatory renin, but, in contrast to patients with an activated RAS early after infarction, PAI-1-Ag levels were unaffected and continued to show the normal circadian rhythm. Also unaffected was tPA-Ag and HRV. β-blockade tended to suppress renin but neither plasma levels nor circadian distributions of fibrinolytic variables were affected. However, the ratio of low to high frequency spectral components of HRV (a measure of sympathovagal balance) was reduced by β-blockade and the morning peak was abolished (p<0.001). In conclusion, we found no evidence of interaction between the sympathetic and renin-angiotensin systems in the modulation of endothelial production of haemostatic substances in patients with stable coronary disease. The potential benefits of ACE-inhibition for protecting against ischaemic events are more likely to be mediated by direct effects on atherogenesis, while our data support the growing consensus that the benefits of β-blockade are mediated, at least in part, by suppressing the morning surge in sympathetic drive.

PLASMA LIPOPROTEIN(a) IS ELEVATED IN PATIENTS WITH CHRONIC STABLE ANGINA AND IS ASSOCIATED WITH COMPLEX LESION MORPHOLOGY
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Lipoprotein(a) [Lp(a)] is an independent risk factor for the development of coronary arterial infarction and cardiac death. However, the association between Lp(a) and the extent and severity of coronary artery disease (CAD) has not been previously studied in well characterised patients with chronic stable angina. We studied the relationship between plasma Lp(a) and angiographic parameters of CAD in 129 pts (age 61 ± 10 yrs, including 43 females) with chronic stable angina who underwent diagnostic coronary angiography.

Plasma Lp(a) was raised in pts [n = 86] with significant CAD (coronary lesions > 50% reduction of lumen diameter) compared to those [n = 41] without significant stenoses (58 ± 54 mg/dl vs 23 ± 28 mg/dl; P = 0.0009, Mann-Whitney U). Pts with or more coronary artery occlusions [n = 41] had higher Lp(a) than those [n = 88] with no occlusive disease (60 ± 53 mg/dl vs 41 ± 47 mg/dl; P = 0.04, Mann-Whitney U). Consistent with this finding, pts with previous myocardial infarction [n = 38] had raised Lp(a) when compared to those [n = 91] without previous MI (67 ± 61 mg/dl vs 39 ± 42 mg/dl; P = 0.02, Mann-Whitney U). Coronary artery disease severity was correlated to Lp(a) in men < 55 years (P = 0.04, Kruskal Wallis) and in women irrespective of age (P = 0.002, Kruskal Wallis) but not men > 55 years. Menopausal women [n = 36] had a higher Lp(a) than those premenopausal (49 ± 49 vs 18 ± 18) but this failed to reach statistical significance. We found no relationship between plasma Lp(a) and left ventricular function, other conventional risk factors.

We noted that in the 19 pts with single vessel disease, Lp(a) was higher in patients with lesions > 50% than in those with smooth lesions. In order to clarify this association we analysed Lp(a) in a further 13 patients with chronic stable angina and single vessel disease. Lp(a) was higher in these pts [n = 18] with complex lesions than in those [n = 14] with smooth lesions (499 ± 97 mg/dl vs 121 ± 49 mg/dl; t = 0.02, Mann-Whitney U). In conclusion we have shown that raised plasma Lp(a) is associated with the presence of CAD and history of MI and correlates with premature CAD in men. In addition, we have found elevated plasma Lp(a) is associated with complex lesion morphology.

COAGULATION AND FIBRINOLYTIC FACTORS, INSULIN RESISTANCE AND THE METABOLIC SYNDROME OF CORONARY HEART DISEASE RISK
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Wyn Division of Metabolic Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, London.

A number of independent risk factors for coronary heart disease (CHD) are now recognised to be part of a syndrome of metabolic disturbances centred on insulin resistance. However, links between this syndrome and the haemostatic system have only been explored in detail with regard to plasminogen activator inhibitor 1 (PAI-1). Methods: Fibrinogen, Factor VII, Factor VIII, protein C, protein S, antithrombin III, plasminogen, PAI-1, tissue plasminogen activator (tPA) and fibrinopeptide A were measured in 47 healthy males (aged 33-68 years, body mass index (BMI) 20.9-32.6 kg/m²). Insulin sensitivity (S, inversely related to insulin resistance) was evaluated by mathematical modelling analysis of intravenous glucose tolerance test (IVGTT) glucose and insulin concentrations. Fasting serum lipids and lipoproteins were also measured. Results: Factor X was significantly associated with IVGTT insulin and C-peptide response (r = 0.41, p<0.006) and r = 0.32, p=0.04, respectively), S, (r=0.38, p<0.02), BMI (r=0.41, p<0.006), systolic and diastolic blood pressures (r=0.35, p=0.02 and r=0.33, p=0.03, respectively), triglycerides (r=0.30, p=0.06) and HDL₃ cholesterol (r= -0.32, p=0.04). Fibrinogen showed significant associations with IVGTT insulin and C-peptide response, S, triglycerides and HDL₃ cholesterol. Factor VII and PAI-1 were associated with IVGTT insulin response and S. The correlation coefficients between PAI-1 and IVGTT insulin response was particularly strong (r = 0.57, p<0.001) but PAI-1 was not related to any other measure. Conclusions: High Factor X and fibrinogen levels are strong candidates for inclusion in the metabolic syndrome. Factor VII and PAI-1 appear to be primarily related to insulin concentrations.
The Difference in Age-related Changes in Myocardial Velocity Gradient in Elite Athletes and Sedentary Healthy Subjects.

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Myocardial velocity gradient (MVG) is a new ultrasonic parameter of systolic and diastolic function. Previous reports showed age-related changes in diastolic MVG in healthy sedentary subjects. The aim of this study was to determine whether these physiological changes in MVG are also present in elite athletes. A group of 51 athletes (AH) (age from 16 to 64 yrs, mean 38 yrs) and 56 age-matched sedentary normals (N) were studied. All AH trained at least 13 hours per week for the last 5 years. Resting MVG was measured across the left ventricular (LV) posterior wall in systole, early (ED) and late diastole (LD). Results: No significant difference was found in MVG measured in systole (AH 4.6 ±1.1 s⁻¹ versus N 4.4 ±1.2 s⁻¹; p=NS) and in LD (AH 3.1 ±1.9 s⁻¹ versus N 2.0 ±1.2 s⁻¹; p=NS) between the groups. In early diastole AH had significantly higher MVG compared to N (9.6 ± 2.3 s⁻¹ versus 7.2 ± 3.1 s⁻¹; p<0.001). In both studied groups, a positive correlation was found between age and MVG measurements obtained during ED (for AH r=0.86; p<0.001; for N r=0.90; p<0.001). However, MVG measured in ED correlated inversely with age only in N (r=-0.89; p<0.001) but not in AH (r=-0.21; p=NS). The stepwise multivariate regression analysis showed that changes in MVG were independent of heart rate, blood pressure or standard echocardiographic assessment of LV regional and global diastolic function including transmitral wave-form pattern and peak rate of wall thinning assessed from digitised M-mode recordings.

Conclusions: These findings suggest that physiological age-related decrease in early diastolic LV (transmyocardial) function is either delayed or does not occur in athletes' hearts.