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>
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<tbody>
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<td>Honorary Secretary</td>
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<tr>
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Please remember to bring this supplement with you to the conference

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CAPRIE: CLOPIDOGREL V ASPIRIN IN PATIENTS AT RISK OF ISCHAEMIC EVENTS
J R Hampton for the CAPRIE investigators

Clopidogrel 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 clopidogrel and aspirin, for the prevention of death, myocardial infarction and stroke, in patients with established vascular disease. Of 9,954 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 960 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 clopidogrel group and 5.53% in the group treated with aspirin, a relative reduction of 8.7% 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.

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 thrombolysis may be obtained within 2 hours rather than 1.

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=0.0005). 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 57% 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.

Angiotein Converting Enzyme Inhibition Improves Coronary Flow Mediated Vasodilatation
A Praus, S Husain, R Cannon III, A.A. Qayoomi. Cardiology Branch, National Institutes of Health, Bethesda, MD, USA.

In patients with coronary artery disease, endothelial dysfunction impairs coronary vasodilation under 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 BK. 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 abnormal 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 that the endothelium contributes less to metabolic microvascular vasodilation than to flow mediated epicardial vasodilation.
**ABNORMALITIES OF INTRACELLULAR Ca²⁺ HANDLING IN ENDOCARDIAL MYOCYTES FROM RABBITS WITH LEFT VENTRICAL DYSFUNCTION.**

P Neary, MA McIntosh, SM Cobbe, GL Smith. Clinical Research Initiative in Heart Failure, West Medical Building, Glasgow University.

Ca²⁺ entry across the sarcolemma and release from the sarcoplasmic reticulum during systole underlie excitation-contraction coupling in cardiac myocytes. Abnormalities of systolic Ca²⁺ release and subsequent diastolic re-uptake have been found in the impaired left ventricular function. Therefore, we have measured Ca²⁺ transients 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. Ca²⁺ transient duration was significantly prolonged in endocardial cells from ligated hearts at stimulation frequencies from 0.1-2 Hz (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 Ca²⁺ release was markedly reduced in endocardial cells (table). A reduction in systolic Ca²⁺ availability would therefore contrac tion amplitude.

**Abnormalities of Ca²⁺ handling which would contribute to both systolic and diastolic dysfunction are therefore observed in endocardial myocytes in this rabbit model of left ventricular dysfunction.**


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**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 only in dilated cardiomyopathy or also in heart failure of other etiologies. 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 accordingly 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 100μg cardiac myosin emulsified in 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 Myocarditis Ab</th>
<th>Anti-myosin TNF Ab</th>
<th>iNOS staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Yes</td>
<td>58.9pg/ml</td>
<td>1:1600</td>
<td>Yes</td>
</tr>
<tr>
<td>Group II</td>
<td>No</td>
<td>3.5pg/ml</td>
<td>absent</td>
<td>No</td>
</tr>
<tr>
<td>Group III</td>
<td>Yes</td>
<td>14.3pg/ml</td>
<td>1:100</td>
<td>Yes</td>
</tr>
<tr>
<td>Group IV</td>
<td>No</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 non-inflammatory model of heart failure.
**Heart Angiotensin-Converting Enzyme 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 8 months later to assess changes in ventricular function.

<table>
<thead>
<tr>
<th>ACE Genotype</th>
<th>Patients at baseline</th>
<th>Baseline LVEF%</th>
<th>6 Month LVEF%</th>
<th>Change in LVEF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>55</td>
<td>28.7 (10.4)</td>
<td>31.1 (11.13)</td>
<td>+2.2 (9.31)</td>
</tr>
<tr>
<td>ID</td>
<td>143</td>
<td>29.5 (10.7)</td>
<td>31.9 (9.97)</td>
<td>+2.4 (6.37)</td>
</tr>
<tr>
<td>DD</td>
<td>93</td>
<td>29.5 (10.9)</td>
<td>32.4 (9.26)</td>
<td>+1.9 (7.70)</td>
</tr>
</tbody>
</table>

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.

**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±4 years, before and after symptomatic benefit by Doppler echo measurements of right ventricular systolic and diastolic free wall motion and tricuspid 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±80 to 70±50 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.

**Acute Effects of Enalapril and Losartan on Autonomic Function in Heart Failure**

NER Goodfield, BJ Leiper, AD Flapan.
Department of Cardiology, Royal Infirmary, Edinburgh.

The potential mechanisms by which ACE inhibitors (ACEI's) improve prognosis in CCF are diverse and include vasodilatation, improved autonomic tone and improved fibrolytic 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 IHD were studied. After performing a standard set of autonomic function tests (AFT's), they were randomised to receive enalapril 10mg (E) or losartan 50mg (L), orally. BP and heart rate (HR) were monitored. The AFT's were repeated 5 hours after drug ingestion. The study was repeated 2 days later using the other drug.

**Results:**

<table>
<thead>
<tr>
<th>AFT's (mean)</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 AHR (30/15 ratio)</td>
<td>1.13</td>
<td>1.13</td>
<td>1.11</td>
<td>1.10</td>
</tr>
<tr>
<td>Respiration AHR (bpm)</td>
<td>11.42</td>
<td>11.74</td>
<td>12.42</td>
<td>12.16</td>
</tr>
<tr>
<td>Postural ABP (mmHg)</td>
<td>-1.95</td>
<td>-4.47</td>
<td>-2.89</td>
<td>-3.95</td>
</tr>
<tr>
<td>Handgrip ABP (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>3.08</td>
<td>4.84</td>
<td>3.74</td>
<td>3.16</td>
</tr>
</tbody>
</table>

Conclusion: In contrast to losartan, enalapril significantly improved the Valsalva ratio suggesting improvement in parasympathetic and/or sympathetic pathways. Losartan on the other hand appears to have neutral effects on all the AFT's. 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 ACEI's may not be solely due to inhibition of AII and may not be a feature of specific AII receptor.

**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 vs0.05), and a reduction in heart rate (59 ± 4 bpm vs 67 ± 2 bpm vs0.05). 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 vs0.01). 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 equimolar dose of phenylephrine. Phenylephrine 0.5ug/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 almost 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 vs0.01).

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?

MP Love, C Plumptre*, DJ Webb†, AF Davenport, LV McMurray.
MRC Clinical 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 abluminal secretion of the 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 anti-cubital 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 23%) for determination of plasma 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 (2.6±0.4 vs 1.7±0.1 pM [p=0.04] and 2.1±0.3 vs 0.6±0.1 pM [p=0.001] respectively) but only a tendency to a higher level of ET-1 (7.2±1.6 vs 4.7±0.5 pM; 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 (0.9±0.01 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.

IMPAIRED ALVEOLAR-CAPILLARY MEMBRANE FUNCTION PREDISPOSES TO EXERTIONAL ARTERIAL DESATURATION IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

S Puri*, DP Outka, BL Baker, JMB Hughes, and J G F Cleland**.
Department of Medicine (Cardiology), RPMs, Hammersmith Hospital,
London, **CCT Liverpool and and ** MRC CRI in Heart Failure, Glasgow.

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%). The pulmonary diffusion capacity for carbon monoxide (DLco) was measured and partitioned into its subdivisions, alveolar-capillary membrane conductance (Dm) and reactive conductance, using the Roughton and Forster method of measuring DLco 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 > 3% from resting (DESAT), while 43(68%) did not (SAT). DLco, Dm and DLo/Dm are shown in Table 1 along with the percentage of given parameter at rest in the table above. (p<0.05). Comparison of these parameters between the DESAT and SAT groups indicates that patients with significant arterial oxygen desaturation have a higher Dm, which in turn is associated with increased perfusion to the lung alveoli. These findings support the hypothesis that arterial oxygen desaturation occurs when the balance of factors that determine pulmonary gas exchange is altered, and that patients with greater Dm and DLo/Dm have a higher potential for recovery and may benefit from increased oxygen delivery.

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 (75±6%). As wall motion became more co-contraction, the loops became more relaxed in shape maintaining 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/cm) 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±0.6, 1.9±0.4 cm/s) and increase in peak AW power production (3.8±13 vs 2.4±10 mw/cm). Conclusion: CABG improves LV systolic function (co-contraction) and incoordinate AW motion is commonly present in stable pts undergoig CABG and is restored by revascularisation. 2) This early improvement in coordination is associated with an increase in regional myocardial work, independent of conventional 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

R Senior, U Raval, A Lahiri. Department of Cardiovascular Medicine, Northwick Park Hospital, Harrow.

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 fraction: 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.

<table>
<thead>
<tr>
<th>DLco (mmol/min/kPa)</th>
<th>Dm (mmol/min/kPa)</th>
<th>DLo/Dm</th>
<th>SaO2%</th>
<th>SaO2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2±2.7</td>
<td>9.3±5.7</td>
<td>72±13</td>
<td>69±1</td>
<td>94±3</td>
</tr>
<tr>
<td>7.6±1.4</td>
<td>12.8±3.8</td>
<td>61±10</td>
<td>98±1</td>
<td>96±1</td>
</tr>
<tr>
<td>p</td>
<td>0.02</td>
<td>0.01</td>
<td>0.004</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Dm is significantly reduced in the DESAT group compared to the SAT group, and forms a larger proportion of the total pulmonary diffusional resistance (DLo/Dm). 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.
**SERUM URIC ACID IS RELATED TO MARKERS OF IMMUNE ACTIVATION IN CHRONIC HEART FAILURE**

F Leyva, SD Anker, WJ Kan, IF Gedalin, PA Poole-Wilson, AJS Coats. Department of Cardiac Medicine and Wynn Division of Metabolic Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, London.

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 hyperuricoemic 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 (sTNFR1), soluble intercellular adhesion molecule-1 (sICAM-1), (all p < 0.001). IL-6 selective and sTNFR2 (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.

**STRUCTURE OF HUMAN INTRAMYOCARDIAL SMALL ARTERIES IN ESSENTIAL HYPERTENSION**

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Treatment of hypertension significantly reduces mortality due to stroke but not myocardial infarction. A potential mechanism for this relative lack of benefit is a failure to regress the structural abnormalities which occur in small intramyocardial arteries in essential hypertension.

Therefore, human intramyocardial small arteries were obtained from the left ventricle of 23 patients undergoing cardiac transplantation for ischaemic cardiomyopathy (IHD), 8 of whom also had a history of hypertension (HT), (11.6 ± 3.4 yrs). Vessels were mounted in a small vessel myograph as a ring preparation for isometric tension recording. Structural parameters were determined by light microscopy and vessel viability confirmed. Supine blood pressure was measured prior to transplantation. Medication included angiotensin converting enzyme inhibitors in all patients, except one in IHD.

<table>
<thead>
<tr>
<th>lumen media</th>
<th>CSA media:lumen</th>
<th>SBP DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>(μm)</td>
<td>(μm)</td>
<td>(μm²/μm)</td>
</tr>
<tr>
<td>IHD 32±12</td>
<td>9.9±0.8</td>
<td>10.4±1.5</td>
</tr>
<tr>
<td>HT 30±17</td>
<td>13±1.4</td>
<td>12.8±0.5</td>
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Despite “normal” blood pressure, intramyocardial small arteries in treated hypertension had a 7% reduction in lumen diameter and a significant increase in both media thickness and the haemodynamically important media:lumen ratio (p < 0.05). There was no increase in cross-sectional area of the vessel wall in HT Despite being normotensive, blood pressure was slightly higher in HT (SBP and DBP, p < 0.05). These results indicate that treated hypertension is still associated with structural changes in human intramyocardial small arteries, probably related to the higher blood pressure parameters. A failure to reverse such changes in hypertension may predispose such patients to critical ischaemia and dysrhythmias.
Nitric oxide (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 iNOS. There has been particular interest in the role of NOS in mediating cardiovascular responses to vasodilatation, hyporesponsiveness to constrictors, hypertension, 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 differences exist in the human and murine/rat NOS synthase gene. In the present study we explored the effects of key inflammatory cytokines (CTX) on the reactivity of a human blood vessel perfused with blood. 

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 7 cm apart. INF (1ng), IL-1β (1ng) or IL-6 (100ng) were instilled. As response curves to noradrenaline [NA] were constructed before and after 1, 6, and 48 h after instillation of CTX. In order to explore the effects of IL-1β on endogenous NA mediated constriction, the deep-breath venoconstrictor response was studied before and 6h after instillation of IL-1β. Synaptic venoconstriction was induced by occluding subjects to take a single deep inspiration over a period of 5 s, to hold this for a comfortable period (approx 10 s), and then to breathe out slowly before returning to normal breathing. Results and summary: IL-1β and IL-6 decreased the maximal coronary hyperresponsiveness to NA which was greatest 6h after instillation (maximum constriction to NA before instillation was 84±10 and 92±13% of control after cytokines). Neither IL-6 nor INF alone had any effect. The NO synthase inhibitors L-NMMA and aminoguanidine (1µmol/min) significantly reversed the hyporesponsiveness induced by IL-1β. Prior administration of hydralazine (100mg) inhibited the effects of IL-1β. Instillation of IL-1β virtually abolished endogenous venoconstriction due to activation of the sympathetic nervous system. Local infusion of L-NMMA restored the ability of the sympathetic nervous system to cause venoconstriction. Our results show for the first time that a) increased NO modelled dilatation following exposure of a human blood vessel in vivo CTX and b) that IL-1β is a key cytokine for increasing vascular NO generation in humans.

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 adenovalve, Ad.nNOS, containing the neuronal isoform of NOS (nNOS), to carry out 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.BGal (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 (LUL) 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.BGal-infected lungs. NOS activities (Mean ± SD, in pmol NO/mg protein) are shown in the table (*p<0.05):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Left Lung</th>
<th>Left UL</th>
<th>Right LL</th>
<th>Right Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad.BGal</td>
<td>6.3 ± 2.7</td>
<td>5.05 ± 2.7</td>
<td>7.5 ± 2.6</td>
<td>6.1 ± 3.3</td>
</tr>
<tr>
<td>Ad.nNOS</td>
<td>18.6 ± 12.8*</td>
<td>14.0 ± 14.5</td>
<td>23.3 ± 10.2*</td>
<td>8.5 ± 3.4</td>
</tr>
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Specificity of NOS activity was demonstrated by inhibition in the presence of N-methyl-L-arginine (1mM), a specific NOS inhibitor.

Conclusions: In vivo adenoviral gene transfer of NOS via the pulmonary artery results in effective 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.
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, BFR=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 (+3.2±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 angiographically demonstrated improvement in flow-dependent dilatation and in the angina threshold. It suggests that generalised endothelial dysfunction underlies MVA.

THE ROLE OF ANGIOPTENSIN II IN MEDIATING ARAL AND SYMPATHETICALLY 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 arteriolar tone in chronic heart failure (CHF), cirrhotic liver disease (CLD) and healthy subjects and 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) or -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 (5% 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 rennin-angiotensin system activation such as sodium depletion. Angiotensin II and CLD. Despite normal responsiveness to noradrenaline, CHF and CLD are associated with impaired reflex sympathetic nervous system vasoconstriction. ACE inhibition may protect against hypertensiveness 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 PPH) remains undefined. Endothelin-1, thromoxane, nitric oxide and prosacitin 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 67.6±7.1 mmHg and 6 patients had PPH with a mean pulmonary artery pressure of 52.4±6.5 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 0.00 hrs. for the measurement of endothelin-1, 6-keto-prostaglandin F3, thromoxane B2 and nitrate/nitrite. Blood samples were taken from 5 control patients with normal pulmonary artery pressure (16.6±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 endothelin-1 levels tended to be higher during the night, this difference was not significant. When compared to the control group, PPH and PPH patients had significantly higher mixed venous (8.7±1.0 and 7.6±1.6 cf. 5.0±0.5 fmoles/ml, p<0.05) and arterial (8.0±1.4 and 8.4±0.9 cf. 1.2±0.6 fmoles/ml, p<0.05) levels of endothelin-1. In contrast, PPH patients tended to have lower mixed venous and arterial levels of nitrate/nitrite when compared to the control subjects (0.059±0.0192 and 0.059±0.0258 cf. 0.1236±0.0187 and 0.1516±0.0424 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 endothelin-1 which may contribute to the increased pulmonary vascular resistance. The role of prosacitin, nitric oxide and thromoxane, 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 ODEMA AND CONTROL SUBJECTS
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Some people who ascend to high altitude develop pulmonary oedema which is reproduced on repeated exposure. The pathophysiology may be related to pulmonary hypertension. Twelve mountaineers, 7 high altitude pulmonary oedema sensitive subjects (HAPE-S) (age 45.0 yrs) and 5 control subjects (age 39.8 yrs) underwent 20 h ambient pulmonary artery pressure recording in a barochamber. After a day at 4800 m altitude (Zürich), an ascent was made over 6 h 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>Group</th>
<th>Systolic</th>
<th>Diastolic</th>
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<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAPE-S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 480m</td>
<td>19.22</td>
<td>7.36</td>
</tr>
<tr>
<td>Night 480m</td>
<td>23.78</td>
<td>10.39</td>
</tr>
<tr>
<td>Day 4000m</td>
<td>30.64</td>
<td>14.26</td>
</tr>
<tr>
<td>Night 4000m</td>
<td>31.12</td>
<td>14.95</td>
</tr>
</tbody>
</table>

* p<0.02, † p<0.009, †† p<0.0005

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.
A COMPARISON OF METHODS FOR PREDICTING CORONARY RISK IN MEN FREE OF VASCULAR DISEASE

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Prediction of absolute coronary (CHD) risk is important for optimal targeting of antihypertensive and lipid-lowering treatment. Estimates of risk based on the Framingham population are widely used, but predictions from this population may not be valid for other populations. We have compared estimates of CHD risk in men free of vascular disease by four risk functions: the Framingham method, the Dundee method based on the UK Heart Disease Prevention Project, the method based on the British Regional Heart Study (RHS), and a risk function derived from the German PROCAM population. All variables required to calculate CHD risk by the four methods were collected prospectively for 206 consecutive hypertensive men recruited from general practices for an intervention trial, and new referrals to the Sheffield Hypertension Clinic. All men were free of vascular disease. The 206 men had mean (SD) age 58.7 (9.3) years; BP 154/91 (18/10) mmHg; cholesterol 6.0 (1.1) mmol/l; and HDL-C 1.1 (0.3) mmol/l. 18% were current smokers, 32% had parental death from CHD, 11% had diabetes and 2% had ECG-LVH. The annual risk of coronary events was calculated for each man using the Framingham, Dundee, RHS, and PROCAM methods. The methods were compared by the Bland-Altman method, Pearson correlations and paired t tests. The estimated annual CHD rates were for Framingham 2.3 (1.2%); for Dundee 2.2 (1.4%); for RHS 0.6 (0.3%), and for PROCAM 2.3 (2.0%). The RHS estimates were fourfold lower than the other methods (all p<0.0001). Bland-Altman plots showed no systematic error between Framingham, Dundee, and PROCAM methods, but a systematic error between these methods and the RHS risk function. The methods were: Framingham-PROCAM r=0.82, Framingham-Dundee r=0.68, Framingham-RHS r=0.55, Dundee-PROCAM r=0.66, PROCAM-RHS r=0.60. Dundee-RHS r=0.72. The agreement between the Framingham, Dundee, and PROCAM methods as regards absolute risk and absence of systematic error. The correlations were relatively weak, with less agreement at very high CHD risk. The RHS method gave much lower estimates of CHD risk, but the high correlation with the Dundee method suggests a systematic (non random) difference which is yet unexplained. The Dundee method has previously been validated against a second British population, and the Dundee, Framingham, and PROCAM estimates of risk are probably correct. If so, the RHS model is not useful in subjects free of vascular disease.

Vascular smooth muscle cells from human atherosclerotic plaques are highly susceptible to p53-mediated apoptosis or growth arrest

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Myocardial infarction (MI) is caused by rupture of an atheromatous 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 degeneration of cell 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 minigenie or Human Papilloma Virus E6 (which degrades p53), or a chimeric p53 protein which could be activated pharmacologically (p53 ERTM). Apoptosis and cell proliferation were determined and quantified by time-lapse videomicroscopy and flow cytometry. Basal levels of p53 expression or activity was similar in plaque or normal VSMCs, as determined by Western blot or transient transfection of a p53 reporter. Suppression of p53 activity blocked growth 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 pathways 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 apoptosis or 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 marked increased sensitivity to p53-mediated apoptosis. However, the mechanism of p53-mediated plaque VSMC apoptosis may be distinct mechanistically from that inducing growth arrest.

A SURVEY OF ATRIAL FIBRILLATION IN GENERAL PRACTICE: THE WEST BIRMINGHAM ATRIAL FIBRILLATION PROJECT

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To investigate the prevalence, clinical features and management of patients with atrial fibrillation (AF), we surveyed patients in 2 general practices (serving a patient population of 16,510) where 4,522 subjects (27.4%) were aged ≥20 years. Of the latter, 111 patients (2.9%) were found to have AF; males mean age 76.6, s.d.1.5; females were aged 50-60 years, 16.2% age 40-54 years, 26.7% age 55-64 years, 20.7% age 65-74 years, 24.3% age 75-84 years, and 12.6% age >85 years old. Female patients were older than males (79 vs 72 years, t-test p<0.01). 81 patients (75%) had chronic AF, whilst 30 patients (27%) had paroxysmal AF. The commonest aetiological factors were hypertension (36.9%), ischaemic heart disease (28.8%), with a previous myocardial infarction in 12), valve disease (25.2%), hyperthyroidism (15.3%), alcohol excess (5.4%) and cardiomyopathy (5.4%); with no obvious cause for AF in 16 patients. Cardiac failure was associated with AF in 34 patients (30.6%), and stroke in 29 patients (18%). Although 40 patients (36.1%) had a recent blood pressure measurement >160/90 mmHg, only 20 patients were recorded as having had hypertension. Only 20 patients (18%) had an echocardiogram and 26 (25.4%) a chest X-ray. 50 patients (52.3%) had their thyroid function test measured at any time. Warfarin was prescribed to 40 patients (36%), with anticoagulation intensity monitoring by the general practitioner (GP) in 3 cases (7.5%), hospital clinic in 30 (75%) and by both GP and hospital in 7 cases (17.5%). Of those not anticoagulated (n=71), only 12 patients (16.9%) had contraindications to warfarin treatment (including dysynergia (n=5), dementia (3), and chronic renal failure (1)). Patients treated with warfarin were younger than those who were not prescribed warfarin (71.3 vs 79.6 years, t-test p<0.01). Moreover, of the 26 patients who had a positive family history of AF, 11 had a history of AF in a first degree relative. 8 of these had received anticoagulation

DRUGS TAKEN BEFORE THE ONSET OF ACUTE CORONARY EVENTS MAY BE SAVING MORE LIVES THAN THOSE TAKEN AFTERWARDS: EVIDENCE FROM THE GLASGOW MONICA PROJECT

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Definitive proof of the potential value of medication is obtained from randomized controlled trials, but population studies are needed to demonstrate their usage and population impact. Data on acute coronary events in men and women aged 25-64 have been collected from North Glasgow during a decade (1985-94) of rapid change in medication. Registration of events which satisfied World Health Organization criteria for definite myocardial infarction or for coronary death yielded 5,472 events in men and 2,139 in women. Among the items recorded were previous medical history, medication prescribed before the onset of the attack, medication after the onset, place of care, place of death and survival up to 28 days from the onset. During the first seven years of registration (1985-91) there was a revolution in medication given after the onset of the attack, with major increases in usage of thrombolytic drugs, aspirin and beta-blockers, but there was little attendant change in population or hospital care fatality. In 1992-94 case fatality fell but most of the decline was in sudden death outside hospital, the remainder occurring in patients reaching coronary care. Cross-sectional analyses show that long-term medication for previous coronary heart disease substantially reduced the risk of out of hospital death in recurrent events. For various reasons the data have to be interpreted with care, but they suggest that secondary prevention may be of greater potential impact on population case fatality, and therefore on coronary deaths, than is emergency care after the onset of the attack.
PUBLICATION BIAS IN STATISTICAL OVERVIEW OF TRIALS: EXAMPLE OF PSYCHOLOGICAL REHABILITATION FOLLOWING MYOCARDIAL INFARCTION
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University of Wales College of Medicine, Cardiff

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, B 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 80 (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 thrombolytically treated prehospital, 80 doses (82%) were of urokinase 2MIU, 10 (10%) anistreplase, and 8 (8%) streptokinase. In 6 cases ventricular fibrillation was reported within an hour of administration of urokinase; 5/6 re-suscitations were successful; one patient had a fatal asystolic 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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National Heart & Lung Institute, Imperial College, European Association of Nuclear Medicine, and AD Little Ltd, London

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 MRI 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 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/angiogram, 2: Ex-ECG/MPI/angiogram, 3: MPI/angiogram, 4: angiogram. 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: £75 (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 were: strategy 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 PERIOPERATIVE MYOCARDIAL INFARCTION: A PROSPECTIVE, BLINDED STUDY
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Dipyridamole-thallium scanning is usually considered as the 'gold-standard' investigation for assessment of perioperative 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.
ADENOSINE STRESS MYOCARDIAL PERFUSION IMAGING USING ECHO-PHANAL 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 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 intravascular electrophysiology via the right antecubital fossa. Two scans were performed, the first at rest and another during the injection of adenosine at a dose of 140 μg/kg/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 prospectively, 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 demed 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=0.03), 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 experience 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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Aim: 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: 1) 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 25% 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±11 to 114±10 pixels and from 651±83 to 640±85 SD(p<0.05) respectively. Percentage reversibility increased from 11±3 to 14±2.5%.Exercise group(n=15):there was a decrease in the mean extent and severity of the defects from 118±12 to 71±12 pixels and 581±58 to 485±80 SD(p<0.05). Reversibility increased from 14.6±3 to 17±5%. Control group(n=10):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 displayed improved myocardial perfusion characteristics. In patients not exercising, the perfusion defect size and severity increases.
**ASSESSMENT 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 0.5mg of sublingual glycerol trinitrate. Systolic wall thickening was assessed by echocardiography. Left ventricular wall division 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 mean 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(56%) and thallium-201 imaging in 296(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 1.90±0.66 (p=NS). Thus, nitroglycerine enhanced Tc-99m sestamibi imaging is comparable to thallium-201 for the detection of viability in severely dysfunctional myocardium.

**ENHANCED DETECTION OF MULTIVESSEL DISEASE BY SIMULTANEOUS INOTROPIC STRESS Tc-99m Sestamibi SPECT IMAGING AND ECOCARDIOGRAPHY.**

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

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 atropine. Rest and stress MIBI and echo studies were analysed using a 12 segment left ventricular model. Five anterior and septal/posterior 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, 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 ≥ 6 mets, ST depression ≥ 2.5mm or hypotension. Coronary angiography was used as the reference standard and ≥ 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; R²=0.29) and adding both had further incremental value (p<0.001; R²=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 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 Tl 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.

**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 revascularization 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 N-13-ammonia, and the metabolic 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.
PERFUSION IMAGING

that decision scans. which pain. to definitely containing routine stress on normal, mixed with 37 who had evidence of defects; thallium in Four Evans, BM Brown, MJ Frenneaux, University Hospital and University of Wales, Cardiff.

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, reconstructed from short axis 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 inacrt. The network was then tested on new sets of 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 anterior in 90% or inferior/lateral in 9%. 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 value 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, and a reproducible method of inducing this is required for preclinical 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 Seldinger 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 0.1mm 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 medial 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 5-7 days of 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 of 5). Conclusion: Creating a stenosis in the carotid artery endoluminally with a fine tungsten wire which disrupts the medial elastic laminae are two simple, effective and reproducible methods of stimulating neointimal proliferation in the mouse carotid artery.

HIGH RESOLUTION M.R.I. OF THE POPPLITEAL ARTERY WALL IN NORMAL SUBJECTS AND PATIENTS WITH ARTERIAL DISEASE

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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 aneurysms. Seven volunteers (3 male, 4 female aged 35 to 47) and ten patients with popliteal aneurysms 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 aneurysm, 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=21 msec, slice thickness 3mm, gap 1.5mm, 8 cm FOV, 512 x 256 matrix, 2NEX, RBW 8 kHz, superior, inferior and anterior spatial partitioning 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 PERIVASCULAR 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 L-arginine (1-8M L-NAME), an inhibitor of NO synthesis with those to non-competitive (NA) in 20 men and 20 pre-menopausal women. Stimulated NO synthesis was assessed by comparing vasodilator responses to substance P (sP, acting through endothelin-derived NO), ni troprusside (NP) and verapamil (Vrp) 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 endothelin-dependent with endothelin-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 transcutaneous 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 measures 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 m-2) were 26-37% greater than those to L-NAME (1-4 pmol min m-2), whereas, in women, responses to NA (1.17% lower than those to L-NAME (19-30%). The gender difference in relative potency was significant (P=0.0007). Vasoconstrictor responses to sP (0.3-10 pmol min m-2), NP (3-24 pmol min m-2) and Vrp (0.3-160 pmol min m-2) were similar (P=0.76) in men (sP: 63%302%, NP: 71-212%, Vrp: 68-267%) and women (sP: 62-283%, NP: 47-169%, Vrp: 51-249%). 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. The potency of vasodilator responses to the NO-dependent agonist sP (relative to comparator vasodilators NP and Vrp) in men and women suggests 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 diabetes or its risk factors, we studied endothelin-dependent vasodilation with BK (250 ng/ml) and acetylcholine (ACH, 0.300 μg/ml), and endothelin-independent vasodilation with sodium nitroprusside (SNP, 40 μg/ml) before and after enalaprilat (EN, 20 μg/ml). In 16 pts, we repeated the infusions in the presence of L-NAME (64 μmol/ml), 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 (5.8±1.4, 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 3.6±1.1 RI) and ACH (5.3±2.6 to 5.4±3.1 RI) responses. These findings suggest that ACEI selectively improve endothelin-dependent vascular function 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 nmol/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 clear onset vasorestriction (p=0.001; both groups) with a peak mean reduction in FBF of 21 ± 4% in patients with syndrome X compared to 36 ± 3% in the control group (p<0.001; between groups). Vasorestriction to endothelin-1 was negatively correlated with plasma endothelin-1 concentrations (r=0.51; p=0.04).


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Recombinant adeno-viruses 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 (β-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) β-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) β-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 10⁹ pfu/ml had little effect on β-Gal expression in-vivo. (2) Endothelial PMN were not seen ex-vivo but increased with viral titer in-vivo (21 ± 4 ± 2). PMN/section at 8 x 10⁹ pfu/ml vs. 2.0 ± 2.4 at 1 x 10⁹ pfu/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 ± 6.0% relaxation at 1 x 10⁵ pfu/ml vs. 53 ± 5.8% in control CA, at 10⁵ μM ACh; p<0.01). (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 10⁹ 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 proliferation and cell regeneration. 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 inhibitors or antibodies are generally not available. We have therefore developed a novel murine 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 homografted 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 eight days after injury. Results are expressed as mean±SEM.

<table>
<thead>
<tr>
<th>Mouse Strain</th>
<th>Group Size</th>
<th>Endothelial Regrowth (%)</th>
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<tbody>
<tr>
<td>Wild-Type Control</td>
<td>4</td>
<td>83±1.3 ± 1.4</td>
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<tr>
<td>ApoE Knockout</td>
<td>4</td>
<td>*68±2.3 ± 2.2</td>
</tr>
</tbody>
</table>

*p<0.04 (Student’s t-test)

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.

INHIBITION OF MYOCARDIAL CONTRACTION BY ENDOTHELIAL CELLS: EFFECTS OF HYPOXIA AND REOXYGENATION
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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 aortic endothelial and right ventricular endocardial endothelial cells were superfused with normoxic (Po2>160 mmHg) or hypoxic (Po2 50-60 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 superfusate from both cell types induced a rapid, reversible reduction, or a total abolition, of twitch contraction (-44±7.3%, mean±S.E.; P<0.05; n=106) and decrease in cell diastolic length (212±6%; n=85), but no significant change in Ca²⁺ transients, (-12±3±0%; P>0.05; n=106). The figure shows the effect of duration of endothelial hypoxia (left) and reoxygenation (right) on myocyte contraction. Thus, cultured endothelial cells reversibly respond to acute moderate hypoxia by releasing an unidentified substance(s) which inhibits myocyte contraction 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.

HIGH ADENOVIRAL LOADS STIMULATE NFκB DEPENDENT GENE EXPRESSION IN HUMAN VSMCs
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To investigate transgene function by direct gene transfer it is important that the vector itself does not exert significant biological effects on the host cell. The high adenoviral loads required to transduce cells are often accompanied by a local inflammatory response in vitro. We have investigated whether infection of human VSMCs with a replication deficient adenoviral vector expressing no transgene (Adβgal) leads to the activation of NFκB (an important mediator of inflammation) and the induction of NFκB dependent gene expression. NFκB activity in human VSMCs was evaluated by direct immunofluorescence using a monoclonal antibody to the p65 subunit of NFκB. Low level activity was observed in unstimulated VSMCs and substantially increased nuclear staining was observed after infection with Adβgal at 1000 pl/ml or 50ng/ml phorbol ester (PMA). Expression of the NFκB responsive gene Interleukin-1β (ICAM-1) was evaluated by flow cytometry using an FITC conjugated antibody. Basal ICAM-1 expression was augmented by 50ng/ml PMA and after infection with Adβgal at 1000 pl/ml. This induction was attenuated by pretreatment with 100μM Ne-α-Tosyl-L-Lysine Chloromethyl Ketone (TLC), a known inhibitor of NFκB activation. In addition, infection with Adβgal at 1000 pl/ml was able to augment β-galactosidase expression from the CMV-Iβ, a promoter with NFκB response elements. This augmentation was also attenuated by pretreatment with 100μM TLC.

Conclusion. Infection with Adβgal at a high MOI results in NFκB activation in human VSMCs. Infection at 1000 pl/ml is able to augment expression from the CMV-Iβ and induce ICAM-1 expression. This effect of the vector itself has important implications when replication deficient adenoviruses are used at a high MOI in experimental gene transfer.

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. Denudometric 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 α 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.

MODULATION OF BCL-2 AND THE RELATED PROTEINS BAK AND BAX DURING IN VITRO AGEING OF HUVEC
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HUVEC have a finite in vitro lifespan which culminates in the apoptosis of the culture. We investigated the levels of protein and messenger RNA for Bel-2 and the related proteins Bak and Bax during the in vitro ageing of HUVEC by Western and Northern analyses. Western analysis of Bel-2 showed low levels of the protein in passage one cultures which increased at passage two but then remained the same throughout the lifespan of the culture. Bak protein was present at a low level during passage one and two. However it exhibited an increase at passage 3 and decreased again at passage 4, during which the culture reached the end of its lifespan and underwent apoptosis. Bak protein levels appeared to remain the same during HUVEC ageing in vitro. Northern analysis for Bax message gave two transcripts: bakβ 1.5kb and bakα at 1.0kb. Bakα mRNA levels fluctuate during the culture lifespan, showing an increase at passage 4 then decreasing at passage 5 before increasing again at passage 6, which was the end of the in vitro lifespan of the culture. Bakβ mRNA levels decreased throughout the lifespan. Bak mRNA levels increased slightly during the lifespan of the culture and decreased at the end of the in vitro lifespan of the culture. In conclusion, it appears that Bak protein may play a role in signalling end of life apoptosis in HUVEC cultures.
Z-VDAD 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-VDAD (Valine-Alanine-Asparagine) which is an irreversible, specific peptide inhibitor, and the protease CPP32/Apopain can be inhibited by the peptide Z-DEVD (Aspartagin-Glutaminine-Valine-Asparagine).

We have investigated whether these inhibitors could prevent HUVEC from undergoing apoptosis in response to serum withdrawal in vitro. Using a tritiated thymidine assay, Z-VDAD gave 82% inhibition of apoptosis over 24 hours of serum deprivation (n=5) and 61% inhibition over 48 hours (n=3). This was confirmed by time-lapse video microscopy. However, high dose CPP32 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.


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 heparins (LMWH), with high anti Xa activity, have advantages over unfractionated heparin (UFH) that may result in greater efficacy and safety.

Method: 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 ECG changes or prompted 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 revascularisation procedures by 30 days and 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 TRANSOESOPHAGEAL 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 filamentosus lines approximately 1 mm in diameter and 1 cm 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%; 1748 (35%) males and 1352 (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 functional importance of the ETA and ETB 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 artery 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 (50μg/min) caused slow onset vasodilation in CHF patients and control subjects, increasing FBF by 30±5% (p<0.001) and 54±10% (p<0.001) respectively after 90 minutes of infusion (CHF vs controls p<0.05). Conversely, BQ-788 (5μg/min) caused slow onset vasodilation 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 appear to play a important role in regulating peripheral vascular resistance in healthy subjects and patients with CHF. The vasodilator effect of BQ-788 suggests that endothelial ETB receptors mediating vasodilation are functionally more important than smooth muscle ETB receptors mediating vasodilation in the peripheral subjects and patients with CHF. Non-selective ET receptor antagonists may therefore be less effective vasodilator agents than ETA selective antagonists.
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CARDIOPULMONARY INTERACTIONS AFTER FONTAN OPERATIONS: AUGMENTATION OF CARDIAC OUTPUT USING NEGATIVE PRESSURE VENTILATION
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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 anaesthesia. 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 3.8±1.5** 79.2 73.5±1.5** acute 2.4±1.2 3.8±1.8 82.1±0.7 76.5±1.7** conv 2.6±0.9 3.6±0.8* 78.1±1.8 72.7±1.8** 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.

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IS ALTERED CENTRAL PROCESSING OF AFFERENT SIGNALS THE CAUSE OF CHEST PAIN IN SYNDROME-X?
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The aetiology of syndrome X (SX, anginal pain and ischaemic-like changes in the stress ECG during 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 further, we have used position emission tomography with H215O 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 (mean) SD) and 9 CAD patients (7 male, age 61 ± 7 years) were studied. No patient had diabetes or other systemic disease. SX, 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 6/9 SX but in no CAD patients (p=NS). During scan 5 (high dose D) chest pain was reported consistently by both groups (6.3 in CAD vs 7.6 in SX; p=NS). During scan 5, ischaemic-like ECG changes were noted in 5/9 CAD and 8/9 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 perfrontal cortex. The central nervous system abnormalities were 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.

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EVALUATING RISKS AND PERFORMANCE IN CARDIAC SURGERY
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INTRODUCTION: The Perioperative 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 (1,634/4,318), 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 Coxum 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 JTCVS 1994; 107:914). However it has no account of variable risk in a mixed practice. Our 'Variable Life Adjustable Display' or VLAD incorporates an expected mortality 'score' 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.

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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 ± 7.8ms. 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 ± 10.8ms 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.

MAPPING AND ABLATION OF VENTRICULAR TACHYCARDIA USING A NOVEL NON-CONTACT MAPPING SYSTEM
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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 electrogams 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.

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 were 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.

Variable % Odds Ratio(95% CI) P
Bystander CPR 38 2.66(2.16, 3.27) <0.001
Witnessed Arrest 67 5.27(3.00, 8.42) <0.001
999 Call - Arrival (per min) n/a 0.93(0.91, 0.95) <0.001
Site of Arrest (not home) 40 1.71(1.40, 2.09) <0.001

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
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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 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.
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 atioventricular (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-utilty. The primary and only end-point will be all-cause mortality. A pilot study to assess feasibility was initiated in August 1993. 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 323.9m. 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?

I L Williams, M R Thomas, R J Wainwright, D E Jewitt.
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In the UK surgical back up has traditionally been required for PTCA, although this is not the case in some 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 whch 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 post 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 catheter 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, 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 / ICSTM, 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 10-365 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% (1SD = 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 18.5%. 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 (≥5mm) CORONARY LESIONS

I L Williams, M R Thomas, A de Beelder, 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 coronary artery stents were used in 634 patients (693 vessels) in this centre. Of these, 59 patients had ≥50mm 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>Complication</th>
<th>Death</th>
<th>SAST</th>
<th>MI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></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></td>
<td>(6.7%)</td>
</tr>
</tbody>
</table>

Target lesion revascularisation at 6 months:

<table>
<thead>
<tr>
<th>Stenting</th>
<th>PTCA</th>
<th>CABG</th>
<th>TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>rPTCA</td>
<td>8/58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(13.7%)</td>
<td></td>
<td>(6.9%)</td>
<td>(20.6%)</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td></td>
<td></td>
<td></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.
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 Jewitt, 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 optimise 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>25/154 (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>0/94</td>
<td>17/94 (18%)</td>
<td>5/94 (5%)</td>
<td>23/97 (23.7%)</td>
<td>28/7 (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>Post procedure</th>
<th>Prox ref</th>
<th>Distal ref</th>
<th>In-stent MLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/12 angio</td>
<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>
<td>1.7 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.

COLLATERAL CHANNELS ARE MAXIMALLY RECRUITED AT AN EARLY STAGE DURING SINGLE VESSEL CORONARY ANGIOPLASTY
MJ Mason, N Jopson, DJ Patel, S Brant, VE Paul, CDJ Illey. 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 grade 3 collaterals. ST segment analysis demonstrated a trend towards a longer time to 2mm 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.

LESION MOULDING CATHETERISATION IN THE ASSESSMENT OF STENT DEPLOYMENT.
S Eccleshall, P Jordan, J Townsend, H 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 phantom using a new lesion moulding balloon catheter (LMBC). By virtue of 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 3PC) a total of 26 times within peroxysm phantom containing a 9 mm NIR stent (deployed at 8 atmospheres). Phantom stenoses were concentric (internal diameters of 3.5 and 4.0 mm) and eccentric (minimum luminal diam 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 strut indentations on the balloon mould in 1 or more views; diameters and length were measured with Vernier calipers. The results are shown below.

<table>
<thead>
<tr>
<th>Stent size* (mm)</th>
<th>Mean diameter (mm)</th>
<th>Range (mm)</th>
<th>2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric</td>
<td>2.85</td>
<td>2.80</td>
<td>2.77-2.84</td>
</tr>
<tr>
<td>Concentric</td>
<td>3.30</td>
<td>3.12</td>
<td>3.04-3.33</td>
</tr>
<tr>
<td>Eccentric</td>
<td>2.50</td>
<td>2.70</td>
<td>2.52-2.88</td>
</tr>
</tbody>
</table>

%* ncol allowing

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

IN VIVO AND IN VITRO ARTERIAL GENE TRANSFER OF TIMP-1 USING AN ADENOVIRAL VECTOR.
CM Dollery, A McClelland, M Rollience, SC Stevenson, DS Latchman, AM Henney, SE Humphries, IR McEvoy. Department of Medicine (Division of Cardiology), University College London Hospitals Medical School, London, W1E 6DB, England and Genetic Therapy Inc, Gutenburg, MD, USA.

Extracellular 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) potentially 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. Ability to express TIMP-1 was assessed in rat primary VSMC versus cells infected with a β galactosidase expressing adenovirus Avl.Bgal and control cells. Western blotting showed a dose dependent protein expression in response to Avl.TIMP-1. Reverse zymography showed biological 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) (n=3). TIMP-1 is a nitrogen in some cell types but no change in H2 thymidine incorporation was seen versus control cells. Balloon injured rat carotid arteries in vivo were exposed to Avl.Bgal 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 derivd growth factor-BB antibody into injured arterial vessel by microporous balloon catheter

WA Martin, R Aggarwal, M Salame, C Rutherford, GAA Ferns and AH Gerberich. Division of Cardiology, University of Leicester, and William Harvey Research Institute, Charterhouse Square, London & 2School 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-ioidine labelled sheep anti-PDGF IgG in PBS pH 7.4 (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/mm² vessel length.

Results: Data presented as mean (ng/mm² 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 88%. 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-Oroudbadi, KJ Beatit, N Spyrou, PG Camici. MRC CSC, RPPMS, 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 F18-fluoro-deoxyglucose during euglycaemic hyperinsulinaemic clamp. PET viability, based on our previous studies, was defined as a metabolic rate of glucose >0.25mmol/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 restenosed 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 index 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-OCORATION

MH El Hablab, J Williams, J Deanfield, PG Rees, I Sullivan, JFN Taylor

Charing Cross, Great Ormond Street Hospital For Children NHS Trust, London, UK.

The aim is to examine the frequency and type of aneurysm formation after balloon angioplasty of aortic re-occoration (BAAC) in children. In the period from 1990 to 1996, 33 patients underwent BAAC (33 re-occoration). 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. 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 appearance 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 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-occoration 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 reputed 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 Kataria, VS Paul, CBJ Bailey

Department of Cardiology, Harefield Hospital, Middlesex.

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 intravascular doppler. Eighteen patients (14 male, 4 female) aged 54±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 (n=6/group), (1)3x30sec inflations, (2)3x90sec and (3)3x90sec. ST segment shift assessed over precordial leads and anginal intensity (0-10 scale) were recorded at peak ischaemia prior to each balloon inflation. 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>Collaterals</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>flow (cm/s)</td>
<td>0.05</td>
<td>1.2</td>
<td>3.0</td>
<td>5.4</td>
<td>6.3</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 reperfusion.
MYOCARDIAL ISCHAEMIC PROTECTION INDUCED BY HEAT STRESS IS ABOLISHED BY KATP CHANNEL BLOCKADE
TJ Pell, GI Baxter, RW Goodwin, DM Yealon
The Hatter Institute, University College London Hospitals & Medical School, London WCl 6DB

Whole body hyperthermia (heat stress) induces delayed myocardial protection against ischaemia, however, the mechanism is unclear. Since opening of ATP-sensitive potassium channels (KATP) has been shown to be protective we examined their role in heat stress protection. Two structurally dissimilar KATP channel blockers, glibenclamide (Gli) and sodium 5-hydroxydecanoate (SHD) were used in an in vivo rabbit model of myocardial infarction. Male New Zealand White rabbits underwent 15 min of heat stress, under pentobarbitone anaesthesia, at a core temperature of 42±0.2°C, sham controls were anaesthetised only. 24 hours later rabbits were reanaesthetised and subjected to 30 min regional myocadial ischaemia and 120 min reperfusion. 10 min prior to occlusion rabbits received either vehicle, 0.3 mg/kg Gli or 5 mg/kg SHD. The animals were subjected to 30 min ischaemia and 2 hours reperfusion. Risk zone was determined by fluorescent microspheres and infarct zone by triazolium staining. Infarct size was expressed as the ratio of infarct to risk zones. Western blotting confirmed increased expression of the inducible 70 kDa heat stress protein, 24 hours following heat stress, in left ventricular tissue. No significant difference in temperature or haemodynamic data was observed. Prior heat stress resulted in significant infarct size reduction in vehicle-treated animals (from 41.3±4.0% (n=9) to 24.1±4.5% (n=9); p = 0.014 by one-way ANOVA). If this reduction in heat stress was abolished in the presence of either Gli (45.2±6.4% n=9) or SHD (41.5±5.0% n=5) these results suggest that opening of KATP channels is involved in delayed protection observed against ischaemia, as a consequence of prior heat stress. How heat stress influences the regulation of these channels remains unclear at present.

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 problems and pharmacological manipulation of PKC. We therefore investigated preconditioning by expressing isotypes of PKC in isolated neonatal rat cardiocytes. 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 (O2<1%). Six hours of simulated ischaemia increased dead myocytes, 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% (ps0.0001) 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 myocardial 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, cardiocytes 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±6.5% (p<0.001) of the pre-ischaemic value whilst those unable to exclude trypan blue decreased from 68.7±2.8% to 46±13.4% (p<0.01).

These studies experiment the mechanical and possible avenues for therapeutic exploitation of ischaemic preconditioning.

PROLONGING THE DELAYED PHASE OF MYOCARDIAL PROTECTION:ANTI-INFARCT EFFECTS OF ADENOSINE A1 RECEPTOR ACTIVATION ARE MAINTAINED DESPITE REPETITIVE DOSING.
A Duna, GI Baxter, JM Walker, DM Yealon
The Hatter Institute, Division of Cardiology, University College London Hospital & Medical School, London.

In rabbit myocardium, a "second window" or delayed phase of preconditioning is induced 24-72 h after brief ischaemia or adenosine A1 receptor activation. In this study we examined if the heat can be maintained in a preconditioned state by chronic, intermittent A1 receptor activation using the selective agonist 2-chloro-N6-cyclopentyladenosine (CCPA). New Zealand White rabbits (n=10 per group) were treated with repeated i.v. boluses of CCPA 100 μg/kg or 0% saline at 48 h intervals. Forty eight hours after the fifth dose (day 10), the animals were anaesthetised and subjected to 30 min coronary occlusion and 120 min reperfusion. Risk (R) and infarct (I) volumes were determined with zinc cadmium microspheres and triazolium staining respectively and the I/R ratio was calculated. To further explore if the rabbits had developed tolerance to the effects of adenosine A1 receptor activation, a subgroup of animals (n=6 per group) were treated with a final bolus of CCPA 100 μg/kg at the end of the reperfusion period and haemodynamic responses were monitored for 10 min prior to excision of the heart.

<table>
<thead>
<tr>
<th>Group</th>
<th>Rcm²</th>
<th>I/R</th>
<th>Response to CCPA Final Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Δ BP (%)</td>
</tr>
<tr>
<td>Saline</td>
<td>11.9±2.5</td>
<td>45.9±5.5</td>
<td>-0.7±2.4</td>
</tr>
<tr>
<td>CCPA</td>
<td>11.2±0.98</td>
<td>26.6±3.7*</td>
<td>-18±1.6</td>
</tr>
</tbody>
</table>

Figures are Means±SEM, *p<0.01 vs saline (Student’s unpaired t-test).
Following 10 days of intermittent treatment with CCPA there was a significant reduction in I/R ratio (45.9±5.5 vs 26.6±3.7%, p<0.001).
Furthermore, CCPA treatment at the end of reperfusion resulted in similar haemodynamic responses in both groups, indicating that there was no downregulation of the A1 receptors after prolonged CCPA treatment. This study demonstrates that rabbits can be maintained in a preconditioned state against re-infarct injury by repeated activation of adenosine A1 receptors, with no evidence of tachyphylaxis to the infarct-limiting or haemodynamic effects of CCPA. This is the first study to show that the delayed phase of myocardial protection can be maintained by intermittent application of this preconditioning stimulus. This finding suggests that adenosine A1 receptor activation may hold promise as a new approach to long term cardioprotection.

RXRα-DEPENDENT SIGNALING AND CARDIAC GROWTH AND HYPERTROPHY IN VIVO
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Signaling pathways involved in the generation of cardiac hypertrophy have been described with less emphasis on potential growth suppressor mechanisms. Signaling via RXR/RAR heterodimers has emerged as an important modulator of cellular growth and survival. RXRα is known to play a critical role in retinoid-dependent hypertrophy suppression. The purpose has been to examine whether RXRα receptor-mediated signaling is important in postnatal cardiac growth and hypertrophy. We have examined if RXRα regulates growth in a RXRα-dependent manner.

Techniques were used to induce oxidative stress, with the aim of identifying RXRα as a potential mediator of cardiac growth and hypertrophy. Oxidative stress is known to induce RXRα-dependent signaling, and to play a role in the regulation of cardiac growth and hypertrophy. As a result, our experiments have demonstrated that RXRα-dependent signaling is involved in oxidative stress-induced cardiac growth and hypertrophy.

These results provide new insights into the mechanisms that underlie cardiac growth and hypertrophy, and suggest potential therapeutic targets for the treatment of heart failure.

**References:**
ACTIVATION OF MITOGEN-ACTIVATED PROTEIN KINASE SUBFAMILIES BY OXIDATIVE STRESS IN THE PERFUSED RAT HEART

P. J. Sugden, S. J. Fuller, A. Clerk
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There are 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 in 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 reperfusion following ischaemia) to activate the MAPKs. Hearts were perfused with H_2O_2 at concentrations of up to 2 mM. Activation of MAPKs in extracts was determined using in-gel kinase assays with myelin basic protein (for ERKs), GST-c-Jun_S(A) (for JNKs) or GST-MAPKAP2 (for p38-MAPKs). ERK activation was also assessed after Fast Protein Liquid Chromatography on a Mono Q column. p54 and p46 JNKs were activated maximally after 30 min perfusion with 0.5 mM H_2O_2. 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 activation was also activated maximally after 30 min perfusion with 0.5 mM H_2O_2. 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 SB-203580 (a selective inhibitor of 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 H_2O_2. Activation of the ERKs was detected after 5 min perfusion with 0.5 mM H_2O_2. 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.

STIMULATION OF CARDIAC GENE EXPRESSION IN NEONATAL RAT VENTRICULAR MYOCYTES BY GaI3
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In the heart cellular stresses such as ischaemia/reperfusion activate the Jun kinase but not the extracellularly-regulated kinase (ERK) members of the mitogen-activated protein kinase (MAPK) superfamily. This same selective pattern of MAPK activation is seen in NIH 3T3 cells in response to an active GTase-deficient mutant of Ga13 (Goq226L), 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, Ga13 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 Ga13, Goq226L or vector control. The effect on genes known to be upregulated in hypertrophy was monitored using 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 Goq226L stimulated ANF-LUX expression to 2.0±0.47, 1.7±0.17 and 3.2±0.76 of vector control respectively (n=4 myocyte preparations), but there was no effect of wild type Ga13 (1.03±0.13, 0.89±0.10 and 1.34±0.16 of control, respectively). Similarly, β-MHC-LUX and Ska-LUX expression was increased by transfection with 1 μg of Goq226L (1.54±0.16 and 1.54±0.28 of control, respectively, but not by wild type Ga13 (1.39±0.42 and 1.01±0.22 of control, respectively). In contrast, neither wild type Ga13 nor Goq226L had any effect on c-fos-SRE expression (1.05±0.05 and 0.93±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 Ga13 may play a role in the response of the heart to cell stress.

SIGNALLING MECHANISMS MEDIATING α1-ADRENERGIC STIMULATION OF SARCOLEMNAL Na+/H+ EXCHANGER ACTIVITY IN VENTRICULAR MYOCYTES
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Current classification identifies α1-adrenoceptor (AR) subtypes as α1-A, α1-B and α1-D-ARs, which correspond respectively to the recombinant subtypes previously referred to as α1-A1, α1-A2, α1-B1 and α1-D1-ARs; transcripts for all three receptors are present in rat ventricular myocytes. Our objectives were to determine the role of (i) α1-AR subtypes, and (ii) extracellularly-responsive kinase (ERK) activation, in α1-adrenergic stimulation of sarcolemnal Na+/H+ exchange (NHE) activity in these cells. As an index of NHE activity, acid efflux rates (JNa) were determined in single myocytes loaded with the pH-sensitive fluorophore carboxy-SNARF-1, following two consecutive intracellular acid pulses in bicarbonate-free medium. In control cells, 4a-PMA at pH 6.9 (JNa) did not change significantly during the second pulse relative to the first. When the second pulse occurred in the presence of 10 or 100 μmol/L phentolamine (non-selective α1-AR agonist), JNa increased by 142% (p<0.05) and 171% (p<0.05) respectively. The increase in JNa induced by 100 μmol/L phenylephrine was unaffected by preincubation with 3 μmol/L chloroethylnitidine, which inactivates α1-B-ARs, but was abolished by preincubation with 3 μmol/L WB-4101, an α1-A/α1-D-AR antagonist. The phenylephrine-induced increase in JNa was also abolished by preincubation with 30 μmol/L 5-hydroxytryptamide, an α1-A/AR-selective antagonist. Phorbol 12-myristate 13-acetate (PMA) mimicked the effect of phenylephrine and increased JNa by 45% (p<0.05) and 18% (p<0.05) at 10 and 100 μmol/L respectively. The inactive stereoisomer of PMA, its trans isomer, at 100 μmol/L bisindolylmaleimide, a selective PKC inhibitor, abolished the increase in JNa induced by 100 μmol/L PMA but only partially attenuated that induced by 100 μmol/L phenylephrine. These results suggest that (i) α1-adrenergic stimulation of sarcolemmal NHE activity is mediated by the α1-A/AR subtype, and (ii) PKC activation is sufficient to increase sarcolemmal NHE activity, but is not the sole mechanism underlying the α1-AR-mediated response.

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) are extracellularly-responsive kinases (ERKs), c-Jun N-terminal kinases (JNKs) and p38-MAPKs. ERKs are involved in cell growth and differentiation and we have previously shown that they are activated by hypertrophic agonists such as endothelin-1 and phenylephrine in neonatal ventricular myocytes. JNKs and p38-MAPKs are activated by cell stresses. We have shown that hyperosmotic shock and protein synthesis inhibitors activate the JNKs. Here, we have studied MAPK activation in cell extracts by H_2O_2, tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) using in-gel kinase assays with myelin basic protein (for ERKs), GST-c-Jun_S(A) (for JNKs) or GST-MAPKAP2 (for p38-MAPK). ERK activation was also assessed after Fast Protein Liquid Chromatography on a Mono Q column. H_2O_2 (0.1 mM) activated ERKs and JNKs maximally after 15-30 min. TNF-α (10 ng/ml) and IL-1β (100 ng/ml) activated primarily the JNKs, although there was some activation of the ERKs. Activation of JNKs by both cytokines was rapid (maximal at 10 min), but whereas activation by IL-1β had declined to basal levels within 1 h, activation by TNF-α was sustained over this period. Although the protein was detected in these cells by immunoblotting, no activation of p38-MAPKs was detected with any treatment. Phosphorylation of the endogenous JNK substrate, the c-Jun transcription factor, was assessed electrophoretically. Maximal c-Jun phosphorylation was detected after stimulation with IL-1β for 1 h. Activation of JNKs by TNF-α was more sustained than with IL-1β, but maximal phosphorylation of c-Jun was not observed until 1.5-2 h after stimulation and was lost. Since reactive oxygen species and cytokines are known to be produced by the heart during, for example, ischaemia/reperfusion, these results suggest that MAPK pathways may be important in vivo responses to pathologically-important forms of cell stress.
UPREGULATION OF TYPE 3 NITRIC OXIDE SYNTHASE IN CARDIAC MYOCYTES NOT CORONARY ENDOTHELIAL CELLS OF HYPERTroPHIED HEARTS

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Recent studies indicate that nitric oxide (NO) regulates cardiac contractile functions, e.g., 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 guanidium 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 hybridization 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 3.2±0.4 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 (1.2±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.

ANALYSES OF RECOMBINANT MUTANT CARDIAC TROPONIN T IN VITRO AND IN MYOCYTE CULTURE.

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

In view of this, and a recent report of a missense TnT (Ile79Asn) producing increased velocity in the (unloaded) motility assay, we have studied 3 missense TnT 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 TnT 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 TnTs (together with troponins C and I and α-tropomyosin) in E. coli. Analyses of the purified proteins will allow us to examine the Troponin-tropomyosin interaction and, by reconstitution, the impact of TnT mutations on the function of the thin filament.

MYOCARDIAL INFARCTION IS ASSOCIATED WITH APOLIPOPROTEIN-E (APO-E) BUT NOT WITH ANGIOTENSIN-CONVERTING ENZYME (ACE) GENE POLYMORPHISM

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In some studies, the deletion (D) polymorphism of the ACE gene has been identified as a potential risk factor for myocardial infarction (MI). APO-E e4 allele has been associated with premature atherosclerosis. APO-E e2 allele has been considered to be "protective" atherosclerosis and has 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 yrs, 85.7% males) with CAD based on angiographic criteria. Previous MI diagnosis was based on complete hospital charts. Lipid profile, (Total Cholesterol, TC,Triacylglycerides-TG, HDL and Lp(a)) was evaluated. ACE and apoE gene polymorphic fragments were amplified by the polymerase chain reaction. ACE genotype was visualised after direct agarose gel electrophoresis of PCR fragments while apoE genotype was determined after ladder digestion of PCR products and subsequent polyacrylamide gel electrophoresis.

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

<table>
<thead>
<tr>
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<th>N=68</th>
<th>N=71</th>
<th>total 139</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>D/I</td>
<td>D/I</td>
<td>D/I</td>
</tr>
<tr>
<td></td>
<td>allele</td>
<td>allele</td>
<td>allele</td>
</tr>
<tr>
<td>e2</td>
<td>3.6</td>
<td>1.3</td>
<td>3.6</td>
</tr>
<tr>
<td>e3</td>
<td>87.5</td>
<td>87.3</td>
<td>87.4</td>
</tr>
<tr>
<td>e4</td>
<td>11.9</td>
<td>6.3</td>
<td>9.0</td>
</tr>
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</table>

A positive association that reached statistical significance (P<0.015) was observed between myocardial infarction and apo e4 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 non aged sex matched controls (D/I frequency % 58.3/41.7 in patients vs. 56.5/43.5 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 hypercholesterolemic 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.
ANIMAL EXPERIMENTAL RESEARCHERS PRIZE

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 male New Zealand White rabbits (3.14±2.9g). The degree of cardiac dysfunction in vivo was quantified with echocardiography 8 weeks after ligation of the marginal branch of the left circumflex 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 ventricle (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 from n=6 SEM were compared with those from sham-operated rabbits.

RESULTS: Rabbis with HF had a significantly lower in-vivo ejection fraction compared to controls (41±2% vs 74±5%, P<0.001). (a) Measurements of LV systolic pressure (Syst P), end-diastolic pressure (EDP), aortic flow (Flow) and isovolumic relaxation time (IVRT) are shown below in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HF (n=6)</th>
<th>Sham (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syst P (mmHg)</td>
<td>110±6</td>
<td>136±7</td>
</tr>
<tr>
<td>EDP (mmHg)</td>
<td>10±2</td>
<td>8±2</td>
</tr>
<tr>
<td>Flow/m(10-3 ml/s)</td>
<td>2.6±0.9</td>
<td>3.6±1.2</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>95±10</td>
<td>82±2</td>
</tr>
</tbody>
</table>

The hearts had a significant decrease in stroke work and an increase in LV end-diastolic pressure compared to controls. The heart rate, aortic flow and IVRT were significantly higher in HF hearts compared to control hearts. The aortic flow was significantly lower in HF hearts compared to control hearts. The IVRT was significantly longer in HF hearts compared to control hearts. The heart rate was significantly higher in HF hearts compared to control hearts.

During FAIR (0.10±0.05 vs 0.30±0.20, P<0.05). (b) Abnormal long transients were observed in HF hearts (n=14) but not in the control group (n=11). Time 30% decay of the calcium transient was 157.3±13.1 ms in HF hearts compared to 122±12 ms 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±0.05 ms/100 ms vs 1.20±0.20 ms/100 ms in controls (P<0.05). There was also an increased dispersion of the calcium transient durations in HF hearts (P<0.001). (c) MAP duration was longer in HF heart (n=14) as measured in the time from 10% to 90% (13±1 ms) vs 11±1 ms in normals (P<0.001) and there was more dispersion when compared with controls (n=13, P<0.05). There was a significant correlation between the time course of calcium transient duration and the MAP duration in HF hearts (P<0.001).

CONCLUSION: 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 heart which is directly related to mechanical dysfunction. Epicardial repolarisation is delayed in these hearts and dispersal is demonstrated both for isometric and calcium transient durations. These abnormalities may form the basis of the arrhythmogenic tendency in HF.

YOUNG RESEARCH WORKERS PRIZE

ATP-SENSITIVE POTASSIUM CHANNELS AND VENTRICULAR REPOLARISATION

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Increased extracellular and intracellular K+ accumulation shortens the action potential duration (APD) during ischaemia, so promoting arrhythmias. Activation of ATP-dependent 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. The KATP-sensitizer, Rb, was loaded into Langendorff-perfused hearts and the fractional efflux rate (FER) during ischaemia (7.5% control flow) was measured using a 31P-nm resonance technique. [ATP] decreased significantly as acidosis was induced by loading hearts with either 30 mM lactate (metabolic): pH=6.85±0.02, n=9 or increasing PCO2, to 15% (respiratory) pH=6.85±0.03, n=10. Low-flow ischaemia (7.5% control flow) caused initial APD shortening from 237±4 ms to 261±5 ms (n=11, P<0.01) followed by shortening to 213±8 ms at 5 minutes (P<0.01 compared to resting APD0). During APD shortening there was no significant increase in the FER of Rb. However, during APD shortening the FER of Rb increased from 1.9±0.3 ms to 10.1±1.9 ms at 5 min (n=5) during the phase of APD shortening and maximal Rb efflux. Addition of 10 mM glibenclamide abolished APD shortening with a -50% reduction in the FER of Rb after 5 minutes of ischaemia (control: 10±1.9±1.9×10^-3 ±2% vs 7±10±10^-3 ±2% respectively) followed by recovery to 106±1% of 107±1% of 6 min acidosis which was inhibited by glibenclamide. This study has shown that during ischaemia APD shortening precedes increased Rb 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 inhibition 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 KATP channel conductance during ischaemia.

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 (HR) are direct on the heart or mediated by a systemic effect. NO may act as a pacemaker reset or a reflex response to the concurrent changes in arterial blood pressure.

Methods and Results In guinea pig isolated spontaneously beating atria we investigated the chronotropic effect of increasing concentrations of two NO donors (NMDG: 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 (0.1-10 μM) and a decrease in beating rate for high concentrations (millimolar). The positive chronotropic effect of 10 μM SNP (n=28) or 30 μM SIN-1 (n=10) was unaffected by ICa, antagonism with nifedipine (0.2 μM) but was abolished after blockade of the hyperpolarization-activated inward current, If, by Cs+ (2 mmol/L) or DZT828 (1 μmol/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 5 μmol/L SNP caused a reversible, Cs+-sensitive, increase in this current (+130% at -70 mV and +250% at -100 mV).

Conclusions 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 ICa, antagonism but is abolished in the presence of If blockade. Direct recordings from 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 sinoatrial node's role in maintaining normal heart rate, and which accompanies pathophysiological conditions associated with an increase in myocardial production of NO (e.g. heart failure and septic shock).

THE IMPORTANCE SLEEP DISTURBANCE IN CHRONIC HEART FAILURE

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Background: Sleep 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 STEPS was a cross-over study of 73 patients (NYHA classes I and II) randomly allocated to receive (a) no treatment (all NYHA classes) and 45 normal subjects 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, cross-over study of nocturnal oxygen vs air. Sleep quality was assessed by polysomnography. Results: Mean (SEM) ESS score was higher in patients than controls (8.3±0.4 vs 6.5±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 (1.0(0.3) vs 0.6(0.4)sec; P<0.01) and they hit more obstacles on the driving simulator (77(7) vs 33(4); P<0.01). Desaturation was more severe in patients than controls, 23/85 patients had CSR. The desaturation index correlated with the reaction time (r=-0.5, P<0.01, n=45). There was no correlation between either desaturation or reaction fraction and the level of cognitive impairment. Serial arrhythmia was not observed. Overnight oxygen stabilised breathing and improved sleep quality. Conclusions: Nighttime 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 investigate further the influence of sleep on heart failure.
CANDOXATRIL IMPROVES EXERCISE CAPACITY IN PRACTICES WITH CHRONIC HEART FAILURE RECEIVING ANGIOTENSIN CONVERTING ENZYME INHIBITION

DE Newby, T McDonagh, PP Currie, DB Northridge, NA Boon, 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 bid) 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.

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

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Plasma levels of endorphin-1 are raised in heart failure and correlate with pulmonary haemodynamics in this setting. We administered endorphin-1 to nine patients with left ventricular dysfunction with or without overt heart failure in an attempt to study local pulmonary vascular effects. Intra-vascular Doppler ultrasonad was used to assess local pulmonary blood flow in the first 4 patients. Haemodynamics were measured by thermodilution catheter and arterial line. Endorphin-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

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<tr>
<th></th>
<th>Baseline</th>
<th>Peak</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>Heart rate</td>
<td>70±15</td>
<td>71±14</td>
<td>ns</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>90±8</td>
<td>106±11</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Mean pulm artery pressure</td>
<td>21±7</td>
<td>21±7</td>
<td>ns</td>
</tr>
<tr>
<td>Pulmonary wedge pressure</td>
<td>13±6</td>
<td>14±7</td>
<td>ns</td>
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<tr>
<td>Cardiac index</td>
<td>2.4±0.2</td>
<td>2.2±0.5</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>1697±397</td>
<td>2048±450</td>
<td>p&lt;0.002</td>
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<tr>
<td>Pulmonary vascular resistance</td>
<td>151±46</td>
<td>142±44</td>
<td>ns</td>
</tr>
<tr>
<td>Resistance ratio (PRV/SVR)</td>
<td>0.09±0.03</td>
<td>0.07±0.02</td>
<td>p&lt;0.001</td>
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Exogenous endorphin-1 causes systemic but not pulmonary vasoconstriction in patients with left ventricular dysfunction. Raised pulmonary endorphin-1 may be a marker, as opposed to a mediator of pulmonary hypertension in heart failure.

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

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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 (V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope) is high in many chronic heart failure patients. The objective of this study was to investigate the prognostic significance of the V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} 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.±14.6%) who had a cardiopulmonary exercise test performed (peak oxygen consumption 15.±7.3 ml/kg/min, V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope 34.8±10.6) were studied. Using 1.96 standard deviations above the mean level of the V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope of 68 healthy age-matched controls (56 men; age 56.±7.5 years; peak oxygen consumption 32.5±6.3 ml/kg/min; V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope 26.±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 V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope (mean 43.1±8.9). In the multivariate Cox proportional hazards model using several variables (age, peak oxygen consumption, V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope, left ventricular ejection fraction), the V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} 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 V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} regression slope had a survival of 95% compared with 69% for patients with a high slope (P<0.0001). In conclusion, the V\textsubscript{E}-V\textsubscript{CO\textsubscript{2}} slope is useful in the prognostic assessment of chronic heart failure patients.

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

J Nolan, PD Batini, 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 the aim. 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 holter variables. We studied 433 ambulant patients with signs and symptoms of CHF (age 62±10 years, NYHA 2.4±0.5, frusemide 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>
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<tr>
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<th>x2</th>
<th>p</th>
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<tbody>
<tr>
<td>SODIUM</td>
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<tr>
<td>SDNN</td>
<td>33.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>NYHA</td>
<td>17.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>CREATININE</td>
<td>14.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>CARDIOTHORACIC RATIO</td>
<td>5.4</td>
<td>0.02</td>
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Odd ratios 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 5.1-23.6). 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.
The predictive value of natriuretic peptide estimation for detecting new heart failure in general practice

Cowie, MR Wilson, The predictive be poor, to new Imperial School, Dundee; London; School, respectively, pred. & NT-ANP referred to a rapid access 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 that 35% of the 122 (29% referred patients had new heart failure. The median level of ANP, BNP & NT-ANP (mmol/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>Peptide</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Pred. Value (%)</th>
<th>Negative Pred. Value (%)</th>
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<tr>
<td>BNP</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>97</td>
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<tr>
<td>ANP</td>
<td>94</td>
<td>72</td>
<td>66</td>
<td>44</td>
</tr>
<tr>
<td>NT-ANP</td>
<td>70</td>
<td>55</td>
<td>54</td>
<td>98</td>
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<tr>
<td>ANP</td>
<td>98</td>
<td>98</td>
<td>98</td>
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</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 Davies, St Mary's Hospital, London, UK. Northwestern Memorial Hospital, Chicago, IL, USA.

Atrial flutter (AFL) results from macroreentry in the right atrium (RA) and was analys 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 electrogroms which are superimposed onto a computer model of the endocardium creating isopotential and isochronal maps.

Maps of AFL were used to guide successful ablation (RF) in all pts with more detailed analysis performed later. 3 pts had failed previous RF. The entire AFL circuit was shown in 1 pt with, and both pts without, previous RF. The istmus (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 AFL 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 TA 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 DYSPEA IN THE ELDERLY

MY Henein, CA O'Sullivan, GC Sutton, AJS Coats, DG Gibson. Cardiac Department, Royal Brompton Hospital, London and Hillingdon Hospital, Middlesex, Uxbridge.

Limitation of exercise tolerance by breathlessness is common in the elderly and has been ascribed to diastolic dysfunction when LV systolic function has been deemed normal. 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, aged 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 dyspea 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 hypokinesis 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 Zaidi, MJ Galloway, KJ Lipscomb, MJ 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 macroneurent circuit in the right atrium (RA), propagating in an antioniclockwise 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, recurrence 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 decapoles 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 posterolateral RA (PLRA) activates late. If conduction persists, the PLRA activates early via the IVC-TAI. After unidirectional (antio clockwise) 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 54 +/- 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 BACHMANN'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.

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

RC Saumarez, J Vandenberg 1, MP Zinkin 1, MD Lowe 2, PJ Taylor 1, DE Ward 1, AJ Camm 2, AA Grace 1
1Department of Cardiological Sciences, St. George's Hospital Medical School, London; 2Departments 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 350 ms and just below VERP.

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 epicardial sites in the perfused ferret heart. LQT1 has been modelled using antisense and to inhibit inactivation of SCN5A-encoded hERG. 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.

THE USE OF ATROPINE TO ENHANCE SUCCESSFUL CARDIOVERSION FROM ATRIAL FIBRILLATION

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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.

β-ADRENOCEPTOR STIMULATION INCREASES DISPERSION OF CARDIAC REPOLARISATION

MD Lowe, PF 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 venous venetron. However, there have been no large studies to examine this hypothesis.

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β1-adrenoceptor stimulation increases in 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 salbutamol 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 Steven
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 cardiac pacing in patients with previous pericardiectomy using direct venous 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 obstruction who had had previous pericardiectomy but in whom epicardial electrodes were exiting exit block. In the study group follow up measurement of stimulation threshold, sensing threshold and chronic lead impedance are comparable to those observed 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 obstruction with previous pericardiectomy.

SHOULD MODE SWITCHING DDDR PACEMAKERS BE USED IN ALL PATIENTS WITH A HISTORY OF ATRIAL TACHYARRHYTHMIAS?
K Khamadva, A Ketkasik, K Tan, G Lloyd, H Bird, C Bucknall, N Sulke, Goy’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 those which do not have the feature. 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) (14 male, mean age 63 (SD 12)) 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 antarrhythmic drugs. The following variables were analysed in a multivariate model to predict the development of chronic persistent AF/AFL: age, sex, incidence 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 the 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 considerable financial savings.

SUBPECTORAL ICD IMPLANTATION: COMPARISON OF PATIENT ACCEPTABILITY UNDER LOCAL AND GENERAL ANAESTHESIA
KJ Lipscomb, NJ Linker, AM Zaidi, A Fitzpatrick. 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 preprocedural 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 submucosally and require testing of defibrillation thresholds at implant. We report the acceptability of local anaesthesia (LA) with conscious sedation in 14 patients undergoing submucosal 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 achieved with 0.5% Bupivacaine. 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
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Baroreflex sensitivity (c) is a useful predictor of prognosis after myocardial infarction, but has traditionally required invasive techniques (intravascular phenylephrine) to measure it. We have compared two non invasive techniques (Valsalva and spectral analysis) with intravascular 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 apine rest were recorded in random order. Phenylephrine (PE) was then infused at up to 200mg/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). Eachual baroreflex sensitivity, c(PE), was estimated from the relationship between AP pressure 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(PE) agreed with measurements of c(mf) (mean difference 1.06 mmHg/min 95% CI -7.4 to 9.6 mmHg/min) and with those of c(hf) (mean difference -0.5 mmHg/min 95% CI -15.4 to 14.4 mmHg/min) but not with those of c(PE). 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.
(108) MIDDLELINE: A ROLE IN THE MANAGEMENT OF NEUROCARDIOGENIC SYCOPE
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 vasoconstrictor in influencing symptoms from 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 syncopal episodes and <20 syncope free days per month) and reproducible syncope during head-up tilt studies were enrolled 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 (electrocardiograph), phasic blood pressure (digital photoplethysmography) and thoracic fluid index (trans thoracic 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<0.001). Eleven patients reported a positive therapeutic response on midodrine (p<0.002) 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 (14.6%) patients had a reproducible syncopal response 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.

(109) ONE STOP CHEST PAIN CLINICS: DO THEY WORK?
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For patients with suspected ischaemic heart disease, exercise stress testing provides important information concerning prognosis as well as diagnosis. In the UK patients with chest pain are usually seen in the outpatient department; an exercise stress test is subsequently booked following which patients are reviewed in the outpatient department. The 'one stop' chest pain clinic provides a more streamlined approach. Patients are seen, exercised, and the results discussed at a single outpatient visit. Patients with immediate and rapid assessment also benefit patients and avoids unnecessary follow-up appointments. However such a service can only work if appropriate patients are referred. This paper reports the results from the first year of a new 'one stop' chest pain clinic in a district general hospital. The service was promoted to general practitioners and broad guidelines were given. One quarter of all new patient appointments were reallocated to the 'one stop chest pain clinic'. 214 patients were referred in the first year, 126 (59%) gave a history compatible with ischaemic heart disease (IHD) whereas the rest had non-cardiac symptoms. Of the 126, 22 had suffered from previous myocardial infarction, 5 had undergone revascularization and the remainder had effort angina only. In all patients, the median duration of symptoms was 19 months (range 1 to over 99). 61 were receiving aspirin, 56 regular nitrates, 43 a calcium channel blocker and 35 beta-blockers. The mean cholesterol was 6.4 mmol/l and only 12 were receiving lipid-lowering medication. All but 2 patients underwent an exercise stress test and there were 60 (29%) positive tests of which 24 (11%) were strongly positive. Median exercise time was 372 seconds (range 44-736) and median heart rate at peak exercise was 152 (range 87-210). In those patients HSS 55 (44%) had positive tests with 23 (18%) strongly positives whereas in those with a non-cardiac history, there were 5 positives. In terms of overall clinical outcome, 29 (14%) patients were referred directly for angiography, 150 (70%) were discharged and only 35 (16%) were brought back for further assessment. In conclusion, nearly one third of patients referred to the clinic had ischaemic heart disease and very few were unsuitable for exercise. For the majority of patients management was decided after just one visit with 14% undergoing angiography and (70%) being discharged back to their general practitioner. One-stop chest pain clinics could be extended to other district general hospitals.

(110) NOTTINGHAMSHIRE OUT OF HOSPITAL RESUSCITATION: IMPACT OF THE CHANGING TYPE OF AMBULANCE SERVICE
LH Soo, D Gray, T Young, AM Skene, JR Hampton Division of Cardiovascular Medicine, University Hospital Nottingham.

The county ambulance service has gradually increased the usage of Paramedic personnel in its response to emergency calls. We examine the impact of this policy by studying a total of 1815 out of hospital resuscitations from 1991 to 1994. All resuscitations were carried out either by Paramedic personnel who have extended ambulance training or by Paramedic practitioners who were only trained in basic life support and the use of a defibrillator. A total of 1394 (76.8%) patients were cardiac in aetiology (ICD of 390 to 429) of which 536 (38.4%) resuscitations were carried out by a Paramedic crew as the only responder without any outside assistance while 451 (32.4%) resuscitations were carried out by a Technician crew as the only responder without any assistance. The mean age of the patients in these two groups were 66.6 and 66.7 respectively. Comparison of the two groups showed no significant differences in sex, history of previous myocardial infarction (25.7% vs 26.9%), arrest being witnessed (76.1% vs 74.4%), initial presenting rhythm of ventricular fibrillation (59% vs 55.4%) or bystander cardiopulmonary resuscitation (35.5% vs 31.6%). Patients attended by a Paramedic crew were more likely to reach the Accident & Emergency Department alive and be admitted to a hospital ward (88 (16.4%) vs 36 (8.0%), Chi-squared = 15.87, p<0.001, df = 1, alpha = 0.05). However there was no significant difference in patients' chances of survival once they had been admitted into a ward (39 (7.8%) vs 24 (5.6%), Chi-squared = 1.57, p = 0.211, df = 1). The unadjusted odds ratio for mortality for patients attended by a Paramedic crew was not significantly different from that of patients attended by a Technician crew (OR = 0.88, CI 0.63 to 1.22).

(111) Aggressive reduction of door-to-needle times increases the incidence of inappropriate thrombolytic therapy in patients with suspected AMI
AD Kelion, M Shahi, JA Bell. Cardiology Dept, Battle Hosp, Reading.

Optimal management of acute myocardial infarction (AMI) requires administration of thrombolytic therapy as soon as possible after admission to hospital, but the benefit applies only to patients (pts) who fulfill specific clinical and ECG criteria. We have employed an aggressive policy to reduce door-to-needle times since Jan93. Pts with chest pain are admitted directly to CCU, where staff have received specific training. We investigated whether this approach has affected the accuracy of administration of thrombolysis.

All pts admitted to CCU with AMI, or who were thrombolysed, were identified retrospectively Oct91-Jan92 and Oct94-Jan95, representing times before and after implementation of our policy. AMI was diagnosed on the basis of 2/3 of the following: 70mm ischaemic chest pain; new Q waves or persistent 1 wave changes in the ECG; peak CK >2x upper limit of normal. Pts were considered eligible for thrombolysis if they had been admitted within 12h of the onset of pain, had no contraindications, and the admission ECG showed ST elevation or new LBBB. Blinded review of the accuracy of thrombolysis was performed.

During the initial study period, 66 pts with AMI were admitted with a mean age (SD) 63(11).j. During the later period, 76 pts with AMI were admitted with an increased mean age (SD) 70(11) (P=0.018). This reflected increased access to CCU now given to elderly pts. The two groups were otherwise comparable. The mean (SD) door-to-needle time for all pts who received thrombolysis on admission decreased from 61(70) to 19(20)min (P=0.0004). The proportion of pts eligible for thrombolysis who received treatment increased from 24/38 (63%) to 30/100 (100%) (P=0.0002). However, the proportion of pts receiving thrombolysis who did not fulfill our criteria also increased, from 3/2 AMI without ECG criteria, 1 unstable anagina/27 (11%) to 11/8 AMI without ECG criteria, 3 unstable anagina/41 (27%) (P=0.117). There were no complications of thrombolysis in the initial study period, but 2 CVAs in the later period: both pts fulfilled our criteria. Their treatment 1 month survival was 52 (79%) for the initial period and 63 (83%) for the later period (P=NS).

We conclude that simple measures greatly reduced door-to-needle times and led to a higher proportion of eligible pts receiving thrombolysis. However, greater pressure on medical staff to make rapid management decisions increased the proportion of pts being thrombolysed inappropriately. This may dilute any potential benefit achieved by aggressively reducing door-to-needle times.
COST OF MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION IN THE THROMBOLYTIC ERA
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In our 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, 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 was obtained from the finance department.

Results: Using data obtained as described above the cost per patient per hospital admission for AMI was £1513. The total cost to the hospital of AMI for the time studied was £14,685,730 or approximately £1.5milsion 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

IM McGee, A Montgomery, HH Morgan
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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% of patients died in hospital and over 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 (median) 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% antiagregants, 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 not knowing whether 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.

ACE INHIBITOR USE AFTER MYOCARDIAL INFARCTION: DOES AUDIT CHANGE CLINICAL PRACTICE?
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Department of Cardiology, Hull Royal Infirmary, Hull

The publication of several landmark studies (SAVE, AIRE, GISSI 3 and ISIS 4) confirming a beneficial effect of Angiotensin Converting Enzyme Inhibitors (ACEI) after myocardial infarction (Ml), 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 notes review of consecutive MI patients admitted to CUU 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).

ACEI + 20 (62.5%) 18 (85.7%) 27 (69%)
ACEI - 11 (37.5%) 3 (14.3%) 12 (31%)

ACEI + 13 (43%) 4 (80%) 16 (50%)
ACEI - 7 (25%) 1 (20%) 6 (50%)

P Value 0.097 (ns) 0.75 (ns) 0.099 (ns)
(+ derived from a Chi squared analysis)
(mean ACEI given, - means no ACEI given)

Despite an 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-INFARCT RISK REDUCTION WITH LIPID THERAPY IN THE UK: THE ASPIRE SURVEY


To measure the potential for secondary coronary prevention in the UK, the British Cardiovascular 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 & 63 yrs) were studied. 121 (51 male) had died by the time of interview and were replaced in the sample. 247 (84%) male & 235 (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 a treatment that was hypolipidemic medication. The respective values for females were 190 (61%), with 18 on hypolipidemic medication. (The number of patients on medication with TC >5.5 was 7 (3%) in males & 5 (2%) in females). The survey found that 63% of male and 61% of female UK AMI survivors <70yrs, further improvement in lipid management was indicated to bring their TC >5.5 mol/l. The 4S study showed a reduction of 37% over 5yrs 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 <70yrs from any one year, this would equate 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 10 consecutive years, for 3555 male 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

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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 years 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 (79.48%) in 1982 to 692 (72.28%) 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 outwith the 12 hour time frame for thrombolysis in 1992. Use of proven drug treatment increased, B blockers from 14% of patients in 1982 to 56% in 1992, aspirin was used in over 70% of patients from 1989 and thrombolysis 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.

Conclusion: Despite an increasing uptake of the "proven" therapies, in-hospital mortality from myocardial infarction did not change between 1982 and 1992 highlighting the differences between results in clinical trials and those applied to a typical hospital population of unselected patients.

EVALUATION OF A COMPUTER GENERATED DISCHARGE SUMMARY FOR PATIENTS WITH ACUTE CORONARY SYNDROMES

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Discharge summaries are usually delegated to junior staff and medical secretaries. Completion rates may be low, the quality of information variable, and delays in preparation and transmission prolonged. Recognising these deficiencies (and pressure from purchasers) led to design of a computer-generated discharge summary for patients with acute coronary syndromes. A structured format was chosen detailing diagnosis, episode of care, risk factors, cardiac history, emergency treatment, complications, further investigations, prevention strategies, discharge medication and follow-up. The summary is integrated with the CCRU database which is relational and tab-driven, using drop-down menus for uniform data-entry. It utilises a relatively limited data set, currently 75 fields, incorporating multiple functions within pre-defined fields for automatic entry of all derived variables. The field-transformation capabilities of the package permit generation of the summary in a separate layout. Seamless retrieval of general practitioners' addresses and fax numbers allow prompt transmission of summaries. During the first year of the computer-generated discharge summary, 90% of the 359 patients treated in the CCRU with myocardial infarction and unstable angina had a summary generated by the system in a median delay of only 5 days to transmission. In order to assess general practitioner satisfaction with the newly designed summary, all local practices were sent a carefully designed questionnaire, together with a 'twinned' example of the computer generated and standard SHO-dictated summaries for 3 separate patients. Of the 85 responses, 64% preferred the computer generated format emphasising its concise style, readability, and ease of access to relevant information. Importantly, 73% of respondents found that the computer-generated discharge summary provided a clearer management plan and 69% favoured the similar format for other specialties. In conclusion, the computer-generated discharge summary, designed for patients with acute coronary syndromes, can be rapidly generated with a high completion rate, reducing the 'unseen' workload of junior staff. Moreover, it is preferred to conventionally prepared discharge summaries by our local general practitioners.

POPULATION SCREENING WITH NARIURETIC PEPTIDES TO DETECT A WALL MOTION SCORE INDEX OF ≤1.2

Cardiology Department, Western Infirmary, *Scottish 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 1089 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% (56), of whom 67% 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>WMI ≤1.2</th>
<th>Median N-ANP (pg/ml)</th>
<th>Median BNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>1.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>3.2</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Receiver Operator Characteristic analysis to detect a WMI ≤1.2 resulted in a BNP concentration of 8.8 pg/ml giving a sensitivity of 80% and a specificity of 57% for detecting a WMI ≤1.2; an N-ANP concentration 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

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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 ≤5.5mmol/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 ≥6.5mmol/l using the PROCAM external standard. The sensitivity and specificity of the various methods is shown in the table below.

<table>
<thead>
<tr>
<th>Method</th>
<th>CHD risk (%) targeted</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>CHD risk when treated</th>
<th>CHD risk when not treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheffield TC</td>
<td>52</td>
<td>96</td>
<td>4.5</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Sheffield TC:HDL</td>
<td>97</td>
<td>82</td>
<td>2.8</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Joint Euro Task Force</td>
<td>100</td>
<td>26</td>
<td>2.6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Joint Euro Task Force</td>
<td>98</td>
<td>37</td>
<td>2.6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>TC 26.5mmol/l</td>
<td>50</td>
<td>51</td>
<td>2.4</td>
<td>2.1</td>
<td></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 unacceptable inaccurate. It remains to be shown whether use of the TC:HDL ratio is accepted readily by ordinary doctors.

LV Systolic Dysfunction After Open Repair of Simple Defects in Infants and Children: Quantification With a Conduit Catheter After Bypass
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 (Ed) elastance. In 13 patients (11ASD, 1 double-chambered RV, 1 supravalvarAS, age0=25.1±4.4 years, weight 3.1±4.6kg) LV function was measured from real-time pressure-volume loops using conductance and microtip pressure catheters placed in the long-axis via the LV apex. Basal dp/dt max normalised to maximal developed pressure [(dp/dt max/Pmax) 3.6% per year]. In 17 (11ASD, 1 double-chambered RV, 1 supravalvarAS, age0=25.1±4.4 years, weight 3.1±4.6kg) LV function was measured from real-time pressure-volume loops using conductance and microtip pressure catheters placed in the long-axis via the LV apex. Basal dp/dt max normalised to maximal developed pressure [(dp/dt max/Pmax), Pmax normalised to end-systolic pressure [(dp/dt max/Ps)] time constant of isovolumic relaxation(t), 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>Procedure</th>
<th>Pre-bypass</th>
<th>Post-bypass</th>
<th>%change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ees(mmHg/ml/kg)</td>
<td>0.3±0.1</td>
<td>0.2±0.1</td>
<td>-40.7(0.001)</td>
</tr>
<tr>
<td>Eed(mmHg/ml/kg)</td>
<td>0.06±0.1</td>
<td>0.1±0.1</td>
<td>78.3(0.57)</td>
</tr>
<tr>
<td>[(dp/dt max/Pmax) 3.6% per year]</td>
<td>8.3±1.42</td>
<td>8.9±1.29</td>
<td>7.7(0.17)</td>
</tr>
<tr>
<td>[(dp/dt max/Ps)] t (sec)</td>
<td>11.75±3.19</td>
<td>10.92±2.4</td>
<td>-7.1(0.24)</td>
</tr>
<tr>
<td>45.8±18.6</td>
<td>44.3±12.8</td>
<td>-3.3(0.76)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: This is the first study to demonstrate the utility of a conduit 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.

The atrial septum in fetal Hypoplastic Left Heart Syndrome
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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 chorionic specimens of 117 fetuses with this syndrome were examined. The site and patency of the foramen ovale together with the attachments and thickness of the flap valve were documented. The same parameters were examined in 21 fetuses without aortic stenosis with similar type of abnormality. The morphology of the foramen ovale showed wide variation. Premature closure was rarely encountered (4/172). The site of the foramen ovale ranged from severe hypoplasia (20/172) to a normal (12/172) or dilated foramen ovale (117/172). 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 stenosis and a patent, hypoplastic mitral valve (group 2, 45 of 117) showed a combination of the features found in groups 1, 2, 3 and 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 more likely to be a result of HLHS whereas severe hypoplasia of the limbus cannot be excluded as a cause for reduced flow into the left heart leading to the syndromes in some fetuses.

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

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The medium term success 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 Tc-99m Sestamibi myocardial single photon emission computed tomography (triple head gamma camera), we studied RV myocardial perfusion, wall motion, wall thickening and ejection fraction in thirteen adolescents/young adults who had undergone atrial baffle repair for simple TGA at median 6 (range 3-30) 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 35/156 (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 thickening 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 (ventricular) septum 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.
GROWTH RETARDED FETUSES SHOW DIFFERENT BIOPHYSICAL PROPERTIES OF THE AORTA: SUPPORTIVE EVIDENCE FOR FETAL PROGRAMMING?
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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<0.001). Spectral analysis of the pulse wave amplitude (the "elastic recoil") was slower (3.38 ±0.74 vs 4.32 ±0.83 mm/s, p=0.0058). There were no differences in the 3rd vs 2nd day of pregnancy in SGA vs N. Measurements of elastic recoil remained lower in the SGA group after birth, but there were no differences in PWV. These differences in intrauterine waveform characteristics support the hypothesis that growth retardation is associated with abnormal arterial development, the origin of which may be either increased arterial wall stiffness, or may reflect the increased afterload of the feto-placental 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,
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Background: Strategies to induce allotraft tolerance can be employed in small laboratory mammals. Objective: To assess at a cellular and molecular level whether tolerance occurs in the cardiac allotraft 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 7 assays following routine orthotopic cardiac transplantation. Limiting dilution analysis is the most qualitative 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 (APCs). Plates were irradiated prior to the addition of an IL-2 sensitive indicator cell line (CTL) 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 compared to CTL frequencies. Tolerance demonstrated by HTL was paralleled by CTL frequencies in 4 of these 5 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>HTL Patient V5 donor APC</th>
<th>Patients V5 donor APC</th>
<th>CTL Patient V5 donor APC</th>
<th>CTL Patients V5 donor APC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (4.0)</td>
<td>1/102218</td>
<td>&lt;1/50000</td>
<td>&lt;1/50000</td>
<td>&lt;1/50000</td>
</tr>
<tr>
<td>D (5.0)</td>
<td>1/108767</td>
<td>&lt;1/50000</td>
<td>&lt;1/50000</td>
<td>&lt;1/50000</td>
</tr>
<tr>
<td>E (6.0)</td>
<td>1/120294</td>
<td>&lt;1/25000</td>
<td>&lt;1/25000</td>
<td>&lt;1/25000</td>
</tr>
<tr>
<td>F (7.0)</td>
<td>1/118300</td>
<td>&lt;1/20000</td>
<td>&lt;1/118305</td>
<td>&lt;1/20000</td>
</tr>
</tbody>
</table>

Conclusions: These data are the first demonstration in man as in the rodent model, prolonged residence of an allotraft can be accompanied by tolerance in T cells with direct alloreactivity. This is in contrast to both donor HLA class I and II molecular determinants. These data have implications for graft outcome, adjustment of immunosuppression, and patient monitoring.
'EARLY' TRANSPLANT ASSOCIATED ORINARY ARTERY DISEASE: ITS RELATIONSHIP TO ACUTE REJECTION, HLA MISMATCH, AND DONOR RECIPIENT PHENOTYPE

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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), later (3-14yrs), none (clear angio>3yrs). 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 Later 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. 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=0.002 at 3 months and p=0.001 at 1 year. We were also able to show the early development of TxCAD portends a significantly worse prognosis compared to the other groups p<0.001, 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 mismatches 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 aetiology of this with HE phenotypes may be found in future studies by using molecular typing methods.

A TWELVE YEAR EXPERIENCE OF HEART-LUNG TRANSPLANTATION IN CHILDREN: A COMPARISON OF RESULTS BEFORE AND AFTER 1990

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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, unremittent 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 re-transplanted 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 re-transplanted and 5 patients have died. OB accounts for 26/30 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


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 practise 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 (13.1mg/ml) whereas CSN doses were 4.8mg/kg (205mg/ml) and 4mg/kg (167mg/ml) respectively. Acute Rejection was diagnosed clinically or by biopsy. Results are 12-month Kaplan-Meier estimates.

<table>
<thead>
<tr>
<th>N</th>
<th>Treated Rejection</th>
<th>Treated Rejection</th>
<th>Patient Survival</th>
</tr>
</thead>
<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 common (74% vs 86%). Hypercholerolemia (9% vs 25%) and gum hyperplasia (9% 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

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We have performed minimally invasive aortic valve replacement on 8 patients with asymptomatic calcific 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 cardioplegic arrest achieved by infusing 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 prothetic 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.

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

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Reperfusion, following myocardial ischaemic arrest with cold blood cardioplegic solutions 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' I 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.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control</th>
<th>Reperfusion</th>
<th>Control</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>2.9±0.3</td>
<td>1.5±0.3*</td>
<td>2.6±0.3</td>
<td>2.8±0.5</td>
</tr>
<tr>
<td>Taurine</td>
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<td>8.9±1.2</td>
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</tr>
<tr>
<td>Glutamine</td>
<td>8.6±0.4</td>
<td>5.8±0.4*</td>
<td>10.0±1.5</td>
<td>10.7±1.7</td>
</tr>
<tr>
<td>Glutamate</td>
<td>5.8±0.5</td>
<td>4.3±0.5*</td>
<td>8.4±0.9</td>
<td>8.7±0.7</td>
</tr>
<tr>
<td>Aspartate</td>
<td>1.4±0.1</td>
<td>1.4±0.1</td>
<td>0.8±0.1</td>
<td>1.2±0.2</td>
</tr>
</tbody>
</table>

Table 1: Values are in μmol/g wet weight and expressed as mean ± SEM (n=9-19). * Significantly different from corresponding control at P<0.05 (ANOVA).

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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Introduction: Measurement of cerebral injury in cardiac surgery by neuropsychological tests is time consuming and prone to many sources of inconstancy. The neuropsychic S-100 protein is released into the circulation following cerebral 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, 2, 6, 12, 24, 48 and 72 hrs postoperatively.

Results: All patients survived the procedure.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</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</td>
<td>0.02</td>
<td>0.2</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>58</td>
<td>100</td>
<td>0.30</td>
<td>1.19</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>56</td>
<td>111</td>
<td>1.09</td>
<td>5.92</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>64</td>
<td>109</td>
<td>2.5</td>
<td>26.06</td>
</tr>
</tbody>
</table>

AUC S-100

Circulatory arrest

S-100 profile

(n=0.9, 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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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±7yrs) 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/s, 9.3±2.8 vs 3.7±1.5 cm/s, n=0.001) while at the LV free wall, SR and LR increased (6±1.4 vs 7.2±2.5 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 1.3±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 been 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.

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 2.5F micromanometer 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 (±SD) 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 % difference between duplicate measurements of a was significantly different, OT = 5.9 (4.1)% and RA = 5.45 (6.0)%; p=0.439. The corrected end-diastolic volume (VEDV) obtained from the OT was 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 such conductance volume measurement may provide a more accurate assessment of true RV volume in patients undergoing cardiac surgery.

ACCURACY OF ULTRAFAST MAGNETIC RESONANCE IMAGING FOR ASSESSMENT OF RIGHT AND LEFT VENTRICULAR VOLUMES AND MYOCARDIAL FUNCTION.

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In this study we investigated the accuracy and feasibility of ultrafast imaging breath-hold cine sequences in the assessment of the RA and RV and left ventricular (LV) volumes and LV mass in comparison with conventional cine gradients echo imaging (GGE) at 1.5T. We investigated 15 healthy volunteers (male, 7female) with mean age 33 years (range 21-59 yrs). Imaging was performed at 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 RA 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 image 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 0.3±13.8 (ml). RV stroke volume comparison showed a mean difference (SD) of 0.12±13.9, 3.3±13.1 and 3.2±13.9 respectively. There was also good agreement of LV enddiastolic (LVEDV) and endystolic volume (LYEVEY). 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 GGE mean differences (SD) of 11.6±23.7, 14.5±21.8 and 15.5±22.6 (g) for FLASH, EPI and SPI. The degree of agreement with GRE remained relatively unchanged among 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 patient was 23 mins. EPI and particularly SPI images were highly susceptible to incorrect shimming. FLASH images appeared more robust 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 highly acceptable accuracy and good agreement with conventional gradient echo imaging in assessing ventricular volumes and mass. We demonstrated the feasibility of these techniques at 0.5T and found an equally high degree of accuracy for all three methods.

CORRELATION OF MYOCARDIAL HISTOLOGICAL FINDINGS IN HIBERNATING MYOCARDIUM WITH DOBUTAMINE STRESS ECHOCARDIOGRAPHY AND NITRATE INFUSION/TECHNETIUM-99m SPECT 

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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 (True Cut) 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. 99mTc uptake was not possible to accurately predict functional recovery (sensitivity = 66%, specificity =42%), nor to correlate percent uptake with quantitative myocardial histological findings. Morphometric histological analysis of biopsies showed significantly less fibrosis in those segments demonstrating inotropic reserve (p=0.05), and significantly less fibrosis in those segments demonstrating an improvement in wall motion post revascularisation (p<0.05). DSE is a valuable diagnostic tool for detection of hibernating myocardial segments with a sensitivity of 100%. We demonstrated a strong inverse correlation between percent fibrosis and percent necrotised cells (r= 0.78. DSE is far superior to 99mTc for detecting hibernating myocardial segments, and an inotropic response correlates with histological findings.
ENHANCED DETECTION OF REVERSIBLE ISCHAEMIA WITH INOTROPIC AS COMPARED TO VASODILATOR STRESS MYOCARDIAL PERFUSION IMAGING, P Soman, 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 arbutamine (inotropic) and dipiridamole (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 SPECT 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 (A PS). The A PS was significantly higher for arbutamine compared to dipiridamole (mean A PS = 8.8 ± 5.5 versus 5.2 ± 4.4 for arbutamine and dipiridamole, respectively, p=0.001). Similarly, a significantly larger proportion of reversible perfusion defects with arbutamine stress was accompanied by reversible wall thickening abnormality compared to dipiridamole (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 arbutamine compared to dipiridamole stress imaging.

POSITRON EMISSION TOMOGRAPHY AND DOBUTAMINE ECHOCARDIOGRAPHY FOR ASSESSING VIABILITY IN PATIENTS WITH MODERATE VENTRICULAR DYSFUNCTION, F Fath-Ordoubadi, KJ Beatt, N Spryrou, D Pagano, PG Camici. MRC CSC and RPMS, Hammersmith Hospital, London, UK.

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 values (PV) only in pts with moderate impairment of LV function. DE (5 and 10 μg/kg/min) and FDG PET during ejecugary 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 WMS by ≥1 grade during DE. S were defined as PET viability, if the mean metabolic rate of glucose (MRG, μmole/min/g) was >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 revasculatized. 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 93% 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, T Hennessy, M Codd, H McCann, D Sugrue. Cardiovascular Research Group, Mater Misericordiae Hospital, Eccles street, Dublin 7, Ireland.

The purpose of this study was to evaluate the usefulness of DSE in the detection of disease remote from the infarcted vessel territory early post acute myocardial infarction. DSE was performed on 125 patients post acute myocardial infarction. Overall, DSE 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 DSE as having ischaemic heart disease but misclassified as having infarct vessel only or multivessel disease. Multivessel disease was correctly identified by DSE in 15 of 53 patients, while 36 were falsely classified as having double or infarct vessel only disease. Sensitivity, specificity, positive and negative predictive accuracy of DSE for detecting remote disease (in 1 or 2 vessels) were 62%, 91%, 95% and 47% respectively. Thus DSE, 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, S Firoozan, K Wei, G Ates, N Goodman, D Skyba, S Keul. Cardiovascular Division, University of Virginia, Charlottesville, VA, USA.

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 (12.5-300μl) 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 video intensity measured over the LAD bed. Microbubble dose was plotted against peak background subtracted videointensity at baseline and during hypersomnia. 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.
USE OF ULTRASONIC INTEGRATED BACKSCATTER TO DETECT REVERSIBLE ISCHAEMIA IN HUMAN Myocardium
J Hancock, M R Thomas, R J Wainwright, D E J ewett, M J Monaghan.
Department of Cardiology, King's College Hospital, London.

Ultrasonic integrated backscatter (IBS) has been shown to increase in the chronic stage after myocardial infarction. Cyclic changes in IBS, which, in normal myocardium, rise to a peak at end diastole and fall to a nadir at end systole, are reduced in myocardial infarction. This is probably secondary to changes in microvascular pulsatile flow. Much less is known about changes in these parameters which may occur during acute myocardial ischaemia. We studied 10 subjects during percutaneous transluminal coronary angioplasty (PTCA) of 16 arteries. All patients had normal wall motion prior to balloon inflation. Myocardial IBS was measured before, during, 5 minutes and 10 minutes after balloon inflation in myocardial segments supplied by the PTCA vessel as well as adjacent regions. All echocardiographic views were taken with the patient in the supine position. The machine settings were unchanged throughout the procedure. The overall level of IBS did not change significantly during inflation in the region of myocardium supplied by the PTCA artery as well as distant areas. However, the cyclic variation in IBS was significantly reduced during balloon inflation, particularly during the first inflation, in the area of myocardium supplied by the PTCA vessel compared with pre-inflation levels. All patients developed chest pain and a wall motion abnormality during balloon inflation. There was no change in cyclic backscatter in adjacent regions. During subsequent inflations, cyclic variations in IBS tended to return towards normal, particularly in patients with multivessel disease, suggesting ischaemic preconditioning or opening of collateral vessels.

Inflation 1 5 post 10 post
Total IBS 19.2 18.5 (NS) 19.8 (NS) 20.7 (NS) 18.6 (NS)
Cyclic IBS 6.5 3.6 (p<0.01) 5.1 (NS) 5.9 (NS) 5.4 (NS)

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
Cardiology Dept, Freeman Hospital, Newcastle-upon-Tyne.
*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 rates is currently one area under study. To perform jet volume calculations using the only 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, and 10mm) 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 (2.31ml, SD 1.51ml).

Calculation times were significantly shorter for the threshold method (2.6 v 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.

CINE MAGNETIC RESONANCE FOURIER VELOCIMETRY OF BLOOD FLOW THROUGH CARDIAC VALVES: COMPARISON WITH DOPPLER ECHOCARDIOGRAPHY
RH Mohiaddin, PD Gatehouse, M Henien, 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 ± 3D, 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 mean 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 (-1.2+2.2) 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 MR 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 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 (-10 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.
PHASE II STUDIES WITH FS069 ULTRASOUND CONTRAST AGENT FOR ECHOCARDIOGRAPHIC PERFUSION IMAGING
J Hancock, H Dittrich, D E Jewett, M J Monaghan
Department of Cardiology, King's College Hospital, London

FS069 is a transpulmonary ultrasound contrast agent consisting of Albunin 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</td>
<td>49</td>
<td>60 (p&lt;0.03)</td>
<td>82 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Kidney</td>
<td>48</td>
<td>55 (NS)</td>
<td>72 (p&lt;0.0002)</td>
</tr>
<tr>
<td>Liver</td>
<td>55</td>
<td>69 (p&lt;0.05)</td>
<td>71 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Qualitative evaluation by two observers demonstrated 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
MI Walters, F Farivall, J Byrse, D Ettles, GC Kaye, MS Norell and JL Caplin.
Department of Cardiology and Radiology, Castle Hill Hospital, Hull.

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/s</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: $\mu$sI</td>
<td>2.6 (1.2)</td>
<td>3.1 (3.5)</td>
</tr>
<tr>
<td>Scattered dose: $\mu$sI/cm²</td>
<td>88 (62)</td>
<td>79 (33)</td>
</tr>
<tr>
<td>Exposure dose: $\mu$sI</td>
<td>9.8 (5.1)</td>
<td>19.0 (7.3)</td>
</tr>
<tr>
<td>Total dose: $\mu$sI</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>
</tbody>
</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.
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 thrombolysis, 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 53 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 150U/Kg were given on admission achieving mean activated clotting time at start of PTCA of 264. 11(21%) pts did not proceed to PTCA, 3 (5.7%) not AMI, 2 (3.8%) had normal arteries; 47(75%) had TIMI 3 flow in IRA and 2(3.8%) unsuitable anatomy. Of 42 attempted PTCA 9(21%) were for repeat events. Left ventricular ejection fraction (EF) was <45% in 18(43%) and <30% in 5(12%). Intra-balloon suction pump was used in 2 pts with cardiogenic shock (BP<90mmHg). There were 5(12%) failures and 3(8%) successes (TIMI 1 flow in the 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); 23.8% strokes (1 fatal, 1 minor); 47.5% transfusions for blood loss; and 4 late transfers for urgent recanalisation 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.

**Primary angioplasty in the District General Hospital: interim analysis of the Exeter primary angioplasty pilot study (EXPAPS)**

LDR Smith and JF Dean
Department of Cardiology, Royal Devon and Exeter Hospital, Exeter, Devon

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**In-stent restenosis: More metal and more symmetry required?**

J Gunn, 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, embedded 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. Strut number vs. lumen CSA +0.24 <0.05 Strut number vs. neointima CSA -0.16 ns Maximum strut separation vs. neointima thickness +0.32 <0.01 Maximum strut separation vs. neointima CSA +0.38 <0.001 Maximum strut separation vs. lumen CSA -0.17 ns

Conclusions. Closely spaced and even strut stents produce little neointima or late lumen loss. Asymmetry of deployment encourages neointimal growth where inter-strut distances are greatest. Closely spaced stents 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-patient outcome and clinical restenosis in benestent and non-benestent lesions.**

I L Williams, M R Thomas, A de Belder, R J Wainwright, D E Jewitt 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 (narrow vessel with stable angina, single lesion, <15mm, vessel >3mm diameter, non-ostial, non-bifurcational, non-restenotic lesion with no thrombus) represent a highly selected group of the general angioplasty population. We have assessed the resting rate in "BS-type" lesions and compared the in-patient outcome and target vessel recanalisation (TLR) 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 remainder achieving a good initial angiographic result (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>Benestent n=68 (patients)</th>
<th>Non-Benestent n=587 (patients)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary success 65 (96%)</td>
<td>529 (90%)</td>
<td>0.09</td>
</tr>
<tr>
<td>MACE 3 (4%)</td>
<td>58 (10%)</td>
<td></td>
</tr>
<tr>
<td>rtp PTCA 0</td>
<td>29 (4.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>CABG 1 (1.5%)</td>
<td>21 (3.6%)</td>
<td>0.31</td>
</tr>
<tr>
<td>TLR 1 (1.5%)</td>
<td>30 (5.2%)</td>
<td>0.03</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.

**LAD**

<table>
<thead>
<tr>
<th>Stent</th>
<th>PTCA</th>
<th>Stent</th>
<th>PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>61</td>
<td>57</td>
<td>76</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2(3.5)</td>
<td>1(1.3)</td>
</tr>
<tr>
<td>MI</td>
<td>3(4.9)</td>
<td>1(1.8)</td>
<td>7(9.2)</td>
</tr>
<tr>
<td>CABG</td>
<td>5(8.8)</td>
<td>4(5.3)</td>
<td>1(1.3)†</td>
</tr>
<tr>
<td>Rtp PTCA</td>
<td>10(17.5)*</td>
<td>11(14.5)</td>
<td>8(10.9)</td>
</tr>
<tr>
<td>Any Event</td>
<td>6(9.8)</td>
<td>12(21.1)**</td>
<td>13(17.1)</td>
</tr>
<tr>
<td>Any Event incl. bailout</td>
<td>6(9.8)</td>
<td>20(35.1)***</td>
<td>13(17.1)</td>
</tr>
</tbody>
</table>

**Non-LAD**

<table>
<thead>
<tr>
<th>Stent</th>
<th>PTCA</th>
<th>Stent</th>
<th>PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>1(1.2)</td>
<td>7(9.2)</td>
<td>2(1.5)</td>
</tr>
<tr>
<td>CABG</td>
<td>6(8.5)</td>
<td>4(5.3)</td>
<td>1(1.3)†</td>
</tr>
<tr>
<td>Rtp PTCA</td>
<td>4(6.9)</td>
<td>10(17.5)*</td>
<td>11(14.5)</td>
</tr>
<tr>
<td>Any Event</td>
<td>13(17.1)</td>
<td>10(13.2)</td>
<td>13(17.1)</td>
</tr>
</tbody>
</table>

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.

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**More metal and more symmetry required?**

J Gunn, N Mallik, L Shepherd, CM Holt, SE Francis, CMH Newman, DC Crossman, DC Cumberland. Sections of Cardiology and Interventional Cardiology, University of Sheffield
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, Tremena 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, CX 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 2.5 (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 referred 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%).

Cardioprotective effect of nicorandil is not modified by ischaemic preconditioning in the rabbit
J Imagawa, GF Baxter, DM Yellon.
The Henley Institute, Department of Academic & Clinical Cardiology, University College London Hospitals, London.

Nicorandil (NIC), a hybrid of potassium channel opener and nitrates, has cardioprotective effects in human and various animal models of ischaemia. We previously showed that ischaemic preconditioning (IP) abolishes the protection afforded by preoperative NIC in an isolated human arterial 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 mild sternotomy under Hypnorm/diazepam anaesthesia. Left coronary branch was occluded for 30 min followed by 120 min of reperfusion. Animals were randomised into four groups: 1) Saline was infused i.v. before and during 30 min ischaemia; 2) NIC (100µg/kg bolus + 10µg/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 tetracyclin 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 haemodynamics between groups.

Table: Ischaemic Preconditioning May Abolish the Protection Afforded by ATP-Sensitive Potassium Channel Openers in Isolated Human Atrium

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>R (cm³)</th>
<th>I (cm³)</th>
<th>L/R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIC</td>
<td>8</td>
<td>0.96±0.07</td>
<td>0.25±0.04</td>
<td>42±12.37</td>
</tr>
<tr>
<td>NIC + IP</td>
<td>8</td>
<td>1.15±0.06</td>
<td>0.15±0.05</td>
<td>13.4±4.32</td>
</tr>
</tbody>
</table>

Mean ± SEM, **P=0.05, ***P=0.01 vs. Saline (ANOVA).

Our results show that NIC has a protective effect against myocardial infarction in our rabbit model and the addition of IP does not influence the effect of NIC. This suggests that NIC can offer an infarct limiting effect with or without intermittent ischaemia, as may happen in patients with unstable angina.

PHOSPHORYLCHOLINE STENT COATING AS A METHOD OF LOCAL DRUG DELIVERY: PREDICTED DATA FROM AN EX VIVO MODEL.
J Armstrong, CM Elahi, P Stratford*, DC Cambierland.
Section of Cardiac Sciences, University of Sheffield, Sheffield and *Biocomputations Ltd, Farrham.

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 their 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 diprydamole (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 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. Diprydamole 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 microscopy. The results showed that the circulating levels of diprydamole at 24 hours was 2-3% of total diprydamole loaded onto the stent. The culture medium used to wash the stented vein immediately after implantation contained slightly higher levels of diprydamole (4% of total loaded onto stent). We are currently looking at circulating levels of diprydamole at various time intervals 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. Diprydamole 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
C S Carr, W B Pigley*, D M Yellon.
The Henley 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 nicorandil, a KATP channel opener, to ischaemic preconditioning. We also investigated the combination of a preconditioning protocol and nicorandil exposure. Methods: human atrial trabeculae obtained from patients undergoing routine coronary revascularisation, were divided on the basis of pre-operative nicorandil 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 mins hypoxic substrate-free perfusion at 3Hz (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) Nicorandil - preconditioning exposure, 90 mins simulated ischaemia and 120 mins reoxygenation. 4) Nicorandil + Preconditioning - preconditioning exposure, 3 mins simulated ischaemia and 7 mins reoxygenation, followed by the 90 mins simulated ischaemia and 120 mins reoxygenation. The endpoint was damage 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</th>
<th>PC</th>
<th>NIC</th>
<th>Nicorandil + PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>%R</td>
<td>27.5 ± 1.1</td>
<td>50 ± 3.6*</td>
<td>55.3 ± 5.3*</td>
<td>29.7 ± 3.1</td>
</tr>
</tbody>
</table>

Nicorandil 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 opener have produced the same effect. These data show that oral nicorandil affords ischaemic protection of human atrium. This protection is lost when an ischaemic preconditioning protocol is added to nicorandil exposure.
A ROLE FOR BOTH ADENOSINE A1 AND A3 RECEPTORS IN ISCHAEMIC PRECONDITIONING OF HUMAN ATRIUM

C S Carr, R J Hill*, D M Teison
The Hatton Institute, Department of Academic Cardiology, University College London Hospitals, London, UK.*Pfizer Central Research, Groton, Connecticut, USA.

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 randomised into 7 groups (40 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 (paced at 1 Hz) 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 + CPA superfused for 5 min, followed by CPA 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, CPA + IBMECA superfused for 5 min, followed by CPA superfused for 5 min. Compounds were evaluated at A1 or A3 selective concentrations based on their Ki 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 contr.), TWOWAY ANOVA.

<table>
<thead>
<tr>
<th>Group</th>
<th>C</th>
<th>PC</th>
<th>CPA</th>
<th>CPA+DPCPX</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</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>
<tr>
<td>HR</td>
<td>28.7±1.2</td>
<td>49.7±3.8*</td>
<td>41.3±2.3*</td>
<td></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 effect of the A3 agonist IBMECA. Thus activation of A3 receptors may play a role in ischaemic protection of human atrium.

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

M D Lowe, SA Newell, E Rowland, 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. Thrombolysis ischaemia reperfusion.
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, PH 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 timing of intervention, left ventricular LV function and outcome of early intervention in these patients. Fifty one patients (age 47 to 84 years, mean 67 (89) with 2 mm ST depression admitted to the coronary care unit in a eight 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)); 33 male; ML in 49%). A had either triple (TVD) or double vessel disease (DSD). Five patients had in hospital main stem atherosclerosis (MSA). 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% (17%). 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%) in 27 patients with revascularisation than those without (6/29 (21%). Table: N = number of patients, ALL = all patients, 2mm = patients with ST depression of 2mm, 1 = hypotension.

<table>
<thead>
<tr>
<th>N</th>
<th>DVD</th>
<th>TVD</th>
<th>LMA/D</th>
<th>ALL</th>
<th>2mm</th>
<th>1mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>14 (33%)</td>
<td>28 (67)</td>
<td>5 (12%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>5 (23%)</td>
<td>17 (77)</td>
<td>4 (18%)</td>
<td></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, requiring the left main. 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 Mably, KP Jennings. 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 majority 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 echocardiography) 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. Radioisotope 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 ISCHAEMIC CARDIOMYOPATHY

GK Davis*, B Mackness, DH Roberts*, PN Durrington, MI Mackness, AM Hasgort
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 genotype have been reported to be associated with coronary artery disease (CAD). We determined the prevalence of both polymorphisms in patients with ischaemic cardiomyopathy (IC) 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<0.05). The angiotrophic Humpona sub(hom) (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 for patients with IL, ID and DD ACE genotypes were similar.

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

THE EFFECT OF AN ACUTE CHEST PAIN NURSE (ACP N) ON DOOR TO NEEDLE TIMES AT AN INNER CITY TEACHING HOSPITAL

C Hughes, K Scott, Dr S Saltini, 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>Time</th>
<th>No. of patients</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 (9-216)</td>
<td>NA</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?

CA Rinaldi, AZ Link, ND Masani, RJC Hall.
University Hospital of Wales, Cardiff, UK.

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 ischaemia, and we examined the effects on LV function of 2 episodes of ischaemia at 3 different time intervals. In 24 patients with 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 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 ischaemia 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 abnoromies were similar to those after Ex1. Echo data are shown (mean±SD).

Results

<table>
<thead>
<tr>
<th>Group 1 (30 minutes)</th>
<th>Group 2 (60 minutes)</th>
<th>Group 3 (4 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SF</strong></td>
<td><strong>IRP</strong></td>
<td><strong>SF</strong></td>
</tr>
<tr>
<td>3.8±2</td>
<td>9.4±1</td>
<td>3.3±1.7</td>
</tr>
<tr>
<td>3.7±2</td>
<td>9.4±1</td>
<td>3.3±1.7</td>
</tr>
<tr>
<td>8.8±10</td>
<td>98±15</td>
<td>3.8±3.8</td>
</tr>
</tbody>
</table>

**Conclusion:** The results in Grp 1 would be consistent with the phenomenon of ischaemic 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.

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BETA BLOCKERS PRESERVE CARDIAC VAGAL TONE UNDER CONDITIONS OF STRESS

JC Vaid, 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 lipolitic beta blockers act centrally to restore vagal activity, preventing ventricular fibrillation during stress. Our aim was to establish whether beta blockers could reverse the impaired vagal tone during stress in humans, and to compare lipolitic (high CNS penetrance) with non-lipolitic 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, 5 minute periods of ECG were recorded at rest, during mental arithmetic (MA) and during head-up passive tilting (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></th>
<th>MA (nu)</th>
<th>TILT (nu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>50.5±4.2</td>
<td>17.6±2.4</td>
</tr>
<tr>
<td>Atenolol</td>
<td>60.5±4.7</td>
<td>24.6±2.1</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50.5±4.4</td>
<td>20.9±4.8</td>
</tr>
</tbody>
</table>

| Values are mean±SD |

**Rest** compared to placebo. Statistics by ANOVA (log HF).

**Vagal activity as measured by HF power was reduced significantly by both MA (p<0.01) and TILT (p<0.001) in all groups. Compared to placebo, atenolol and metoprolol significantly increased HF power at rest and under conditions of mental and orthostatic stress. The effects of atenolol (lipolitic) and metoprolol (non-lipolitic) were not significantly different. Conclusion: beta blocker therapy preserves vagal control during stress. This may be a major mode of their action in reducing sudden death in cardiac disease.**

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EPISODIC HYPOTENSION DURING DAILY ACTIVITY IN HYPERTROPHIC CARDIOMYOPATHY AND PROPENSITY TO SUDDEN DEATH: UTILITY OF BEAT TO BEAT BLOOD PRESSURE MONITORING.

K Prasad, JP Freedman, M Gould, W McKenna. Cardiological Sciences, St. George’s Hospital Medical School, London, UK

**BACKGROUND AND 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 alternating 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 mm Hg or MAP >20 mm Hg 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 did 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.

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PREVALENCE OF CARDIOINHIBITORY CAROTID SINUS HYPERSENSITIVITY (CICH) IN ACCIDENT AND EMERGENCY ATTENDANCES WITH FALLS OR SYCONE

D A Richardson, R S Benton, F E Shaw, J E Bond, R A Kenny

Cardiovascular Investigation Unit and Regional Cardiothoracic Unit, New 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 CICH 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 CICH 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 CICH - defined as “greater than 3 M or 1E of asystole or supine or upright. %

<table>
<thead>
<tr>
<th>CICH</th>
<th>50 – 64yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>22%</td>
<td>&gt;64yrs</td>
</tr>
</tbody>
</table>

**Overall Mean Age**

<table>
<thead>
<tr>
<th>Falls with syncope</th>
<th>Unexplained fallers</th>
<th>Recurrent fallers</th>
</tr>
</thead>
<tbody>
<tr>
<td>72.8yrs</td>
<td>63%</td>
<td>37%</td>
</tr>
</tbody>
</table>

**Possible drug associated CICH**

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 Steeds, A Sivaguru, P Galnes, J Beard, G Venables, K Channer

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 stenosis greater than 70% luminal diameter enrolled in a multicentre study comparing carotid endarterectomy (CEA) and carotid angioplasty (PTA). Blood pressure (BP) was measured 48 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. 109.4 mmHg ± 11.7) but this difference was not significant. We calculated the change 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 -19.7 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 -3.8 to 2.6, p=0.75), mean BP (-1.7 mmHg, 95% CI -5.3 to 1.9, p=0.34). There were no significant changes in heart rate in either group. The fall in BP noted in patients undergoing 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 intim-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>0.47</td>
</tr>
<tr>
<td>Ambulatory pulse pressure</td>
<td>0.36</td>
<td>0.48</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 final model. These findings promote a role for ABPM in guiding aggressiveness of anti-hypertensive therapy in an attempt to limit potential target organ damage.

DO AORTIC COMPLIANCE AND CORONARY CALCIFICATION PREDICT THE PRESENCE OF CORONARY ARTERY DISEASE?


National Heart & Lung Institute, Royal Brompton Hospital and *Hilligdon Hospital, London, UK

Unmatched control studies have suggested that abnormal aortic compliance measured by magnetic resonance imaging (MRI) and abnormal coronary calcification measured by electron beam computed tomography (EBCT) may predict the presence of coronary artery disease. There are however no case-control studies to support this hypothesis. We have measured thoracic aortic compliance and coronary calcification in patients with known coronary artery disease and in age matched control subjects selected from the same geographical region. Sixty-two patients (mean age 60 years, SD 7, range 49 to 69) and 62 control subjects (mean age 60 years, SD 7, range 49 to 70) were recruited. Coronary calcification was measured successfully in all subjects but aortic compliance was only possible in 37 patients and 55 healthy volunteers because of claustrophobia and degraded image quality. Compliance (mean±SD mmHg/ml) in the mid-descending and mid-descending aorta and coronary calcification (Hounsfield units * mm²) were 21±11, 17±8 and 103±237 respectively in the control group, and 18±6, 13±7 and 657±757 in the patients (P=0.1, <0.001 and <0.001). Areas under the ROC curve were 0.52, 0.65 and 0.89 respectively with optimum sensitivity/ specificity of 70%/50%, 70%/60% and 80%/75% respectively. We conclude that coronary calcification has reasonable accuracy for the detection of coronary artery disease. Aortic compliance however is less accurate, possibly because of the reduction in compliance caused by healthy ageing.

Tissue Inhibitors of Metalloproteinas tos as Markers of Aldosterone Related Myocardial Fibrosis in Hypertension

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Dept of Biochemistry, Dept of Cardiology, St. Bartholomew's Hospital, Glasgow

Introduction: Aldosterone(Aldo) and Angiostatin 11 have been shown as mediators of myocardial fibrosis in hypertensive left ventricular hypertrophy. Elevated levels of procollagens 111 peptides have been found in patients with hypertensive left ventricular hypertrophy (LVH). Tissue inhibitors of metalloproteinas tos (TIMP) inhibit matrix metalloproteinas tos (MMP) which are responsible for breakdown of excess 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, group1) with no other chronic medical illness or previous surgical procedure and good echo for analysis and a matched population of normotensive controls (n=16, group2) 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>Variable</th>
<th>TIMP ng/ml</th>
<th>Aldo nmol/l</th>
<th>P111P U/ml</th>
<th>LV Mass g/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP(Gp 1)</td>
<td>493</td>
<td>0.358</td>
<td>0.68</td>
<td>129.94</td>
</tr>
<tr>
<td>Control(Gp 2)</td>
<td>187</td>
<td>0.349</td>
<td>0.54</td>
<td>96.9</td>
</tr>
<tr>
<td></td>
<td>p=0.008</td>
<td>p=NS</td>
<td>p&lt;0.001</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

P111P and TIMP 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.
WHITE COAT HYPERTENSION IS ASSOCIATED WITH LESS LONG TERM CARDIOVASCULAR COMPLICATIONS COMPARED TO EUTENSION
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 carotid 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) at a mean of 9.9 ± 3.5 years earlier. White coat hypertension was defined as an ambulatory systolic BP<140mmHg and diastolic BP<90mmHg. Those with either a mean systolic BP>140mmHg or diastolic BP>90mmHg were designated overt hypertension. At follow-up, echocardiography and carotid ultrasonography were performed to derive LV mass index (LVMi) and carotid intima-media thickness (IMT). 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 over their adverse metabolic and neurohormonal effects. Dopamine agonists have natriuretic and vasodilatory 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 neurohormonal 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 64±134 with ibopamine (P=0.05). 24 hour urinary sodium excretion at weeks 2 and 4 (P<0.05) and 24 hour urinary volume at week 2 (P=0.0001) 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 inflamed and normal heart failure 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 ambulatory intra-arterial cross-over trial comparing the effects of 3-month treatment each with 20 and 5 mg od of losinopril (L20 and L2) 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 L2 with the L20 treatment phases, during equivalent peak dobutamine stress and maximal exercise tests, the haemodynamic data showed trends toward higher cardiac performance with L20 therapy:

Dobutamine (dB) CO CPO Emax dB CO CPO
L20 123 10.1 2.0 W 139 12.2 2.7 W
L2 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 L20, with peak oxygen uptake of 21.2 (L2) vs 19.6 ml.min/kg^-1, p<0.01. Twenty-four adverse reactions were reported during L20 compared to 38 during L20 treatment periods. Conclusion: The aerobic exercise capacity of patients is shown in this study to be higher with the lower dose losinopril. The answer to whether the low or high dose of losinopril will confer greater longevity will be available when the ATLAS mortality study has been analysed.

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(21 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(HD) and 11 (mean age 49±8 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 mVO2. The group with DCM had greater right ventricular RV excursion (2.4±0.5 vs 1.5±0.5cm, p<0.001) and peak lengthening velocity(9.9±3.7 vs 7.3±1.6cm/s, p<0.05). This compares with the 11 normal controls (mean age 51±7 years) in whom RV excursion was 2.6±0.3cm and peak lengthening velocity 10.5±2.1cm/s. The DCM group exercised for longer on the treadmill compared to those with IHD (79±14 vs 49±09 sec, p<0.001). They also achieved a higher mVO2 (26.0±7.5 vs 18.5±3.9ml/kg/min, p<0.001) with a lower VE/VCO2 slope (30.9±6.4 vs 35.6±5.5, p<0.05). The 11 normal controls achieved a mean exercise time of 952±106 sec, an mVO2 of 31.5±4.6ml/kg/min and a VE/VCO2 slope of 25.4±8.37. Within the patient group as a whole RV systolic excursion correlated with mVO2 (R=0.59, p<0.01). Conclusion: In patients with dilated, impaired left ventricles, preserved right ventricular function predicts a better exercise time and mVO2.

EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON 24 HOUR BAROREFLEX SENSITIVITY IN HEART FAILURE
JC Vallee, TJ Stallard, PJ Jordan, JH Coote1, JN Townsend, WA Little2
Departments of Cardiovascular Medicine and Physiology1, 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 42%) 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 (Oxford method), before and after 16 weeks of treatment with quinapril (Q) incremented to 20mg bd. 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 sequences 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 were mean ±SD:

<table>
<thead>
<tr>
<th></th>
<th>Awake BRS</th>
<th>Asleep BRS</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60 ±7.2</td>
<td>89 ±4.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>CHF pre-Q</td>
<td>5.4 ±0.9</td>
<td>6.4 ±1.6</td>
<td>p&lt;0.02 20.5%</td>
</tr>
<tr>
<td>CHF post-Q</td>
<td>5.4 ±1.3</td>
<td>7.3 ±2.1</td>
<td>p&lt;0.01 43.2%</td>
</tr>
</tbody>
</table>

Effect: Compared to control, p<0.05 compared to CHF pre-Q.

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 in treatment with quinapril. 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 effect of sleep. In heart failure ACE inhibition increases BRS and restores the normal diurnal variation.

SERUM URIC ACID AS A MARKER OF IMPAIRED OXIDATIVE METABOLISM IN CHRONIC HEART FAILURE
P Levy, SD Acker, TP Chan, IF Godalda, JC Stevenson, AJ Coats, Wyna Division of Metabolic Medicine and Department of Cardiology, 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<0.001), 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
Brooklands St, Basildon PD, Nolan J, Andrews R, Lindsay HSP, Mullen 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 ischemic heart disease. Recently, a few small studies have indicated that QT dispersion can be used to identify patients with congestive heart failure (CHF) who have a higher mortality rate. 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 (QTMax) was 492 ± 47.8 ms and rate corrected QT interval (QTd) was 80.6 ± 32.1 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 (<0.001), age (p<0.001), CRT (<0.001), QTMax (p<0.001), sodium (p=0.001), albumin (p<0.001), heart rate (p=0.003), ejection fraction (p<0.0009), bundle branch block (p=0.005), and QTd (p=0.01). 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 age (p<0.001), CRT (p=0.01), sodium (p=0.008) and ejection fraction (p=0.015) as the only independent predictors of all-cause mortality. Strong and QTd 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.

QT INTERVAL PARAMETERS ON A 12-LEAD ECG AS PREDICTORS OF MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE
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LEFT VENTRICULAR DIASTOLIC FUNCTION IN HYPERTROPHIC CARDIOMYOPATHY AFTER SUCCESSFUL NON-SURGICAL SEPTAL REDUCTION
MY Henein, A2 Kurban, C Knight, U Sigwart, DG Gibson. Royal Brompton Hospital, London.

Diastolic left ventricular function has proved important in predicting long term follow-up in different cardiac diseases. Non-surgical septal reduction has also proved successful in reducing the systolic outflow tract gradient and improves symptoms. In order to assess its possible effects on diastole, we studied 12 patients, aged 51±18 years 6 female, with M-mode and 2 D echo-Doppler technique and compared them with 21 normal subjects of similar age. Before-procedure: Left ventricular dimensions reduced 4.2±0.9 vs 4.9±0.5 cm (vs normal) at end-diastole and 2.4±0.7 vs 3.3±0.5 cm at end-systole, with peak thinning rate 8.2±2.6 vs 11±2.7 cm/s but fractional shortening was increased 43±8% vs 30±10%, p<0.001 each. Interventricular septum was thickened 2.6±0.8 vs 1.0±0.1 cm as was the posterior wall 1.5±0.5 vs 1.0±0.1 cm, p<0.001 each. Transmitral A wave velocity was high 76±29 vs 50±10 cm/s and E/A ratio low 1.1±3 vs 1.4±0.4, p<0.01 each. Post-procedure: Left ventricular outflow tract gradient fell from 67±42 to 11±8 mmHg, peak thinning rate did not change.

Conclusion: Successful non-surgical septal ablation reduces left ventricular outflow tract gradient and improves symptoms. Although it ablates part of the proximal septum, it does not alter the overall diastolic ventricular function.

HIBERNATING MYOCARDIUM IS CHARACTERISED BY AN IMPAIRED CORONARY VASODILATOR RESERVE
D Pagano, RS Bouseer, JN Townsend, FG Camici Queen Elizabeth Hospital Birmingham & MRC RPMS Hammersmith Hospital London

Resting (RES) myocardial blood flow (MBF) may be within normal limits in most chronically dysfunctional LV segments which improve function after coronary artery bypass (hibernating myocardium). Aim of this study was to assess coronary vasodilator reserve (CVR) in hibernating myocardium (HIB) before and after coronary artery bypass (CABG). We studied 20 patients (mean age 59±7 years) with multivessel disease and a mean left ventricular ejection fraction (EF, MUGA) of 24±7% and 21 age matched controls (53±8 years, p=NS vs patients). MBF (ml/g/min) at rest (RES) and after dipirydamole (DIP, 0.56 mg/kg in 4 minutes) was measured with positron emission tomography using oxygen-15-water. CVR was computed as MBF-DIP/MBF-RES. Regional wall motion was assessed with echocardiography. Before CABG 38/271 revascularised segments (SEG) were normal and 233/271 were dysfunctional (DYS). Six months after CABG EF improved to 35±9% (p<0.001 vs basal) and 145/233 (62%) DYS SEG improved function and therefore considered hibernating (HIB) while 88/233 (38%) were unchanged. Before CABG, MBF-RES in HIB was comparable to MBF-RES in controls (0.92±0.3 vs 0.99±0.2, p=NS). By contrast CVR in HIB was significantly lower than in controls (1.5±0.7 vs 3.2±1.3, p<0.0001). Six months after CABG MBF-RES in HIB was unchanged (0.97±0.3, p=NS vs basal) and CVR increased significantly to 1.98±0.9 (p<0.001 vs basal), although it was still lower than in controls (p<0.01). In conclusion this study confirms that 1- MBF at rest in HIB myocardium is within normal limits in most segments and 2- HIB myocardium is characterised by an impaired CVR which improves significantly after CABG.
A GENE LOCUS FOR ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY MAPS TO CHROMOSOME 17p1-3q

AS Coonar, N Coonar, A Tassopoulos, A Mihaylou, VA Murray, RJ Eales, RH Siffi, MI Oster, RK Matta, WJ McKenna

St George's Hospital Medical School, London, & Yannis 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 identified for autosomal dominant forms of the disease. Identification of the genetic basis of ARVC is dependent on the highly accurate determination of disease status. This is difficult because of the unknown nature of early disease, the high rate of non-penetrance and variable expression, and phenotypic copies due to other causes.

Protonotarios identified the phenotype of Naxos syndrome (ARVC+ palmoplantar keratodermia + waxy 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 146 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 17p1-3q was identified. The peak 2 point lod score was 4.07 at 0. Further, we have sequenced the disease haplotype and have identified this across the 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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Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne

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 1983-92 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 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), unexplained 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 occur 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 underestimated total arrhythmia deaths.

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


Great Ormond Street Hospital, London.

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 (titrated 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, 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 dilatation) (FMD) was compared to that of GTN (endothelium-independent dilatation) (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>
<th>p</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>
<td>NS</td>
</tr>
<tr>
<td>Enalapril</td>
<td>3.59 (0.57)</td>
<td>3.56 (0.57)</td>
<td>3.56 (0.48)</td>
<td>NS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FMD (%)</th>
<th>Placebo</th>
<th>2.3 (2.7)</th>
<th>2.9 (3.4)</th>
<th>3.0 (2.6)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>1.6 (2.4)</td>
<td>2.6 (2.7)</td>
<td>2.8 (2.9)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GTN-MD (%)</th>
<th>Placebo</th>
<th>18.3 (7.6)</th>
<th>18.7 (9.4)</th>
<th>19.6 (7.5)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>17.5 (8.0)</td>
<td>16.9 (8.1)</td>
<td>18.4 (8.3)</td>
<td>NS</td>
<td></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

R Crook, I Cox, OA Salomone, PM Elliott, C Hann, JC Kaski

Department of Cardiological Sciences, St. George's Hospital, London

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 = 0.006, p < 0.001 and p = 0.01 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.
ENDOTHELIN-1 RECEPTORS IN EXTERNALLY STENTED AND UNSTENTED PORCINE VENOUS - ARTERIAL GRAFTS

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External, loose fitting, porous stents reduce media and intimal thickening in autologous porcine saphenous vein (SV) grafts (VG). The underlying mechanisms, however, remain to be elucidated. Blood vessels synthesise the vascular smooth muscle cell (VSMC) mitogen, endothelin-1 (ET-1) which may contribute to intimal thickening. We used autoradiography to study the distribution of ET-1 receptors in porcine saphenous vein-carotid artery grafts (stented and unstented). Immunohistochemistry was used to identify specific cell types of stented VGs (SV VG), unstented VGs (VG), ungrafted SV and carotid artery (CA) one month after implantation. Autoradiography was used to localise [125I]-ET-1 binding sites and ET-A and ET-B receptor subtypes identified using 125I- PDE1/2/4 and 125I-BOP20, respectively. There was marked medial thickening and neointima formation in VGs both of which were significantly reduced by external stenting. ET-A and ET-B receptor binding was associated with the media (SV > VG > SVG > CA) and neointima (in VGs only) and with the nonoedentitina (ADV) (table).

Table. eta and etg receptor density (dpm x 1000 / mm 2) (mean ± SEM) in the media and ADV of porcine vesse. *p < 0.05 relative to SV. ND not detectable.

<table>
<thead>
<tr>
<th></th>
<th>eta</th>
<th>etg</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>SV</td>
<td>VG</td>
</tr>
<tr>
<td></td>
<td>73 ± 6</td>
<td>42 ± 7</td>
</tr>
<tr>
<td></td>
<td>21 ± 3</td>
<td>11 ± 2</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>19 ± 4</td>
</tr>
<tr>
<td></td>
<td>4 ± 0.5</td>
<td>4 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>5 ± 1*</td>
<td>5 ± 1*</td>
</tr>
</tbody>
</table>

CONCLUSIONS 1) The down-regulation of ETA and ETB receptors in the media of both stented and unstented VGs, which tends toward that in the carotid artery, indicates an adaptive response in both VGs and SVGVs to arterial haemodynamic conditions. The pathogenic implications of this finding warrants further investigation. 2) ETA and ETB may play a role in neoadvulointimal biology, including micromangiosis. 3) The lack of differences in overall ET-1 receptor density between stented and unstented VGs indicates that alterations in this peptide do not play a role in modulating the inhibitory effect of the external stent on VG thickening.

Supported by the British Heart Foundation

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 ECO confirmation). Of 488 patients (mean aged 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 minutes (range 10 to 121 minutes). 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 minutes (range 5 to 145 minutes; p<0.001). Nurse Specialists thrombolysed 86 patients (median "door to needle" time 15 minutes; range 5 to 30 minutes) and doctors thrombolysed 48 patients (median "door to needle" time 26 minutes; range 5 to 145 minutes; 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.

INTRAVENTRICAL L-ARGININE IMPROVES ENDOTHELIAL FUNCTION IN CIGARETTE SMOKERS.


Introduction: Endothelial dysfunction is an important early event in atherogenesis; we have previously demonstrated impaired endothelium 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 athero-sclerosis.

Methods: Eight current smokers were studied (mean age 32, range 25-35; mean pack years 11, range 4-20). Subjects were not diabetic nor normotensive, norcholesterolamaic 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 per cent to 2.63 ±2.35 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 (r² = 0.74, p=0.01), which may represent smooth muscle cell sensitisation to chronic 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.

Topical Use Of Streptokinase For Wound Debridement Causes An Antibody Response Sufficient To Neutralise A Subsequent IV Dose For Intravenous Thrombolysis.

M. Bux, MK Baig  A Brown, D Armstrong, E Rodrigues,  John Moores University of Liverpool; Aintree Hospitals, Liverpool.

Background - Streptokinase (SK) is commonly used topically to debride cutaneous wounds consisting of devitalised tissue. Anti-SK antibody occur following standard intravenous (iv) SK use and limit it's further use in the same individual. Whether topically used SK elicits a similar humoral response has not been investigated previously.

Methods - 42 consecutive patients (74±14 years) with SK treated wounds (TOP), 63 consecutive patients (65±12 years) with acute myocardial infarction (STREP), and 40 patients (59±14 years) with non-SK treated wounds (CONT), were studied over a period of 13 months. Serum was analysed for the presence of anti-SK antibodies, using an enzyme-linked immunosorbent assay, and plasma for neutralising antibody titre (NT) to assess anti-SK antibody resistance, prior to commencement of treatment, and subsequently at intervals of 7 days, 1 month, and 6 months.

Results - TOP group developed a significant elevation in anti SK antibody levels at one month (108±9±7±2±5±mL/p<0.05), but mean level was significantly lower than STREP group (108±5±9±7±2±5±mL/p=0.04); by 1 month, 13±14% patients in TOP group had sufficient titers to neutralise 1±5±ml of SK; 4±4% patients had sufficient NT to neutralise >3000iu of SK (figure 1). At 6 months, anti SK levels in TOP group had returned toward baseline values (59±5±2v±30±6±5±mL/p=NS). STREP group developed a significant elevation of antibody levels (170±6±1v±63±5±iu/mL/p<0.001), whereas CONT group did not (84±4±3v±63±5±iu/mL/p<NS), over the 6 month period.

Conclusions - Topical SK administration generates significant antibody levels, but titres sufficient to neutralise a subsequent dose of 1±5±ml of iv SK occur in only a few patients. To ensure subsequent thrombolytic efficacy therefore, it is preferable to avoid iv SK in patients treated with topical SK in the preceding six months.

Figure 1
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 prothrombin 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 variables contributing to the diurnal rhythm of ischaemic events in coronary artery disease. To test this hypothesis 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-1Ag), and plasma renin. Baseline fibrinolytic activity showed a circadian pattern with morning peaks of PAI-1Ag and tPA-Ag (p<0.001). ACE-inhibition produced a huge increase in circulating renin but, in contrast to patients with an activated RAS early after infarction, PAI-1Ag 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. The ratio of low to high frequency spectral components of HRV (a measure of sympathetic 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. 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 artery 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 = 0.0099, Mann-Whitney U). Pts with 1 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 mass.

We noted in the 19 pts with single vessel disease, Lp(a) was higher in patients with lesions 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 those pts [n = 18] with complex lesions than in those [n = 14] with smooth lesions (499 ± 97 mg/dl vs 121 ± 49 mg/dl; t test = 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.

BLUNTED RESPONSE TO HYPOXIA BUT EXAGGERATED DYSFUNCTION DURING REOXYGENATION IN DIABETIC HEART

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Clinical and experimental data indicate the existence of a specific diabetic cardiomyopathy. Brief episodes of myocardial hypoxia cause both systolic and diastolic dysfunction in the normal heart, but the response in the insulin-dependent diabetic heart is not well characterised. We compared the effects of hypoxia (10 min) in isolated buffer perfused isovolumic 6 week streptozotocin (STZ)-induced (55mg/kg) diabetic rat (n=4) and matched normal hearts (n=7) (constant coronary flow and heart rate, 37°C). LV pressure (LVP) was measured via a balloon in the LV and normalised by the heart weight, and LV relaxation was assessed by an exponential time constant, τ. At baseline there was no significant difference in LVP between the two groups (Normal: 52±2mmHg; STZ: 63±7mmHg), but T was significantly prolonged in STZ compared to normals (Normal:28±1ms; STZ: 43±6ms, p<0.05). During hypoxia LVP fell in both groups but significantly more so in normals, whilst during reoxygenation LVP returned to prehypoxic levels in both groups (Fig). Similarly there was a greater prolongation of T in STZ compared to STZ, indicating a cardiovascular response to hyperglycaemia. These findings may be relevant to myocardial dysfunction in the diabetic heart, particularly in the context of demand ischaemia.

COAGULATION AND FIBRINOLYTIC FACTORS, INSULIN RESISTANCE AND THE METABOLIC SYNDROME OF CORONARY HEART DISEASE RISK

IF Goddard, M Sidhu, D Crook, JC Stevenson.
Wynn 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 X, 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 liproteins 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 HDL cholesterol (r=-0.32, p=0.04). Fibrinogen showed significant associations with IVGTT insulin and C-peptide response, S, triglycerides and HLDL cholesterol. Factor VII and PAI-1 were associated with IVGTT insulin response and S, the relationship 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.

Palka P, Lange A, TRD Shaw, GR Sutherland, KAA Fox. Department of Cardiology, Western General Hospital, Edinburgh.

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 LD (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.