THURSDAY 20 MAY 1993

from 8.15 Registration
8.45–10.30 Grand Hall
Young Research Workers Prize Final
Judges: Prof M J Davies (chairman), Prof W J Remme, Prof S Cobbe, and Dr P Weissberg

Severn I & II
Epidemiology
(chairman: Prof D Wood)
Papers 102–107

9.30–4.00 Avon I & II
NURSES’ DAY (Coffee available from 8.30 in the Exhibition Hall)
(chairmen: Dr Roger Hall (Cardiff) and Mr Tom Quinn (York))

10.30–11.15 Coffee and poster viewing in the Exhibition Hall

11.15–12.15 Grand Hall
Arrhythmias
(chairman: Dr K Dawkins)
Papers 108–111

Avon III
Hypertrophic Cardiomyopathy
(chairman: Prof S Cobbe)
Papers 112–115

12.15–2.00 Lunch and Poster Viewing in the Exhibition Hall – Authors present

2.00–4.00 Grand Hall
Practical Cardiology
Dr A McLeod, Prof R Vincent, Prof R W F Campbell, Prof J Petrie and Dr G Murray

2.00–3.30 Avon III
Coronary Flow/Syndrome X
(chairman: Prof A H Henderson)
Papers 121–126

3.30–4.30 Tea and Poster Viewing in the Exhibition Hall

4.30–5.30 Grand Hall
Strickland Goodall Lecture
Clinical Value of Assessment of Diastolic Ventricular Function
Dr Derek Gibson

7.30 for 8.00 Annual Dinner at the Natural History Museum
CENTRAL ROLE OF THE C-MYC PROTO-ONCOGENE IN VASCULAR SMOOTH MUSCLE CELL PROLIFERATION AND CELL DEATH

M R Bennett, G I Evan* and A C Newby
Department of Cardiology, University of Wales College of Medicine, Heath Park, Cardiff
*Biochemistry of the Cell Nucleus Laboratory, Imperial Cancer Research Fund, 44 Lincoln’s Inn Fields, London

Overactivity of the c-myc proto-oncogene has been observed in atherosclerotic plaque vascular smooth muscle cells (VSMCs) and may therefore be implicated in the excessive VSMC proliferation characteristic of atherosclerosis. We have examined the role of c-myc expression in growth inhibitory responses of cultured rat VSMCs to heparin, interferon-γ, serum reduction and cyclic nucleotide analogues. We have compared normal VSMCs and those in which a c-myc gene was transfected, so as to provide constant normal or elevated Myc protein levels. In normal cells c-myc mRNA fell rapidly by >90% over 2-4 hours with serum reduction and interferon-γ treatment, but more slowly over 24-48 hours with heparin and cyclic nucleotide analogues. In transfected cells constant c-myc expression at normal or 1.5% normal levels abolished growth inhibition from all agents, but instead induced programed cell death (apoptosis) with serum reduction and interferon-γ. Conversely, reduction of c-myc expression using antisense oligodeoxynucleotides increased VSMC proliferation by >75% without cell death. We conclude that c-myc expression drives VSMC proliferation and down-regulation of c-myc by heparin abolishes this process to down-regulate c-myc induces apoptosis. These data show that deregulated c-myc expression causes both excessive VSMC proliferation and cell death, processes which have both been observed in atherosclerotic plaques.

RELEASE OF PLATELET-DERIVED GROWTH FACTOR ACTIVITY FROM ARTERIOVENOUS BYPASS GRAFTS

SE Francis†, S Hunter†, CM Holt, PA Gadsden, S Rogers, T Taylor°, AC Newby„ GW Duff‡, GD Anglin* Departments of Cardiac Surgery†, Pathology*, Molecular Medicine*, University of Sheffield, Sheffield; Department of Cardiology°, UWCM, Cardiff, Department of Cardiac Surgery§, University of Bristol, Bristol, U.K.

Intimal smooth muscle cell proliferation is the main cause of late saphenous vein bypass graft failure. It has been suggested that the production of growth factors by the cells of the vessel wall may provide the stimulus for this event. To test this hypothesis segments of pig arteriovenous bypass graft removed 1 and 4 weeks after implantation were cultured in serum-free media for 24 hours. Tissue viability as assessed by adenosine triphosphate (ATP) concentration (nmol/g wet weight) was maintained throughout the culture period (239±21 [SEM], n=26, 0 hrs and 240±24, n=17, 24 hrs). Cell proliferation as assessed by incorporation of [3H]-thymidine occurred (893±113 DPM/μg DNA, n=17). Autoradiography showed that proliferating cells were in the neointimal and medial layers. These cells were identified as smooth muscle cells using a monoclonal antibody to α-actin. Graft conditioned media were tested for mitogenic activity using a fibroblast proliferation assay. Media conditioned for 24 hours produced significant stimulation of cells (FACS) (103%±13, n=17) above that in culture medium alone. This mitogenic activity was inhibited by 61%±9, n=8, with a polyclonal neutralising antibody to plasminogen activated growth factor (PDGF). Reverse transcription polymerase chain reaction analysis (RT PCR) using heterologous primers based on human sequences, showed increased expression of PDGF B mRNA in arteriovenous bypass grafts compared with ungrafted vein. These data constitute direct evidence for active growth factor production and gene expression within the cells of the vein graft. They also suggest that endogenously produced PDGF may play a role in regulating smooth muscle cell proliferation in this model.
RISK FACTORS

CORONARY HYPERGLYCAEMIA, OBESITY, HYPERTENSION, HDL-CHOLESTEROL AND PHYSICAL INACTIVITY

The strong threshold-free association between cholesterol and heart disease mortality (and non fatal cardiac events) in many cohort studies led to the population approach to heart disease prevention and to many large randomised controlled trials to reduce cholesterol (22 trials, > 40,000 individuals). A statistical overview (or meta-analysis) of these trials shows that mortality is unchanged; relative risk (RR) of death = 0.99, 95% CI (0.94-1.04). In patients with angina, but modest reductions in heart disease deaths, RR = 0.88 (0.82-0.95) are offset by increases in other cause deaths RR = 1.09 (0.99-1.20). While the findings of statistical overview depend somewhat on inclusion criteria and relative weighting of individual trials, all published overviews concur. This experimental finding might have been anticipated, since change of cause without overall reduction of mortality corroborates the epidemiological evidence of the cohort studies (32 studies, > 550,000 individuals) that gave rise to the trials. A statistical overview of cohort studies shows that the relationship between cholesterol and mortality is gently U-shaped; through most of its distribution cholesterol is not a "risk factor" for death but rather a "risk marker" for cause. Effectiveness of (population based) preventive medicine programmes should be judged more on an ability to swap cause but on their ability to reduce total mortality. Both epidemiological and experimental evidence suggest that treating the middle of the cholesterol distribution (3.0-6.5 mmol/l) does not reduce mortality.

LINOILE ACID AND RISK OF CORONARY HEART DISEASE IN WOMEN

T L Roberts, D A Wood, R A Riemersma, P J Gallagher, P C Lampe. Preventive Cardiology, Department of Medicine, University of Southampton, and Cardiovascular Research Unit, University of Edinburgh.

Linoleic acid is inversely related to the risk of coronary heart disease (CHD) in men and so the relationship between this essential fatty acid and CHD in women was examined in a population case control study of angina pectoris (AP), acute myocardial infarction (AMI) and sudden cardiac death (SCD).102 Inclusion criteria were CHD (18 SCD, 54 AMI and 39 AP) in women under 65 years with no medical history of CHD were identified from the population. Adipose tissue was sampled by suction biopsy from the anterior abdominal wall in 77 (78%) cases and fatty acid composition (%) measured by gas liquid chromatography. 209 age and sex matched healthy controls were drawn from general practices with which cases were registered and adipose tissue was obtained from 181 (78%) and analysed in the same way. The laboratory blind. The estimated relative risk (95% confidence interval) was 5.0 (3.57-44.8) for SCD; 5.3(1.7-16.2) for AMI and 1.6 (0.64-5.3) for AP when comparing the lowest and highest tertiles of adipose linoleic acid distribution in the control population. Linoleic acid is inversely related to the risk of the major clinical manifestations of CHD in women.

CORONARY RISK FACTORS AND NON-INSULIN-DEPENDENT DIABETES (NIDDM) IN BRITISH MIDDLE-AGED MEN

I J Perry, C Mannamethes, M Walker, A G Thomson, A G Shaper. Department of Public Health & Primary Care, Royal Free Hospital School of Medicine, London NW3 ZPF

NIDDM is a major contributor to the population burden of vascular disease. Coronary risk factors, such as hyperglycaemia, obesity, hypertension, dyslipidaemia and physical inactivity have been shown (in selected populations) to predict NIDDM. However, it has not been possible to examine in a population based sample, inter-relations between all of the major coronary risk factors and the development of NIDDM. In a prospective study of cardiovascular disease in 7735 middle-aged men, there were 186 new (incident) cases of NIDDM, 12.3 years follow-up. Cases were ascertained on the basis of regular, systematic reviews of primary care records and a questionnaire to them. We have examined the association between a range of cardiovascular risk factors and the development of NIDDM. Prevalent cases of diabetes and men newly diagnosed at screening were excluded (n=119). In univariate analysis, glucose and body mass index (BMI) were dominant risk factors with 5th quintile to 1st quintile relative risks of 8.0 and 11.5 respectively. In multivariate analysis (with adjustment for age and BMI) systolic blood pressure, heart rate, HDL-cholesterol and triglyceride concentration, physical activity level (inverse association) and prevalent ischaemic heart disease (IHD) emerged as significant predictors of NIDDM. On further adjustment for serum glucose at screening, only physical activity level, triglyceride concentration and prevalent IHD emerged (with glucose and BMI) as significant predictors of NIDDM. Relative risk of NIDDM for moderate or higher level of physical activity versus the lowest level, was 0.47 (0.21, 0.76). Results were unchanged in an analysis from which men diagnosed within 5 years of screening (n=58) were excluded. These findings emphasise the inter-relations between risk factors for NIDDM and cardiovascular disease.

SEVERE SYMPTOMATIC CORONARY ARTERY DISEASE (CAD) IS ASSOCIATED WITH ELEVATED LIPROPROTEIN(a) CONCENTRATION INDEPENDENT OF THE APOLIPROPROTEIN(a) ISOFROM EXPRESSED.

M Farrer, C J Albers, F L Game, M F Laker, KGMM Alberri, P C Adamas. Cardiology Department of the Royal Victoria Infirmary Newcastle upon Tyne and University of Newcastle upon Tyne.

Lipoprotein(a) is quantitatively associated with CAD and predictive of coronary events. Its circulating concentration has a strong inverse relationship with the molecular size of the circulating isoforms of apolipoprotein(a) (its specific glycoprotein). Whether particular isoforms of apolipoprotein(a) are atherogenic or is it the circulating concentration of any apolipoprotein(a) isoform which determines coronary artery disease (CAD) risk is unknown. Between October 1988 and December 1989, 318 subjects with severe CAD (CAD patients) were studied along with 468 asymptomatic healthy control subjects (C) recruited from volunteer populations. Apolipoprotein(a) isoform (10 classes identified by SDS polyacrylamide gel electrophoresis and Western blotting) and serum lipoprotein(a) concentration (ELISA; Biopool Umea Sweden, coefficient of variation 3-8%) were determined in addition to other clinical variables and traditional risk factors. Lipoprotein(a) concentrations were almost twice as high in CAD patients (152 mg/l GM; 139-166, 95% CI vs C 84, 78-89, p<0.001). Lipoprotein(a) concentration in CAD patients was higher than in asymptomatic controls for "null", single, and double band phenotypes, and for almost every isoform mobility in both single and double band phenotypes. The frequency of expression of the various isoform classes was almost identical with a small excess of lower slower "null", "slow" isoforms in the CAD group. As there were differences between subject groups in other risk factors these were adjusted for by multivariate linear regression analysis with circulating lipoprotein(a) concentration as dependent variable. In stepwise models mean isoform mobility, number of isoform bands, and CAD were the three strongest independent determinants of lipoprotein(a) concentration (p<0.001 for all three). We conclude that CAD is associated with increased lipoprotein(a) concentrations independent of the isoform of apolipoprotein(a) expressed and concentration rather than isoform determines CAD risk.
INDEPENDENT ASSOCIATION BETWEEN CARDIOVASCULAR RISK FACTORS AND RENAL SODIUM HANDLING IN A POPULATION STUDY. 

PP Capewell1, P Serazur1, E Partamian1, M Tevian2, 
1Blood Pressure Unit St George’s Hosp, Med, School, London; 
2nd Med School, Napels (1), SUNY at Buffalo, NY (USA).

Both hypertension and non-insulin-dependent diabetes are associated with greater morbidity and mortality from coronary heart disease and stroke. They also express some abnormalities of the renal handling of sodium suggesting a possible primary role in these conditions. However, no systematic study has ever been carried out to date to investigate the possible association between renal sodium handling and cardiovascular risk factors. Aim of the present study was to investigate for the first time in an epidemiological setting the relationship between proximal tubular function and cardiovascular risk factors in 568 unrated male workers (age 21-65 yrs). A renal clearance study in the fasting state was performed in all participants after an oral load of 8.1 mmol of lithium (Li) the night before according to a standard protocol. Fractional excretion (FE) of Li was taken as an index of proximal sodium handling. The table reports age-adjusted values according to tertiles of FE of Li (<21%, 21.6-25.4%, >25.4%). P values are by ANCOVA.

<table>
<thead>
<tr>
<th>FE Li</th>
<th>n</th>
<th>Wt</th>
<th>DBP</th>
<th>TC</th>
<th>HDL</th>
<th>LDL</th>
<th>Glu</th>
<th>UA</th>
<th>Ac</th>
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<tr>
<td>1st</td>
<td>189</td>
<td>75.8</td>
<td>87.4</td>
<td>5.87</td>
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<td>87.4</td>
<td>3.90</td>
<td>5.05</td>
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<tr>
<td>2nd</td>
<td>196</td>
<td>72.9</td>
<td>5.62</td>
<td>1.51</td>
<td>3.78</td>
<td>303.5</td>
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<tr>
<td>3rd</td>
<td>189</td>
<td>72.8</td>
<td>85.7</td>
<td>5.62</td>
<td>1.51</td>
<td>3.77</td>
<td>491.3</td>
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<tr>
<td>p</td>
<td></td>
<td>0.004</td>
<td>ss</td>
<td>0.017</td>
<td>ss</td>
<td>ss</td>
<td>&lt;0.001</td>
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</table>

In separate multiple regression analyses after fixed adjustment for age, smoking, alcohol intake and sodium excretion, FE Li was inversely related to DBP (T=1.88,p=0.06), weight (T=2.34,p=0.018), serum triglycerides (T=2.63,p<0.004), serum uric acid (T=4.47,p<0.001) and directly to serum HDL-cholesterol (T=1.88,p=0.06). The present study describes a clear independent association between risk factors for cardiovascular disease and an increased proximal sodium reabsorption at the renal tubule consistent with an overall relationship between insulin resistance and tubular sodium handling.

LATE COMPLICATIONS OF THIRD GENERATION CARDIOVERTER-DEFIBRILLATORS

SS O Nuna, TG Trount, M Roeilke, YH Kim, B McGovern, H Garan, JN Ruskin. Massachusetts General Hospital, Boston, USA.

Between September 1989 and August 1992 one hundred and thirty nine patients underwent implantation of a tiered-therapy implantable cardioverter-defibrillator (ICD). Pulse generators from three different manufacturers were used. In 37 patients a complete non-thoracotomy lead system was employed. Of these 139 patients, 26 % have experienced late post-operative ICD-related problems. Nineteen patients have required system revision within 36 (mean 5.7 ± (SD) 3.7) months of surgery. Reasons for revision were: spurious or aborted shocks due to electrode fractures (4) or electrode adaptor malfunction (1); failure of endocardial rate-sensing electrodes (3); superior vena cava or right ventricular coil migration (5); failure to correct tachyarrhythmia due to a post-implant rise in defibrillation threshold (5) or pulse generator failure (1). One of these patients required system removal for infection after revision of an endocardial lead. Thirteen patients have received inappropriate countershocks for atrial fibrillation with a rapid ventricular response or sinus tachycardia. In two of these patients inappropriate anti-tachycardia pacing for atrial fibrillation induced ventricular tachycardia which was terminated by ICD shock countershocks. In one patient back-up bradycardia pacing repeatedly induced ventricular tachycardia resulting in ICD discharges. Three further patients received shocks in normal sinus rhythm- two because of autogain induced oversensing and a third because of a mechanical induced lead noise from a redundant rate sensing lead. CONCLUSION: Despite advances in ICD technology a significant proportion of patients continue to experience mechanical complications or receive inappropriate shocks for tachycardias of supraventricular origin.

HAEMATOCRIT AND THE RISK OF ISCHEMIC HEART DISEASE

G Wannamethee, A.G. Shaper, P.H. Whincup, Department of Public Health and Primary Care, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF.

The haematocrit is a strong determinant of blood viscosity and there is growing evidence that blood viscosity plays an important role in the development of atherosclerosis. However the relationship between haematocrit and major ischaemic heart disease events in population studies has remained uncertain. While most of these studies have assumed a linear relationship between haematocrit and outcome, it has recently been suggested that risk may be increased only above certain threshold levels of haematocrit. The relationship between haematocrit and risk of major ischaemic heart disease (IHD) was examined in 2735 middle-aged men drawn from general practices in 24 British towns. During the follow-up period of 9.5 years in the 7346 men with available data on haematocrit (mean 44.47% and SD 3.162), 580 men suffered a major ischaemic heart disease event (non-fatal and fatal). Risk of major IHD events was significantly increased only above haematocrit levels of >46.0%. Moreover, a high haematocrit (>46.0%) showed a 32% increase in relative risk of IHD (RR = 1.32, 95% CI 1.10-1.57; p = 0.01) compared with those with levels below 45.0%. After adjustment for age, social class, smoking, body mass index, physical activity, blood cholesterol, lung function (FEVI) and pre-existing evidence of heart disease, systolic blood pressure reduced the risk slightly but it remained significant (RR = 1.27, 95% CI 1.06-1.51; p = 0.02). The relationship was seen in men with and without existing evidence of IHD. The study suggests that an increased haematocrit plays a role in the development of major IHD events independent of the established coronary risk factors.

VENTRICULAR TACHYARRHYTHMIA TERMINATION BY THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR: THE ACUTE EFFECT ON LEFT VENTRICULAR FUNCTION

PA Broadhurst, G Timmins, CJ Hinds, NW Nathan. Departments of Cardiology and Anaesthesia, St Bartholomew’s Hospital, London.

Patients with the Implantable Cardioverter-Defibrillator (ICD) often have impaired left ventricular (LV) function and further myocardial depression following tachyarrhythmia and shock delivery may be deleterious. We examined the acute effects of induced ventricular fibrillation (VF) and ventricular tachycardia (VT) followed by ICD shocks on LV function in 10 patients (9 male), with a mean age of 55 (range 27-70) years and mean ejection fraction (EF) of 38% (range 20-60%), as measured at angiography. LV function was continuously monitored beat-to-beat with a miniature, non-imaging high temporal resolution nuclear probe (Cardioscint, Oakfield Instruments Ltd, Oxford, UK) before, during and for 2 minutes after shock delivery. Eight episodes of VF were induced, and these were followed by a transient (but significant) fall in mean EF (SD) from 54.2(8.7)% just before arrhythmia induction to 39.9(7.4)% in the 10 seconds after the shock (p=0.015); by 20 seconds this had recovered to 49.3(10.1)% (p=0.04 relative to baseline). Seven shocks were delivered following induced VT and these were followed by a significant fall in EF from 57.9(9.7)% to 50.5(6.4)% (p=0.047) but with recovery to 56.1(6.6)% by 20 seconds (p=0.09 relative to baseline). LV EF did not differ significantly from baseline in the two groups at 2 minutes post-shock. Four episodes of spontaneously terminating induced VT produced a similar fall in EF in 10 seconds post-termination and again recovery by 20 seconds. We conclude that shocks delivered by the ICD in response to induced ventricular tachyarrhythmias produce only transient disturbances of LV function.
MECHANICAL, BUT NOT INFECTIVE, PACEMAKER EROSION MAY BE SUCCESSFULLY MANAGED WITH PACemaker RE-IMPLANTATION.
MJ Griffith, JP Mountney, RS Bexton, MP Holden. Cardiac Department, Freeman Hospital, Newcastle upon Tyne.

An eroded pacemaker box is usually managed by explantation, with implantation of a new contralateral pacemaker. At this centre, in the absence of evidence of systemic infection, we attempted cleaning and re-implantation of the pacemaker in the same site. Results: Over ten years, 62 patients underwent pacemaker re-implantation, 18 undergoing re-implantation twice. Re-implantation had proved successful, after at least 6 months follow up, in 38 patients (61%), 9 of whom had attempted it twice. Mean hospital stay for all patients was 21.3 days, for successful patients 12.5 days and for unsuccessful patients 35.4 days. Of the patients with successful re-implantation 31/38 (82%) had no bacterial growth from wound swabs. Wound swabs grew bacteria in 17/24 (71%) patients with unsuccessful re-implantation (p<0.001).

Bacteria were grown in 7/8 patients with a protruding wire compared with 9/23 patients with a protruding pacemaker (p=0.05). Thin and older patients were more likely to have successful re-implantation, but neither of these factors reached statistical significance. A clinical impression of infection was not helpful. If only the patients with negative wound swabs had had attempted re-implantation, the success rate would have been 82%, with a cost of £4,492, compared with a cost of £6,509 for explantation and a new contralateral pacemaker. Conclusion: These data support the thesis that pacemaker erosion is caused by two mechanisms, primary infection or a non infective process, probably mechanical pressure. Pacemaker erosion which is not due to infection may be successfully managed by ipsilateral re-implantation, and this approach can also be justified on financial grounds.

TWO FURTHER DISEASE LOCi FOR HYPERTROPHIC CARDIOMyOPATHY
HC Watkins, CA MacRae, LH Thierfelder, WJ McKenna, JG Seidman and CE Seidman. Harvard Medical School, Boston, USA, and St George’s Hospital Medical School, London, England.

Familial hypertrophic cardiomyopathy (FHC) is caused by missense mutations in the β cardiac myosin heavy chain gene in less than half of affected individuals (locus designated CMH1). Neither the gene nor chromosomal location of any other FHC locus is known. Therefore, the clinical benefits of genetic diagnosis are confined to a subgroup of patients with this disease. To identify the location of other genes involved in this disorder, two large kindreds in whom the disease locus does not map to the CMH1 locus were studied (families AU and SB). Linkage analyses were performed with highly polymorphic short tandem repeat sequences dispersed throughout the genome. Analyses in family AU led to the identification of a novel disease locus, designated CMH2 (LOD score 8.5). Analyses in family SB also led to the identification of a new disease locus, designated CMH3 (LOD score 4.2). Studies in smaller families with FHC not linked to the CMH1 locus revealed linkage to the CMH2 locus in two and to the CMH3 locus in one, with yet other families not linked to either locus. Thus mutations in at least four genetic loci can cause FHC. Sarcomeric contractile protein genes that map to the vicinity of the new loci are candidate FHC genes.

NON-INVASIVE ATRIAL AND VENTRICULAR PACING USING AN ESOTHRACIC PACING SYSTEM
D McEneaney, J Adgey, J Anderson. Cardiac Unit, Royal Victoria Hospital, Belfast

Transcutaneous non-invasive cardiac pacing has several disadvantages – low success rate, a poor patient tolerance, and lack of AV sequential pacing capability. We have developed a novel esothoracic pacing system capable of non-invasive atrial(A), ventricular(V) and AV sequential pacing. The flexible polyethylene Gastro-Oesophageal(GO) electrode is passed into the stomach after which the distal 6cm is angled to 90° using an internal pulley system. The electrode is then withdrawn until it meets the resistance of the GO junction, thus positioning the electrode tip in the gastric fundus. V pacing is performed using a cathodic point source mounted on the electrode tip; the indifferent electrode (anode) is either a high impedance chest pad placed medial to the cardiac apex (unipolar V pacing, UV) or a ring electrode positioned 2cm proximal to the GO electrode tip (bipolar V pacing, BV). UV was compared with BV in 20 patients (14 male, 6 female; age 68.4±12.5) with stable bradyarrhythmias. V capture was more successful with UV(19/20,95%) than with BV(10/20,50%); p=0.001. Where capture was obtained by both methods (pulse duration 40ms) threshold current (I) for UV was lower (UV 22.6±2SD,9, BV 33.3±2SD,7; p=0.03). Four ring electrodes (1,2,3,4) proximal to distal) positioned proximally on the GO electrode and thus lying in the lower orophagus are used for A pacing. Unipolar A (UA) pacing is performed using one ring electrode as cathode and a high impedance chest pad positioned medial to the apex as anode. Conducting ring electrodes (1,2,3,4,5,6) are used for bipolar A pacing (BA). In all patients A capture could be achieved using both UA and BA. Threshold current (pulse duration 9ms) for A capture was similar (UA 25.4±4SDS,8, BA 21.7±4SDS,9; p=ns).In 6 patients where all combinations of UA and BA were investigated failure to capture was more common with UA(9/24) than with BA(6/36). In conclusion the optimal electrode configuration for esothoracic pacing uses BA and UV. This pacing system was useful in the elective evaluation of conduction disorders and for emergency AV sequential pacing during acute bradyarrhythmias.

ALTERED CARDIAC BETA-ADRENERGIC RECEPTOR DENSITY IN HYPERTROPHIC CARDIOMYOPATHY: EVIDENCE FOR ABNORMAL CARDIAC SYMPATHETIC NERVE FUNCTION
D C Lefroy, R de Silva, L Choudhury, N G Uren, T Crake, C G Rhodes, H Boyd, P Nihoyannopoulos, C M Oakley, P G Camici
MRC Cyclotron Unit, Hammersmith Hospital, London

Myocardial β-adrenoceptor density (BRD) was measured in 11 patients (age 37.10 years, mean(S.D.); 10 male) with hypertrophic cardiomyopathy (HCM) and 8 normal male control subjects (age 28.7). none of whom had previously received β-blockers or amiodarone. Positron emission tomography (PET) with 2-C[14]CGP 12177 (a high-affinity, hydrophilic, non-selective β-adrenoceptor ligand) was used to determine BRD in the left ventricle (LV). Myocardial blood flow (MBF) was measured by PET using H2[15]O as a flow tracer. Plasma adrenaline (A) and noradrenaline (NA) concentrations were determined (*p<0.01 vs control):

<table>
<thead>
<tr>
<th>BRD(pmol/g)</th>
<th>MBF(ml/min/g)</th>
<th>A(ng/ml)</th>
<th>NA(ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls 10.1(2.2) 0.9(0.21) 0.27(0.09) 0.77(0.19)</td>
<td></td>
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<tr>
<td>HCM patients 7.2(1.9)* 0.91(0.22) 0.40(0.19) 0.93(0.38)</td>
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</table>
| MBF and BRD in 4 LV regions (anterior, lateral, posterior and septum) and 5 adjacent transverse scan planes were uniform within both groups. BRD in each region in the HCM patients was significantly lower compared with the corresponding region in the controls, although MBF was similar. In the HCM patients, BRD in regions of greatest LV wall thickness was not significantly different from BRD in regions of least LV wall thickness (9.0(2.2) vs 7.9(1.6)pmol/g). Repeat PET after 4 months in 4 subjects showed a variability of 17.8% in BRD between measurements. Thus in HCM, there is a diffuse reduction in left ventricular BRD. In the absence of significantly raised plasma catecholamine concentrations, β-adrenoceptor downregulation may be due to increased cardiac sympathetic nerve release of NA. This may contribute to the LV hypercontractility and dysrhythmias seen in HCM, and to the development and maintenance of LV hypertrophy.

British Heart Journal: first published as 10.1136/hrt.69.5_Suppl.P56 on 1 May 1993. Downloaded from http://heart.bmj.com/ on September 18, 2023 by guest. Protected by copyright.
ROLE OF THALLIUM-201 REINJECTION IN THE ASSESSMENT OF MYOCARIAL VIABILITY FOLLOWING MYOCARDIAL INFARCTION
S Basu, B Sridhara, R Senior, D M Duncker, U Raval, C E Handler, E R Raftrey, A Lahiri
Northwick Park Hospital, Harrow, Middlesex

We have compared the diagnostic accuracy of TI-201 redistribution and TI-201 rest re-injection after exercise in the detection of myocardial viability in 36 patients (pts) within one week of acute myocardial infarction (MI). Planar TI-201 imaging was performed after exercise, 4 hrs later and on a separate day 1 hr after rest re-injection of the tracer. A panel of 3 blinded observers reported all data sets from unprocessed and computer enhanced images. Segmental TI-201 images were scored as normal, reversible ischaemia, fixed or mixed type of uptake. In 27 (70%) pts the scan was abnormal at stress and 170 out of the total 486 segments were abnormal. Redistribution occurred in 29 out of 170 (18%) abnormal segments at 4 hrs. However, after re-injection of TI-201, 55 (37%) segments normalized. Compared to redistribution, rest re-injection showed a significantly higher number of reversible segments (19%) (p<0.03). In 6/27 (22%) pts the diagnosis was changed from purely infarction to reversible ischaemia (p<0.02). A substantial number of pts showed evidence of viability in regions which would otherwise be considered necrotic. These data suggest that TI-201 redistribution imaging may be misleading. Thus, a separate rest TI-201 study is essential for the accurate measurement of myocardial viability in pts with recent MI.

INDEPENDENT ORIGIN OF IDENTICAL MYOSIN MUTATIONS IN HYPERTROPHIC CARDIOMYOPATHY
HC Watkins, LH Thierfelder, R Anan, CA MacRae, WJ McKenna, JG Seidman and CE Seidman. Harvard Medical School, Boston, USA, and St George’s Hospital Medical School, London, England.

The origins of the β cardiac myosin heavy chain (MHC) gene missense mutations that cause hypertrophic cardiomyopathy (HCM) in fifteen families have been evaluated. Of nine different mutations, five were present in single families, while four occurred in two or more apparently unrelated families. Two explanations could account for the finding of identical mutations in different families; this might reflect either a founder effect or recurrent identical mutation. To investigate the origins of these four shared mutations we defined the β cardiac MHC haplotypes of each of the mutation-bearing chromosomes by determining the alleles present at three intra-genic polymorphic loci. These included two tandem repeat polymorphisms which are highly variable, with multiple alleles present within a population. Thus unrelated individuals will tend to have different haplotypes, i.e. different patterns of alleles within the gene. Two of the mutations (Arg53Cys and Val606Met) have arisen independently in each of three families, being found on different chromosomal backgrounds. A third mutation (Gly584Arg) is associated with identical haplotypes in two families with Portuguese ancestry, suggesting a founder effect. Haploype analysis was uninformative for the fourth mutation (Arg403Gln). Thus, HFC-causing mutations have arisen independently in at least thirteen of the fifteen families studied, suggesting that the majority have arisen recently as new mutations. This finding predicts the prevalence of HFC-causing mutations to be similar in all population groups.

Adenosine and Exercise Stress: Are Thyllium Defects Comparable?
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Adenosine Thallium imaging has been proposed as a useful way of assessing coronary artery disease in patients unable to exercise with several studies reporting that thallium defects are larger with adenosine coronary artery disease compared to exercise. A blinded observer, with exercise and adenosine data from 55 patients (28 males, 27 females) was carried out on a separate day from both exercise (symptom limited bicycle ergometer) and adenosine (infused at 50mcg/kg/min) using a triangle (84±280) beats/min. A significant difference was found in thallium uptake (94±20) beats/min) while adenosine produced no significant change (84±20) beats/min). Each scan was analysed planar images and divided into 5 segments. Exercise produced abnormal defects in 4490 (anterior view) 4495 (40 LAO) and 4595 (75 LAO). Adenosine produced 53/100, 44/100, 52/100 abnormal segments in the Anterior, 40 and 75 views respectively. The total number of abnormal segments was similar in both groups (EX339/200 & AD149/200). Each abnormal segment was analysed for degree of change between stresses using a 5 point scoring system. Exercise produced 8 segments which were larger by 1 point and 44 segments larger by 2 points while adenosine produced 17 and 44 segments larger by 1 and 2 points respectively. LV uptake was significantly greater in the adenosine group (1.12±.05% vs 0.64±.05% p<0.01) but RV uptake was similar in both groups. LV uptake was greater in the adenosine group (2.28±0.13 vs 1.18±0.18 p<0.01). Lung uptake was similar for both forms of stress (1.41±0.67 vs 1.39±0.97). In summary adenosine produces thallium defects comparable to exercise. Despite no significant change in Double product with adenosine, thallium defects were of similar size and frequency to those produced by exercise, probably due to the relatively greater LV uptake of thallium with adenosine.

ALPHA MYOSIN HEAVY CHAIN GENE MUTATIONS ARE NOT A MAJOR CAUSE OF FAMILIAL HYPERTROPHIC CARDIOMYOPATHY
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A gene for Familial Hypertrophic Cardiomyopathy (FHC) has been linked to chromosome 14q1 in several large pedigrees. RNase protection has detected 9 different cardiac β myosin heavy chain (MHC) gene mutations in probands from affected kindreds. To assess the sensitivity of RNase protection in this context we performed linkage analysis on 13 kindreds in whom no mutations had been found on screening the β MHC gene. Highly informative dinucleotide repeats in the 3' untranslated region and in intron 24 of the cardiac β MHC gene were used for linkage analyses as these kindreds had been too small for previous linkage studies using RFLPs. Alleles were amplified from genomic DNA using PCR primers bracketing the polymorphic repeat sequences. Nine kindreds were informative using one or other of the polymorphisms and in every case linkage to the MHC genes was excluded (LOD scores of <2 in favour of linkage at θ = 0). In each of the 4 kindreds which were not informative at least one crossover was evident. These data confirm that RNase protection is a sensitive method for screening for mutations within the cardiac β MHC gene. The results further support previous estimates suggesting that approximately 50% of cases FHC are due to missense mutations in the cardiac β MHC gene with other loci responsible for the remainder. Finally, mutations in the non-coding regions of the β MHC gene and mutations in the α MHC gene are excluded as significant causes of FHC.
ADENOSINE COMBINED WITH EXERCISE FOR THALLIUM-201 MYOCARDIAL TOMOGRAPHY IMPROVES IMAGING AND REDUCES SIDE-EFFECTS.

Adenosine is being used increasingly for thallium imaging, but it causes high splanchnic uptake and frequent side effects. We studied the value of adding exercise to adenosine in 362 patients. Randomisation was performed in 300 to adenosine alone, or adenosine with supine bicycle exercise, whilst 62 were excluded because of asthma, dyspиридamide medication or caffeine intake. A perfusion score from 0 (normal) to 36 was calculated from the extent and severity of defects in the tomograms. Coronary angiography was performed in 165 (55%). Exercise significantly reduced the incidence of flushing, headache, nausea, anxiety and dizziness (all p<0.01). Dyspnoea and fatigue, but not chest pain, were more common with exercise (both p<0.02). Dysrhythmia was more common with adenosine alone (p<0.0001) including 2° and 3° heart block, sinus bradycardia, sinus arrest and premature ventricular beats (all p<0.05). One cardiac arrest occurred in the adenosine only group. There were no differences between groups in detection of coronary artery disease (overall sensitivity and specificity 98% and 80%). Thallium scores for stress and rest were similar between groups but the reversibility score was higher in the exercise group (6.9 vs 5.3 p<0.05). The heart to gut counts ratio was significantly higher with exercise (1.77 vs 1.34 p<0.02).

The addition of exercise to adenosine for thallium imaging is safe and reduces the incidence of cardiac dysrhythmias and unpleasant vasodilatory non-cardiac side effects. Image quality is improved by the reduction of splanchnic uptake and greater reversibility is seen.

MAGNETIC RESONANCE IMAGE ENHANCEMENT OF NECROSSED MYOCARDIUM USING GADOLINIUM BOPTA
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Magnetic resonance imaging (MRI) can now be used to detect, localise and size an acute myocardial infarction (MI) using spin echo techniques. We report the use of the contrast agent Gd-BOPTA (Gd) which enables the infarcted myocardium to be visualised using T1 sequences.

Twenty patients (aged 44 to 65) were imaged 5 to 7 days after their first MI. MRI was performed before and after the administration of Gd BOPTA using T1 and spin echo techniques. Five patients received a Gd BOPTA dose of 0.55mmol/Kg, 5 received 0.1mmol/Kg and 10 0.2mmol/Kg.

No obvious differences were detected on MRI T1 scans using the smaller doses. Seven of the 10 patients receiving a dose of 0.2mmol/Kg had a technically satisfactory scan. In all 7 of these there was a difference observed between the normal and necrosed myocardium using the T1 scan after Gd BOPTA administration. The mean density of myocardial tissue using T1 scan was 568 (95% C.I. 495 to 690). Following the administration of Gd BOPTA the mean density of normal myocardium was 639 (95% C.I. 530-738) and of infacted tissue 1070 (95% C.I. 968-1190).

When analysed with the paired T test the mean difference between normal and infarcted tissue was 423 (p<0.001).

We conclude that T1 MRI scans can be used to identify infarcted tissue using Gd BOPTA.

CIGARETTE SMOKING CAUSES DOSE-DEPENDENT AND POTENTIALLY REVERSIBLE ENDOTHELIAL DYSFUNCTION IN HEALTHY YOUNG ADULTS
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In order to assess whether smoking is associated with endothelial dysfunction, we studied non-invasively the brachial arterial-venous difference (GTN, Pi) initially from a large group medically defined of 'deterioration' are usually based on group mean data. In 51 CAD patients (mean age 56; 42 men), 95% prediction intervals (PI) - the statistically ordered limits within which an individual's subsequent measurement should lie with 95% probability - were derived for prognostic left ventricular ejection fraction (LVEF) indices to suggest the minimum change from baseline that might be considered clinically important, alerting clinicians to review the need for coronary angiography or revascularisation in the individual. Exercise radioiodine ventriculography (RNAV) was used to measure LVEF indices at baseline and 6 months later without interruption of medication. None suffered a cardiac event in the 6-month interval and ensuing 9 months. At 6-month RNAV, 22 patients showed apparent deterioration in exercise LVEF or the change in LVEF with exercise (CLVEF). Only 2 patients had 6-month values outside of 95% PI, compared with 15 for 95% group confidence intervals (z = 3.33, P < 0.001; 95% CI = 0.27 to 0.91). When CLVEF = 0 at baseline, the lower limit of 0.25 was achieved in only 2 of 7 patients (just 13%). For a baseline exercise LVEF of 50% (just normal), the lower limit of 54% PI was 38%, i.e. the exercise LVEF could be measured as low as 38% ≥ 6 months later without necessarily indicating or missing true significant deterioration. Thus, in the follow-up of the minimally symptomatic individual with CAD, long-term 'deterioration' in prognostic LVEF indices can be interpreted more meaningfully with reference to 95% prediction intervals. This approach may be applicable to other test modalities when the interpretation of serial changes relates to the individual rather than to a group.
THE EFFECT OF OESOPHAGEAL STIMULATION ON CORONARY BLOOD FLOW
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Regional Cardiac Unit, Papworth Hospital, Cambridge

It has been shown previously that in patients with established coronary artery disease, oesophageal stimulation by instillation of acid can bring on attacks of angina. To investigate the hypothesis that oesophageal stimulation may affect coronary blood flow, we studied the effect of oesophageal acid stimulation on coronary blood flow in 32 patients with chest pain, a positive exercise test and normal coronary arteries (Syndrome X group) and 18 heart transplant patients (HT group). All anti-anginal medications were stopped 48 hours prior to the study. A fine tube was introduced through the patient's nose in to the distal oesophagus prior to the catheter study. A standard femoral approach was used for the cardiac catheter and 10,000 units of heparin was given. A 3.6F intracoronary Doppler catheter (Schneider, U.K.) was positioned in the proximal left anterior descending coronary artery. The coronary blood flow velocity (CBFV) and mean arterial pressure were recorded. Oesophageal instillation of 0.1M hydrochloric acid was commenced (60 ml over 5 minutes) and the measurements were repeated after the infusion. Patients were instructed before the study to report any chest pain during the oesophageal stimulations. Twenty patients in the Syndrome X group reported their usual chest pain on the instillation of acid. None of the patients in the HT group experienced any chest pain. There was no significant difference in mean arterial pressure before and after infusions in both groups. The coronary blood flow velocity was significantly reduced by the acid oesophageal stimulation in the Syndrome X group: CBFV pre-acid 10.8 ± 0.9, CBFV post-acid 6.3 ± 0.6 cm/sec (p < 0.01, Wilcoxon signed-rank test). However, there was no significant difference in the mean CBFV in the HT group: CBFV pre-acid 7.7 ± 0.94, CBFV post-acid 7.7 ± 0.97 cm/sec (p = NS). We conclude that oesophageal stimulation can produce typical anginal chest pain and significantly reduce coronary blood flow. The lack of any significant effect in the HT group, in whom the heart is denervated, suggests a neural mechanism affecting the coronary vascular tone.

MECHANISMS OF COLD INTOLERANCE IN PATIENTS WITH EXERTIONAL ANGINA
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Cold intolerance is common in patients with angina but the mechanism has not been defined in clinical studies. We have measured the effects of cold exposure on peripheral vascular resistance and the perception of exertional myocardial ischaemia in 12 male patients with coronary artery disease all of whom had ST segment depression and chest pain during treadmill stress testing. The patients underwent sequential treadmill stress tests in a temperature-controlled chamber at 22°C and 6°C in random order. Vascular resistance was measured in the brachial artery bed using Doppler measurements of brachial flow. The perception of myocardial ischaemia was inferred from anginal latency: the time from onset of 0.1mV ST depression to angina. Before exercise, vascular resistance in the cold was similar to vascular resistance at room temperature (2.03 ± 0.20 versus 1.78 ± 0.18 mmHg litre⁻¹ min⁻¹, p=0.2), but mean arterial pressure was significantly higher (122±4 versus 96±6 mmHg, p=0.01). However, at peak exercise both vascular resistance (1.43 ± 0.16 versus 0.96 ± 0.12 mmHg litre⁻¹ min⁻¹, p=0.001) and mean arterial pressure (138±11 versus 118±9 mmHg, p=0.04) were markedly higher in the cold. In addition to the increase in vascular resistance, cold exposure also tended to heighten the perception of myocardial ischaemia. Thus anginal latency was shorter in the cold compared with room temperature (85±26 versus 141±42 s, p=0.15). In conclusion, cold intolerance in patients with exertional angina is caused principally by increments in peripheral resistance. However, there is some evidence that heightened perception of myocardial ischaemia may play a contributory role.

VESEL WALL INJURY AT A CORONARY STENOSIS CAUSES CORONARY MICROVASCULAR CONSTRUCTION
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Texas A&M University Health Science Center and University of Texas Medical School, TX, USA and University of Wales College of Medicine, Cardiff

Vascular injury at coronary stenoses (VICS) leads to cyclic flow variations (CFVs), mediated by the release from aggregating platelets of vasoactive substances, such as thromboxane A2. We hypothesised that thromboxane A2, released at sites of VICS, constricts downstream microvessels. To test this, we measured coronary microvascular diameters (range 33-206 µm) and systemic haemodynamics in the beating canine heart using fluorescent microangiography during stroboscopic epi-illumination synchronised to the cardiac cycle (1) before and during intracoronary infusion of the stable thromboxane analogue, U46619 (10 and 30 nM, 10,000 puffs, 28 vessels), in 12 normal animals and (2) at 10 minute intervals after VICS before and after administration of a thromboxane A2 receptor antagonist SQ29548 (0.4 mg/kg i.v., 12 vessels) in 5 animals. In the normal group (Study 1), U46619 did not change haemodynamics, but constricted coronary microvessels (-72±1% and -112±1% diameter, both p<0.05). After VICS (Study 2), systemic haemodynamics were unchanged, but coronary microvessels progressively constricted (-62±2% diameter at 30 minutes, p<0.05). The constriction was not significantly reversed by SQ29548 (+32±4% diameter, NS). Thus, U46619 introduced into the upstream coronary artery is a potent constrictor of coronary microvessels, supporting the possibility that thromboxane A2 (10±10 seconds) may cause coronary microvascular constriction during CFVs. However, the results demonstrate that injury and stenosis of an upstream large coronary vessel leads to coronary microvascular constriction, which is not mediated by thromboxane A2. This phenomenon contrasts with the microvascular dilatation seen with coronary stenosis in the absence of vascular injury, and may contribute to coronary blood flow reductions in patients with coronary stenosis and unstable angina.

HYPERINSULINAEMIA IN ISCHAEMIC HEART DISEASE - THE IMPORTANCE OF LEFT VENTRICULAR FUNCTION
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Hyperinsulinemia is associated with ischaemic heart disease and has often been described in patients following myocardial infarction. The groups studied have been heterogeneous and the importance of left ventricular impairment has not been addressed. This study compared the insulin response to a 75g oral glucose load in normal controls (N), patients with stable angina (SA), NYHA grade III chronic heart failure (CHF, mean LVEF 20%) or recent uncomplicated myocardial infarction assessed either at 3 weeks (MI-1, mean LVEF 38%) or at 3 months (MI-2, mean LVEF 39%). Ninety-one patients with fasting glucose <6.7 mmol/l were screened to identify those with normal glucose tolerance (120 minute glucose <7.8 mmol/l) and 21 with impaired glucose tolerance were excluded because of the known association with hyperinsulinemia. The mean insulin (muU) results are given in the table.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Normals</th>
<th>SA</th>
<th>MI-1</th>
<th>MI-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.3</td>
<td>9.1</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>30</td>
<td>57.7</td>
<td>64.7</td>
<td>80.5</td>
<td>70.2</td>
</tr>
<tr>
<td>60</td>
<td>74.4</td>
<td>90.1</td>
<td>107.3</td>
<td>105.3</td>
</tr>
<tr>
<td>90</td>
<td>53.4</td>
<td>86.7</td>
<td>102.4</td>
<td>104.9</td>
</tr>
<tr>
<td>120</td>
<td>36.0</td>
<td>42.0</td>
<td>87.2**</td>
<td>87.7***</td>
</tr>
</tbody>
</table>

p < 0.05, **p < 0.01, ***p < 0.001 (unpaired t test v Normals, where ANOVA revealed a significant difference between the 5 groups)

Conclusion: Fasting hyperinsulinemia was only a feature of ischaemic heart disease in the presence of moderate to severe heart failure. Stimulated hyperinsulinemia was present in chronic heart failure and for at least 3 months after recent myocardial infarction in the absence of heart failure. Hyperinsulinemia was not prominent in patients with chronic stable angina and normal glucose tolerance.
INSULIN RESISTANCE AND METABOLIC RISK FACTORS IN PATIENTS WITH ANGINAL CHEST PAIN
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Associations between metabolic abnormalities and angiographically defined coronary artery disease (CAD) were investigated. The purpose of this study was to examine metabolic risk markers in patients with anginal chest pain referred for coronary angiography. Three groups of patients were investigated. Group 1 (n = 39) presented with chest pain and angiographically normal CAD. Group 2 (n = 38) had chest pain with normal coronary angiography and group 3 (n = 40) were asymptomatic, clinically healthy volunteers, with no angiography. All were non-obese (80-120% ideal body weight) males and the groups were of similar mean age and body mass index. Insulin sensitivity was calculated from insulin and glucose levels during an intravenous glucose tolerance test. We also measured serum lipids, lipoproteins and body fat distribution (ratio of android to gynoid fat by dual energy X-ray absorptiometry). Both chest pain groups had 26-28% lower insulin sensitivity compared to normal men, with no difference in fasting insulin levels. Android/gynoid fat ratio showed a significant trend through the groups, increasing from group 3 to group 1. The major differences in lipids were observed between the asymptomatic normal males compared with either chest pain group (whose profiles were not significantly different). The following table shows mean values (±SEM) for selected variables:

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin sensitivity (min (mU/mI))</td>
<td>2.2±2.16</td>
<td>2.59±*</td>
</tr>
<tr>
<td>Android/gynoid ratio</td>
<td>(+0.22-0.23)</td>
<td>(+0.23-0.26)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>205±5.3</td>
<td>200±6.7</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>141±(10-10)</td>
<td>132±(10-9)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>41±1.4</td>
<td>40±1.3</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>8.8±0.7</td>
<td>9.3±0.8</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>128±3.1</td>
<td>131±6.3</td>
</tr>
</tbody>
</table>

* = p<0.05, ** = p<0.01 for group 1 vs groups 2 or 3; † = p<0.05, †† = p<0.01 for group 2 vs 3. (ANOVA significant at 5%)

Insulin sensitivity was positively related to HDL cholesterol and negatively related to triglycerides, android/gynoid fat and systolic blood pressure. This study provides further evidence for the role of insulin resistance in the development of CAD. Both angina groups had disturbed metabolic risk markers regardless of the angiographic appearance, indicating a previously unrecognised metabolic link. It cannot be assumed that normal coronary angiography is associated with a normal metabolic profile risk for CAD.

LOW SERUM MAGNESIUM LEVELS ARE NOT ASSOCIATED WITH VENTRICULAR FIBRILLATION.
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Intravenous magnesium given early following acute myocardial infarction (AMI) may reduce the incidence of ventricular fibrillation (VF) and mortality. There is, however, little evidence associating low serum magnesium concentrations with VF. We measured admission serum magnesium levels (ref. 0.7-1.00 mmol/l) in 803 CCU patients over 12 months. The mean serum magnesium in AMI patients (n=553) was 0.81±0.08 mmol/l slightly lower than the mean level in non AMI patients (0.82±0.08 mmol/l, n=450) [p<0.05]. Early VF (within 24 h of symptoms) occurred in 30 patients (16 predmission and 2 pacing related). The mean serum magnesium level in patients whose VF occurred after sampling (n=12, all AMI) was 0.80±0.07 mmol/l and was statistically different from patients who did not have VF (0.82±0.08 mmol/l). Only one patient who had VF was hypomagnesaemic (0.60 mmol/l). There was no difference in the mean serum magnesium value in patients taking diuretics compared to those not on diuretics (0.81±0.08, n=196 vs 0.81±0.08 mmol/l). However, 20 (4.9%) of the diuretic group were hypomagnesaemic compared to 21 (3.7%) of non diuretic takers [p<0.01]. In the 750 patients with potassium results hypokalaemia (k < 3.50 mmol/l) was present in 13 of 36 (36%) patients with hypomagnesaemia compared to 127 of the remaining 716 (18%) [p<0.01]. Serum magnesium levels were unaffected by predmission beta blockers (0.81±0.08 mmol/l, n=196 vs 0.81±0.07 mmol/l, n=680). Conclusion: Low serum magnesium levels are rare on the coronary care unit, are not associated with prior diuretic use and hypokalaemia but are not associated with ventricular fibrillation.

ADMISSION QT DISPERSION DOES NOT PREDICT VENTRICULAR FIBRILLATION FOLLOWING ACUTE MYOCARDIAL INFARCTION.
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Academic Cardiology Unit, Freeman Hospital Freeman Road, Newcastle upon Tyne.

QT dispersion (QT maximum minus QT minimum) reflects underlying dispersion of myocardial repolarization and is increased following acute myocardial infarction (AMI). Initial evidence suggests that increased QT dispersion might be a marker for ventricular fibrillation (VF) during the acute post infarction period. This study examines prospectively whether QT dispersion measured from the admission ECG predicts early VF following AMI. 217 patients with AMI had ECGs recorded on admission. 44 patients were excluded from this analysis because of antiarrhythmic drug therapy and 8 because of atrial fibrillation. 16 patients developed VF within 24 hours post admission. The mean admission QT dispersion in patients with no VF (n = 161) was 77 ± 28 ms versus 82 ± 22 ms in patients who had VF (p = 0.53 NS). Admission levels of QT dispersion were unaffected by infarct size (anterior v inferior v lateral) = 79 ± 30 v 77 ± 25 v 92 ± 41 ms, NS); presence of previous AMI (74 ± 26 v 79 ± 29 ms, NS) or predmission beta blocker therapy (77 ± 29 v 78 ± 29 ms, NS). QT dispersion showed a weak negative correlation with plasma potassium levels (Spearman’s r = -0.29, p < 0.001). A subset of patients were studied closely with frequent ECG recordings over 100 h. Marked dynamic changes were observed particularly during the first hours and with reperfusion. The mean slope of the reduction in QT dispersion with ECG evidence of reperfusion (n = 7) was -3.4 ± 3.9 versus -5.3 ± 5.4 in those who did not reperfuse (n = 5) (p < 0.01). Conclusion: QT dispersion measured from an admission ECG does not predict VF. This may be due to subsequent dynamic changes post admission resulting from continuing ischaemia / infarction. Successful reperfusion is associated with a fall in QT dispersion.
(242) POSTER

Initiating Sequences in Exercise-Induced Idiopathic Ventricular Tachycardia
Cardiological Sciences, St George's Hospital Medical School, London.

Initiating sequences for ventricular tachycardia (VT) can suggest the underlying arrhythmogenic mechanisms. This study examines the initiating sequences for exercise-induced idiopathic VT. Thirty two pts (18 males, mean age 33.4±13.2 (SD) years, with exercise-induced VT in the absence of clinical cardiac abnormality, were divided into 2 groups on the basis of the VT initiating sequence: 1) the long-short sequence of RR intervals prior to the onset of VT (initiating/pre-initiating cycle length <0.78 and 2) absence of cycle length changes prior to VT. Inferior (inf) axis of VT was defined as 0 to 180°, and a superior (sup) axis as <0 to -180°.

Results: VT axis was inferior in all patients of group 2 (p=0.02), and in patients with VT on Holter monitoring, no patient had sustained VT in group 1. Sustained (sust) monomorphic VT could not be initiated by programmed ventricular stimulation (PVS) in any of the patients in group 1.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD) years</td>
<td>33.1 (11.9)</td>
</tr>
<tr>
<td>VT axis inf/sup</td>
<td>9/5</td>
</tr>
<tr>
<td>VT cycle length (ms) (SD)</td>
<td>368.4 (67.0)</td>
</tr>
<tr>
<td>Holter VT non-sust/sust</td>
<td>7/0</td>
</tr>
<tr>
<td>VT during exercise/recovery</td>
<td>4/7</td>
</tr>
<tr>
<td>Sust VT on PVS</td>
<td>0/12</td>
</tr>
</tbody>
</table>

Conclusions: The long-short initiating sequence would suggest triggered activity due to early afterdepolarisations and VT initiated without CL change would suggest triggered activity due to delayed afterdepolarisations, or re-entry. The results demonstrate that at least 2 different arrhythmogenic mechanisms exist in patients with idiopathic VT. The two groups exhibit differences in electrophysiologic characteristics of the VT which may aid classification of this arrhythmia.

(243) POSTER

RADIOFREQUENCY CATHETER ABLATION OF IDIOPATHIC VENTRICULAR TACHYCARDIA.

In 16 patients (8m, 8f, mean age 40 ± 12 years) with recurrent, symptomatic idiopathic ventricular tachycardia (IVT) despite treatment with several antiarrhythmic drugs, radiofrequency catheter ablation of the tachycardia was attempted. During VT 11 patients had a left bundle branch block (LBBB) and 5 patients a right bundle branch block (RBBB) pattern on the surface electrocardiogram. Two quadripolar catheters were used during electrophysiologic study, one in the right ventricle for pacing and a second catheter with a 4 mm tip electrode for mapping and ablation. Monomorphic VT was reproducibly induced in all patients with standard pacing protocols (sustained VT in 11, nonsustained in 5), and detailed endocardial mapping performed. During LBBB VT, earliest endocardial activation occurred in the right ventricular outflow tract (septally in 7, free wall in 4). During RBBB VT earliest activation occurred in the mid-inferoseptal region of the left ventricle in 4, and the apical septum in 1 patient. At the target site, endocardial activation preceded the QRS complex in the simultaneously recorded surface leads by 27 ± 17 msec. Pacing from this site showed that the QRS complex was identical with the clinical VT in >10 surface leads. A mean of 9 ± 5 applications of radiofrequency energy were delivered in the unipolar mode. No recurrences of tachycardia were observed both at baseline state and following intravenous isoproterenol infusion in 15/16 patients following the procedure. There were no complications associated with the procedure; the x-ray exposure time was 43 ± 24 minutes. Over a follow-up of 4.2 ± 2.2 months, no patient with initially successful ablation had a recurrence of VT. All antiarrhythmic medications were discontinued. In patients without ischemic or structural heart disease, radiofrequency catheter ablation allows successful cure of VT.

(244) POSTER

Verapamil Suppresses Idiopathic Ventricular Tachycardia of Left Bundle Branch Block-Like Morphology
Cardiological Sciences, St George's Hospital Medical School.

This study examines the efficacy of verapamil for the suppression of idiopathic ventricular tachycardia (VT) of left bundle branch block (LBBB)-like morphology. Forty-two patients (mean age 36.2±12.1 years, 20 males) with VT, without any underlying clinical cardiac abnormality, were studied. The inducibility of the clinical VT was examined by Holter monitoring, treadmill exercise testing, programmed ventricular stimulation (PVS) in a drug-free state. In 27 patients, VT was inducible by exercise testing, in 20 by PVS and 23 patients had evidence of VT on Holter monitoring. Following baseline testing, patients were treated with verapamil 120 mg thrice daily for at least 5 half lives before evaluation.

Results:

<table>
<thead>
<tr>
<th>VT suppressed</th>
<th>VT exacerbated</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter VT</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Ex VT</td>
<td>15 (+5 partial)</td>
<td>0</td>
</tr>
<tr>
<td>PVS VT</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

Sustained monomorphic VT at PVS

In patients with a partial response to verapamil treatment, rate of the VT was unaffected (baseline: 355 (SD 72), verapamil treatment: 338 (SD 61) ms), although the duration of the arrhythmia was reduced. No patient with Holter response to verapamil had VT with a superior axis, but otherwise there were no differences between responders and non-responders to verapamil.

Conclusions: Idiopathic VT of LBBB-like morphology can be suppressed in approximately 2/3 of patients by verapamil. In patients with a partial response, the rate of VT is unaffected.

(245) POSTER

SEX DEPENDENCE OF NORMAL LIMITS OF THE SIGNAL AVERAGED ELECTROCARDIOGRAM
T F Yang, J Kennedy, P W Macfarlane
Department of Medical Cardiology, University of Glasgow, Royal Infirmary, Glasgow.

The presence of Ventricular Late Potentials (VLPs) has been claimed to be associated with ventricular arrhythmias. Since our previous studies on the normal 12-lead ECG have shown that the mean QRS duration in men is 8 ms longer than in women, it was felt worthwhile to assess whether separate criteria for males and females are necessary in using parameters for the detection of VLPs. A total of 195 apparently healthy individuals (160 men and 35 women, aged 40 to 69) were studied. Signal averaged X,Y,Z leads were recorded and analysed twice using bidirectional Butterworth filters (frequency ranges of 25-250 Hz and 40-250 Hz). The vector magnitude parameters studied were: filtered QRS duration (QRSd), duration of the low amplitude signals < 40 μV (LAS 40), and root mean square voltage of last 40 ms (RMS 40).

Results:

<table>
<thead>
<tr>
<th>Type</th>
<th>25-250Hz</th>
<th>40-250Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>QRSd ms</td>
<td>102.0±9.4</td>
<td>94.0±13.8</td>
</tr>
<tr>
<td>83-123</td>
<td>77.1-113</td>
<td>80-122</td>
</tr>
<tr>
<td>LAS 40 ms</td>
<td>25.7±9.0</td>
<td>25.1±9.0</td>
</tr>
<tr>
<td>11-45</td>
<td>11-43</td>
<td>12-49</td>
</tr>
<tr>
<td>RMS 40 μV</td>
<td>58.1±39.8</td>
<td>74.1±44.0</td>
</tr>
<tr>
<td>13-174</td>
<td>18-153</td>
<td>9-103</td>
</tr>
</tbody>
</table>

* Statistically significant difference between sexes(P<0.05)

Conclusions: Existing internationally recommended criteria for VLPs (40-250Hz) require to be made sex-related as follows: (A) QRSd<114 ms (male); QRSd>104 ms (female); (B) LAS40>38 ms; (C) RMS 40 <20 μV. VLPs should be regarded as present when A+B or C is true, giving a specificity of 97% in males and 100% in females. Current sex independent criteria defining VLPs as the presence of any two of A+QRSd<114ms), B, C are non specific, viz 85% for males and 91% for females.
**(246) POSTER**

**INCREASED SUSCEPTIBILITY OF EPICARDIAL COMPARISON WITH ENDOCARDIAL IMPLANTABLE CARDIOVERTER DEFIBRILLATOR LEAD SYSTEMS TO MALSENSING WHEN EXPOSED TO EXTRANEOUS ELECTRICAL INTERFERENCE**


Implanted permanent pacemaker systems show oversensing and noise detection when exposed to 50 Hz extraneous electrical interference. Using maximum sensitivity settings to optimize ventricular fibrillation detection, cardioverter defibrillators may be particularly vulnerable to electrical fields. Eight patients with implanted Medtronic PCD 7217B cardioverter defibrillators with backup bipolar VVI pacing were studied; 5 had epicardial leads and 3 had epicardial patches. All were exposed to a whole body electrical field simulated using a custom built bedside current injection unit, current passing between shoulders and feet. Patients were continuously monitored on ECG and by telemetry from the PCD. Sensitivities were unaltered at 0.3 mV, tachycardia detection was enabled, but PCD therapies were disabled. Epicardial current levels were smoothly increased from 0 to 550μA. During current injection, endocardial systems showed no pacemaker inhibition, electrical reset or arrhythmia misdiagnosis. However, both epicardial systems misinterpreted electrical noise as ventricular fibrillation. Epicardial current levels ≥250μA detection criteria were satisfied. One epicardial system also showed ventricular oversensing causing pacemaker inhibition at ≥50μA. Malssensing and oversensing could be overcome by decreasing sensitivity. This increased sensitivity reflects the greater surface area of epicardial patches and their perpendicular alignment to the electrical field. PCDs with epicardial patches could deliver inappropriate therapies if exposed to electrical interference at levels potentially encountered by patients in day to day life.

**(247) POSTER**

**EFFECTS OF DIGOXIN IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION: ANALYSIS OF HOLTER DATA**

F D Murgatroyd, B Xie, D E Ward, M Malik, J A Camm, for the Controlled Randomized Atrial Fibrillation Trial Investigators *St Georges Hospital Medical School, London*

The effects of digoxin on the frequency of episodes of paroxysmal atrial fibrillation (PAF), and on the heart rate in sinus rhythm (SR) and atrial fibrillation (AF) are unknown. We analysed 24-hour Holter recordings from 37 patients participating in CRAFT-1, a multicenter, double-blind, placebo-controlled crossover trial of digoxin in PAF. Recordings were made after a 10 day loading period, during which time patients took digoxin/placebo at a dose based on estimated creatinine clearance. The mean digoxin dose at the time of recording was 336 ±70.3 μg/day, and the mean blood level was 0.93 ±(0.31) μg/l. A full disclosure of each of the 74 tapes was made, and the precise timing of each of the 979 episodes of AF was entered into a computer. These data were combined with downloaded records of every R-R interval on each tape, to allow separate analysis of SR and AF. Results are expressed as mean (sd).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Digoxin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seconds of AF</td>
<td>6598</td>
<td>5483</td>
<td>0.692</td>
</tr>
<tr>
<td>No of episodes of AF</td>
<td>117.5 (31)</td>
<td>12.7 (23.0)</td>
<td>0.034</td>
</tr>
<tr>
<td>Mean episode duration</td>
<td>3905 (7755)</td>
<td>1746 (4263)</td>
<td>0.432</td>
</tr>
<tr>
<td>Mean heart rate in SR</td>
<td>75.5 (9.2)</td>
<td>72.3 (9.46)</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean heart rate in AF</td>
<td>125.2 (25.4)</td>
<td>122.1 (27.5)</td>
<td>0.688</td>
</tr>
</tbody>
</table>

No significant change in the frequency or length of AF episodes was detected. Although the heart rate in sinus rhythm was slightly reduced, the mean heart rate in AF appeared unchanged.

**(248) POSTER**

**LIMITATIONS OF THE EJECTION FRACTION AS AN INDEX OF VENTRICULAR FUNCTION IN ATRIAL FIBRILLATION**

S.MC Hardman, G.E. Young, M.M. Noble, W.A. Seed. *Charing Cross & Westminster Medical School, London*

The use of the ejection fraction (EF) to assess left ventricular (LV) function assumes that other influences such as the inotropic state of the ventricle and LV filling remain relatively constant. In atrial fibrillation (AF) both are known to vary on a beat by beat basis and so the present study was undertaken to see whether or not the EF still provides a useful index of LV function in such patients. Recordings of LV diameter were made using M mode echocardiography, continuously over 100-200 beats in five patients in AF (without mitral regurgitation) who were undergoing cardiac catheterization. Similar recordings were made in 4 control subjects at rest in sinus rhythm. In both groups EFs were calculated for each of the recorded beats. EFs in the control group varied by no more than 12.5% (SD +/- 3.0 to 3.4%). In the AF patients the EFs varied by between 30 and 57% (SD +/- 5 to 10%), as a function of variations of EDD as well as end systolic diameter. Since the end systolic diameter is influenced by inotropic effects, simultaneous measurement of the maximum rate of rise of LV pressure (LVdP/dtmax) was examined in these 5 AF patients as well as recordings of LVdP/dtmax from another 10 (also in AF). In all 15 there was an inverse relationship between LVdP/dtmax and the pre-preceding RR interval (Spearman rank correlations SR -0.56 to -0.86, pvalues ≤ 0.0001). This potentiation of LVdP/dtmax could not be attributed to changes in EDD. The EDD of the pre-stimulated beats showed no change with the correlation with LVdP/dtmax which was therefore accepted as an index of the inotropic state of the ventricle. The determinants of the beat to beat inotropic variations were further explored (in all 15 AF patients) using transfer function modelling which showed that as much as 92% of the variation in LVdP/dtmax could be explained by the variations of between 4 and 6 preceding RR intervals (through the decay of postextrasystolic potentiation). The LV function of the AF patients was also assessed angiographically and ranged from normal to severe dysfunction, however, in all points measured EFs did not consistently reflect the degree of LV dysfunction. Thus in atrial fibrillation the ejection fraction appears to be dominated by interval dependent influences including inotropic effects as well as beat to beat variations in LV filling. The resulting variability of the ejection fraction, from one beat to the next, makes it a poor indicator of left ventricular function in atrial fibrillation when assessed conventionally.

**(249) POSTER**

**SURGICAL MAPPING AND TREATMENT OF ATRIAL FLUTTER**

RC Saunders, FD Murgatroyd, DJ Parker and AJ Camm. *St George’s Hospital, London SW17 ORF*

A device has been developed for mapping activation in the triangle of Koch during surgery which allows acquisition of electrograms with the anatomy of the region. The position of the mapping electrode is sensed by a mechanical system and displayed to the surgeon who can thus build a map by interacting with the computer display. Common atrial flutter is supported by a slowly conducting substrate that allows atrial tissue to recover before reexcitation by the advancing edge of the flutter circuit. In three patients with disabling, paroxysmal common atrial flutter, areas of slow and anisotropic conduction have been mapped and identified at the junction of the left atrium and the inferior vena cava. Electrograms in the slowly conducting regions show marked fragmentation suggesting disruption of fiber to fiber conduction in these regions. Cryolesions across the entrance to the triangle of Koch in one patient and an incision running from the tricuspid annulus to the foramen ovale in two others have been curative in one patient and converted long standing atrial flutter to exercise induced atrial fibrillation in two others. These preliminary results suggest that mapping and surgical ablation of the substrate of atrial flutter is feasible.
THE MAJORIT OF PATIENTS WITH AV NODAL RE-ENTRANT TACHYCARDIA HAVE THREE OR MORE PATHWAYS.

N J Morgan-Hughes, J M McComb
Department of Cardiology, Freeman Hospital, Newcastle upon Tyne.

Dual AV nodal pathways have been proposed as the mechanism of so-called AV nodal re-entrant tachycardia. Traditionally dual AV nodal pathways have been defined by an increment or "jump" of >50ms in the A2-H2 interval with a decrement of 10 or 20ms in the S1-S2 coupling interval. This view of AV nodal electrophysiology has been recently challenged, both in normal subjects and in patients undergoing AV nodal modification. Twelve consecutive patients with documented AV nodal re-entrant tachycardia refractory to drugs underwent detailed electrophysiological evaluation of AV nodal conduction. All patients had the common slow fast form of AV nodal re-entrant tachycardia demonstrated on ≥1 occasion during study and no patient had an accessory pathway. Three patients (group A) exhibited 2 discrete discontinuities in antegrade conduction with 2 jumps of ≥50ms occurring with a 10-20ms decrement in S1-S2. Four patients (group B) had similar curves to patients in group A, but with 1 of the discontinuities only represented by a single point in the antegrade conduction curve. Four patients (group C) had a single antegrade discontinuity. One patient (D) had a continuous antegrade conduction curve. Eight patients had single discontinuities in the retrograde conduction curve, 3 patients had a continuous retrograde curve and 1 patient had VA block. Four patients (1 group A, 1 group B, 2 group C) demonstrated ≥2 re-entrant circuits during tachycardia, as evidenced by cycle length alternans during a single tachycardia (n = 2), 2 distinct tachycardias (n = 2) or 2 distinct AH intervals at initiation (n = 1). Thus 9 patients (75%) had evidence of 3 or more AV nodal pathways. These data suggest that the traditional view of AV node duality in patients with AV nodal re-entrant tachycardia is outdated. Rather the AV node and paranodal tissues are complex structures providing multiple potential pathways with different conduction velocities.

P Sritara, D Shanit, R A Greenbaum
Cardiovascular Research Unit, Edgware General Hospital, Edgware

To evaluate the diurnal variation of the onset of symptomatic paroxysmal atrial fibrillation (PAF), we studied 150 patients with paroxysmal atrial fibrillation (PAF) in 150 patients with symptomatic paroxysmal atrial fibrillation (PAF) in 150 patients with paroxysmal atrial fibrillation (PAF). In 150 patients with paroxysmal atrial fibrillation (PAF), we studied 150 patients with symptomatic paroxysmal atrial fibrillation (PAF). In 150 patients with symptomatic paroxysmal atrial fibrillation (PAF). In 150 patients with symptomatic paroxysmal atrial fibrillation (PAF). In 150 patients with symptomatic paroxysmal atrial fibrillation (PAF). In 150 patients with symptomatic paroxysmal atrial fibrillation (PAF). In 150 patients with symptomatic paroxysmal atrial fibrillation (PAF).

The difference between patients' experience of symptoms and documented arrhythmia was highly significant (Chi square = 482.4; P<0.0001). The times of onset of all arrhythmia events was recorded and compiled into 4 hour time periods for the purpose of analysis. Significant differences were noted in the diurnal pattern of PSVT and PAF (chi square=14.6; P=0.0012). Peaks of onset of PSVT were recorded between 9:00-13:00 and 17:00-21:00, while peaks of PAF were documented between 13:00-17:00.

We conclude that relying solely on patients' reported experience of symptoms is ineffective in the assessment of symptomatic paroxysmal supraventricular arrhythmia. It is necessary to correlate such reports with ECG findings. TEM is a reliable means to this end. We also conclude that the occurrence of paroxysmal supraventricular arrhythmias shows diurnal variation and differs between these groups, PSVT having two peaks and PAF - one.

INTRA- AND INTER-OBSERVER VARIABILITY IN THE ANALYSIS OF LOCAL ELECTROGRAM CHARACTERISTICS AT CATHETER ABLATION OF ACCESSORY PATHWAYS.

Y Bashir, D Katrisa, SC Heale, A Staunton, AJ Camm, DE Ward, St George's Hospital Medical School, London.

Mapping criteria used to guide catheter ablation of accessory pathway (AP) sites are based on the timing and morphology of local electrograms recorded at target sites. However, these signals are often complex/fractionated and subjective differences in inter-pretation may lead to significant discrepancies. To assess intra- and interobserver variability in the determination of local electrogram characteristics, three experienced operators independently reviewed recorded target sites during ablation of 22 APs, on two different occasions. Characteristics analysed were the atrioventricular interval ( AV), the interval from onset of the QRS complex to local ventricular activation (QRS-V), and the presence/absence of a possible AP potential. All intervals were measured separately to the onset, intrinsic deflection and peak of the local signal. The independent variation in the timing of QRS onset and of local ventricular activation (V) was also assessed by using a fixed reference point. Intra- and interobserver variability were expressed as the percentage of paired electrogram analyses for which timings differed by >15ms or there was disagreement about the presence of an AP potential:

<table>
<thead>
<tr>
<th>Electrogram Characteristics</th>
<th>INTRA-</th>
<th>INTER-</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-V</td>
<td>6.7%</td>
<td>26.0%</td>
</tr>
<tr>
<td>QRS-V</td>
<td>12.1%</td>
<td>30.7%</td>
</tr>
<tr>
<td>QRS onset</td>
<td>9.9%</td>
<td>20.9%</td>
</tr>
<tr>
<td>AP potential</td>
<td>5.4%</td>
<td>17.0%</td>
</tr>
</tbody>
</table>

Electrogram timings based on signal onset were found to be significantly more reproducible than measurement to the intrinsic deflection (p<0.02) or peak amplitude (p<0.05). There was no difference in variability at successful (n=22) vs. failed (n=36) sites. In summary, electrogram analysis by independent observers is associated with major discrepancies in the reporting of up to 30% of signals. This variability is sufficient to influence selection of target sites and may be one reason why different studies have failed to reach agreement about the optimum mapping criteria for catheter ablation of APs.

INTRAVENOUS ADENOSINE REVEALS INTERMITTENT PREEXCITATION BY DIRECT AND INDIRECT EFFECTS ON ACCESSORY PATHWAY CONDUCTION.

N J Morgan-Hughes, M J Griffith, J M McComb
Department of Cardiology, Freeman Hospital, Newcastle upon Tyne.

The short half-life of adenosine has made assessment of its effects on antegrade refractoriness of accessory pathways difficult. Intermittent preexcitation offers a unique opportunity to examine the effects of adenosine on accessory pathways which have an antegrade refractory period that may exceed the sinus cycle length. We therefore studied responses to intravenous adenosine in 6 patients with intermittent preexcitation but absent preexcitation at the time of study. Increasing doses of adenosine of up to 280 µg/kg were injected until atrioventricular (AV) block or preexcitation occurred. Two differing responses were seen, reflecting the early direct effects of adenosine on the heart, and later secondary sympathetic activation. In 3 patients preexcitation was seen early, coincident with the onset of AV nodal block. In these 3 patients the P delta intervals seen with preexcited beats were <5 the PR intervals seen in the resting state. The PP intervals preceding preexcited beats were ≤ the PP intervals seen in the resting state. No patient developed preexcitation due to delayed AV nodal conduction. These findings suggest a direct effect of adenosine on accessory pathway conduction. In 4 patients preexcitation was seen late, during secondary sinus tachycardia following AV block suggesting enhanced accessory pathway conduction due to sympathetic activation. Adenosine administration was repeated in 3 patients following intravenous propranolol (10mg). β-adrenergic blockade failed to prevent early preexcitation but abolished late preexcitation related to sinus tachycardia. These data suggest that adenosine has 2 effects in patients with intermittent preexcitation: an immediate direct effect on accessory pathway conduction and a secondary indirect effect due to sympathetic activation. Intermittent preexcitation may therefore be unmasked by adenosine, by one of two mechanisms, both independent of AV nodal block.
POSTER

IMMUNOHISTOCHEMICAL LOCALISATION OF THE INNERVATION IN THE HUMAN CARDIAC CONDUCTION SYSTEM
Department of Histochemistry, Royal Postgraduate Medical School, London W12 ONN. Department of Paediatrics, Surgery, National Heart and Lung Institute, Dovehouse St, SW3 6LY.

Immunohistochemical and histochemical techniques were used to visualise the general innervation and the distribution of nerve subpopulations. Use of the antiserum to general neuronal marker protein gene product 9.5 revealed a dense supply of nerve fibres and fascicles throughout the conduction system. The sinus and atrioventricular nodes contained a higher density of nerve fibres than did the penetrating bundle, bundle branches and surrounding myocardium and exhibited a differential pattern of innervation. The transitional region of the atrioventricular node contained more nerves than the compact node. The dominant subpopulation of nerve fibres and fascicles in the sinus node and transitional region of the atrioventricular node displayed acetylcholinesterase (ACHE) activity, whereas a similar proportion of AChE-positive and neuropeptide Y- (NPY) immunoreactive nerves was observed in the compact node. NPY- and tyrosine hydroxylase (TH)- immunoreactive nerves showed a uniform distribution in both nodes and represented the main population of peptide containing nerves. Vasoactive intestinal polypeptide, somatostatin, substance P- and calciitonin gene-related immunoreactive nerves represented a relatively small proportion of the overall innervation. This study has demonstrated the complex innervation of the conduction tissues consisting of AChE-positive nerves (presynaptic, sympathtic), TH- and NPY-immunoreactive nerves (presumptive sympathetic) as well as other peptide-containing nerves, some considered to be sensory in nature.

(254) POSTER

(256) POSTER

AUTONOMIC TESTING AND MANAGEMENT OF 180 CHILDREN WITH SYMPNODE
S. Balaji, P.C. Oslizlok, M.C. Allen, C.L. Case, P.C. Gillette
South Carolina Children’s Heart Center, Charleston, South Carolina, USA.

Between November 1986 and August 1992, 180 children (age 4-18.5, mean 13.1 years) with a normal heart were seen for syncope or presyncope. None had arrhythmia or long QT syndrome. All were evaluated by an autonomic testing protocol which included tilt testing, carotid sinus massage, depth reflex, Valsalva manoeuver, and response to graded intravenous boluses of isoproterenol and Phenytoin. The tilt test reproduced symptoms of syncope or presyncope (tilt +) in 120 (67%). Sixty (33%) were asymptomatic during tilt alone (tilt -). Type of syncope was classified into vasodepressor (presumably origin and mild tachycardia) in 41 (34.5%); cardioinhibitory (asystole > 5 sec) in 7 (7.5%), and mixed (hypotension and bradycardia) in 72 (60%). Carotid hypersensitivity was seen in 4.

Of the 120 tilt + patients, 116 were treated with fludrocortisone and salt (F/S) with no further symptoms in 82 (72%), partial improvement in 15 (13.5%) and no change in 19 (16.5%) at follow-up of 1-65 months (mean 25). Of the 19 who were not improved on F/S 17 were treated with β blockers with symptom resolution in 14. Three patients who did not respond to β blockers were evaluated for psychological overlay of syncope. F/S was discontinued in 5 (4.9%) due to side effects of weight gain and/or worsening headache.

Of the 7 cardioinhibitory patients, 4 had pacemaker implantation, the other 3 opted for drug therapy with F/S. One patient had presyncope despite pacemaker and needed additional medical therapy.

Conclusion: Tilt testing and carotid massage were the only useful maneuvers during autonomic testing. F/S therapy was effective in controlling syncope in most patients and β blockers helped the rest. Tilt testing does indeed help the guide the management of children with syncope.
(258) POSTER

DO PATIENTS WITH NEUROLOGICALLY MEDIATED SYNCOPE HAVE AUGMENTED VAGAL TONE?

The vasovagal reaction consists of both resistance vessel vasodilatation and bradycardia due largely to sympathetic withdrawal and increased vagal activity respectively. We have studied parasympathetic function in patients with neurally mediated syncope (NMS) using both heart rate variability (HRV) analysis as a measure of tonic activity and baroreceptor sensitivity (BRS) to assess maximal vagal reserve. Temporal and spectral indices of HRV were computed from 24 hour Holter recordings of 33 patients with tilt induced NMS and an age matched control group of 31 patients in whom 45 minute 60° tilt tests were negative. None of the patients had evidence of important structural heart disease. Power spectral plots were quantified into three frequency bands (0.04-0.15 Hz and high frequency (0.15-0.40 Hz) band-widths)); and the power spectral density of the low frequency (0.04-0.15 Hz) band was quantified. Table 1 shows the mean BRS and NMS for all patients and their respective controls. BRS was determined using a bolus injection of phenylephrine.

<table>
<thead>
<tr>
<th>Temporal Measures</th>
<th>NMS</th>
<th>Controls</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR ms</td>
<td>149 ± 57</td>
<td>141 ± 46</td>
<td>0.070</td>
</tr>
<tr>
<td>SD ms</td>
<td>13.9 ± 12</td>
<td>13.0 ± 14</td>
<td>0.840</td>
</tr>
<tr>
<td>PNN50 (%)</td>
<td>13.7 ± 13</td>
<td>13.0 ± 14</td>
<td>0.840</td>
</tr>
</tbody>
</table>

(259) POSTER

METOPROLOL, DISOPYRAMIDE AND ETILEFRINE IN THE PREVENTION OF TILT INDUCED HYPOPOTENSION IN PATIENTS WITH REPRODUCIBLE NEUROLOGICALLY MEDIATED SYMPTOMS

Head up tilt testing provides not only a diagnostic test for neurally mediated syncope, but may also be used to gauge the efficacy of treatment. The poor efficacy of physiological pacing in patients with primarily vasodepressor syncope has prompted interest in pharmacological therapy. Ten patients (aged 17 to 73, 7 men) with recurrent syncope and tilt induced vasovagal reactions, which were reproducible on at least two occasions, were assigned to drug therapy, were enrolled in an open randomised crossover study. Patients were tilted for 45 minutes at 60° on a table with footplate support. A positive test was defined as a fall in systolic blood pressure below 90 mm Hg. Patients were retested after 48 hours treatment with metoprolol 50 mg bd, disopyramide 200 mg tds and etilefrine 10 mg bd in random order with a washout period of at least 5 days.

RESULTS: Three patients were unable to tolerate disopyramide. Two patients were rendered tilt negative by metoprolol, 2 by etilefrine and 1 by disopyramide. The mean duration of tilt tolerated was 10.6±5.7 min at baseline, 22.0±17.1 min on metoprolol (p<0.05), 21.6±13.3 min on disopyramide (p=0.6) and 25.7±13.1 min on etilefrine (p<0.001). One patient was made substantially worse by metoprolol, time to syncope falling from 10 to 6 minutes. None of the metoprolol nor etilefrine had any significant impact on the maximum heart rate at the time of syncope while disopyramide resulted in an increase from 43±3 to 72±36.8 bpm (p<0.05).

CONCLUSIONS: In contrast to previous reports, none of the drugs tested was effective in preventing tilt induced vasovagal reactions, although all prolonged tilt duration. The relevance of these findings to long term symptom control remains to be determined.

(260) POSTER

MULTIVARIATE ANALYSIS OF SURVIVAL IN PATIENTS IN WAITING LIST FOR HEART TRANSPLANTATION
A Biagian, S Berti, G Kraft, R Podoli, R Fiocchi, S Severi, F Mampini, M Leonetti, C Michelassi, M Seni, F Polli
CNR Clinical Physiology Institute Pisa and Cardiovascular Department Bergamo, Italy

In most centers the mean waiting time for heart transplantation is 6 months; therefore many patients (pts) die waiting for a transplant, while among survivors many show a good prognosis, indicating the great heterogeneity of this population. In 380 consecutive pts in waiting list for transplant, we tried to identify the predictors of death analysing 40 variables for each pt. During the follow-up (ms 6.9±10.1 months), 65% of the pts underwent transplantation, 36% died and 31% are still waiting. The actuarial survival by Kaplan Meier method, at 24 months was 55.6%. Multivariate analysis by Cox regression model, revealed 5 independent and additive predictors: systolic pulmonary (p<0.0003), pulmonary wedge (p<0.0007), right atrial pressure (p<0.009), giugular engorgement (p<0.01), systolic aortic pressure (p<0.03). The actuarial survival at 24 months in 5 groups of pts, divided according to the systolic pulmonary pressure, was: 88%, 55% and 12% respectively in pts with pressures >35, between 36-55 and >56 mmHg; while the % of pts transplanted was respectively 31%, 34% and 35%.

In our pts we identified 3 groups with significant different risk of death. Our pts were transplanted without taking into consideration the different probability of survival while it would have been possible to identify, at the entry the the pts who should have the priority for transplantation.

(261) POSTER

PREDICTIVE VALUE OF ULTRAFAST CT SCANS FOR ACCELERATED CORONARY ARTERY DISEASE IN CARDIAC TRANSPLANT RECIPIENTS.
N. Berhirt, PF.Ludman, TJ Bowker, A Bell, BS, Rees, DA. Wood and M. Yacoub, Barfreight Hospital, Middlesex and Royal Brompton Hospital and Clinical Epidemiology, National Heart and Lung Institute, London.

Detection of asymptomatic accelerated coronary artery disease (CAD) in cardiac transplant recipients requires annual coronary angiography. Ultra-fast computed tomography (UFCT) scans can detect coronary calcification which is a sensitive and specific marker for the presence of non transplant coronary artery atherosclerosis. One hundred and two cardiac transplant recipients (80 males) had UFCT scans, a median of 4.6 years post-transplant; the median intervals from the most recent coronary angiogram being 39 days. Angiograms and scans were reported blindly and independently. Scans were reported as a calcification score, and angiograms as the maximum % stenosis, for each major vessel. Forty one patients (40.2%) had at least 1 major vessel with a stenosis >25% and 46 (45.1%) had a total calcification score >0. The positive (PPV) and negative predictive values (PVN) of UFCT were 73.9% and 87.5% respectively, with a sensitivity (S) of 82.9% and specificity (SP) of 80.3%. Predicators which were similar for both sexes. Disease (as defined above) was present in the LMS on UFCT in 5, and angiographically in 1, in the LAD in 14 and 32; Cx in 16 and 23; and RCA in 35 and 30 respectively. The sensitivity (S) and SP of UFCT findings were for each vessel: LMS = 20T, 100T, 100X and 965; LAD = 85.7%, 77%, 37.5% and 97.1%; Cx = 83.8%, 81.2%, 30.4% and 84.7% and RCA = 65.7%, 89.4%, 76.7% and 83.1%. No quantitative relationship between the UFCT score value and the degree of radiographic stenosis was evident. The negative predictive values of the UFCT scan in this population with a 40.2% prevalence of CAD make it a useful screening tool which could reduce the number of cardiac angiograms required for transplant patients.
OUMTCR AFTER CARDIAC TRANSPLANTATION IN PATIENTS OVER 55 YEARS OF AGE.

G Parry, C D Scott, J H Dark
Cardiopulmonary Donation Unit, Freeman Hospital, Newcastle upon Tyne.

Relaxation of selection criteria and the wider range of indications for cardiac transplantation has resulted in older patients (pts) being considered for this form of therapy for end-stage cardiac disease. In view of the continuing donor shortage, morbidity and mortality in older pts should approach that of younger pts for this policy to be sustained. In 1988 age selection criteria at this unit were relaxed to include pts ≥55 years of age. Mortality and morbidity were compared according to age in the 166 adult pts transplanted since then. Morbidity criteria examined included significant rejection events, serum creatinine, development of graft coronary disease, and 41% (mean 1.7 years follow-up) and 35 were ≥55 years of age (1.4 years follow-up). Actuarial survival at 30 days (86.2% vs 85.7%), and at one (80.2% vs 82.3%), two (79.1% vs 76.8%), three (74.9% vs 76.8%) and four years (74.9% vs 76.8%) was similar in these age groups. Rejection (≥ grade 2, ISHT standardized grading system) occurred at some stage during follow-up (mainly within 3 months) in 33 pts (31%) ≥55 years of age, compared with 11 pts (30%) ≥55 years of age (p=0.43). Serum creatinine was higher in the older pts (156.9 ± 135.3 µmol/l vs p=0.0017). Survival correlates most closely with creatinine and has been performed in 69 pts (41%) to date (10 pts ≥55 years). Graft coronary disease has been detected in 41% ≤55 years of age and in 50±55 years (ns). General morbidity was similar in the two groups across the whole spectrum of conditions possibly/probably/depositly related to the transplant and immunosuppressive therapy (ANOVA p=0.58). However thoracic vertebal collapse/fracture has occurred in 3 pts (all ≥55 years of age) probably provoked by steroids in the presence of pre-existing osteoporosis. Thus from these data, more rigid selection in older pts 1: Mortality and general morbidity are similar in the two age groups; 2: Elevation of serum creatinine during follow-up may reflect an increased sensitivity to cyclosporin, and/or more severe renal dysfunction pretransplant due to more longstanding heart failure in the older pts 3: Pre-existing osteoporosis may need more adequate identification in older pts.

ASSOCIATION OF HLA ANTIGENS WITH PRIMARY DISEASE IN CARDIAC TRANSPLANT RECIPIENTS

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The frequencies of HLA A2, B7, B8, B27, DR4 and DR5 have all been shown to be an increased, observed, and that of DR3 decreased, among patients with idiopathic dilated cardiomyopathy (DCM). A recent meta-analysis found an increase in DR4 among 361 patients with DCM. In patients with inhaemic heart disease (IHD) and congestive heart failure, DR4 has been reported as under-represented. We examined the frequency of HLA A, B, and DR antigens among our population of cardiac transplant recipients to determine if any HLA antigen was associated with either DCM or IHD. No pre-transplant matching is performed for these antigens, hence the results are not confounded by selection of common antigens from the donor pool. Frequencies were compared with controls from transplant recipients in England and Wales in 1985. HLA typing (12 HLA A, 18 B and 10 DR antigens) was performed using standard lymphocytotoxicity techniques and a reliable panel of antisera used for transplant analysis. Data tabulated are for antigens showing the largest differences from controls. DR4 and DR5 data are also listed.

<table>
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<tr>
<th>A11</th>
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Correction of p values for multiple antigens tested (40) showed no statistically significant differences. No association was detected between HLA antigens and primary disease among patients who have received a cardiac transplant.

IMMUNOHISTOCHEMICAL AND HISTOCHEMICAL ANALYSIS OF THE HUMAN ENDOCARDIAL PLEXUS

Department of Histology, Royal Postgraduate Medical School, Hammersmith Hospital, London.

The endocardium is an important regulator of myocardial function. It produces several potent vasoactive factors which have an effect on cardiac contraction and relaxation. The effect of these factors may be mediated by the extensive innervation of the endocardial plexus. This innervation was investigated using immunohistochemical and histochemical techniques, applied to whole mount preparations of human endocardium, in conjunction with image analysis. The overall distribution of the neural plexus, was demonstrated using antisera to the general neuronal marker PGP 9.5. Subpopulations of nerves were distinguished according to their immunoreactivity for neuropeptide Y, vasoactive intestinal peptide, somatostatin and substance P as well as the catecholamine synthesising enzyme tyrosine hydroxylase. Acetylcholinesterase activity, representing presynaptic cholinergic nerves, was also demonstrated histochemically and proved dominant throughout the heart. NPY immunoreactive nerves were the most prominent nerve subpopulation, and were most frequently associated with sympathetic nerves delineated by tyrosine hydroxylase. Somatostatin, VIP and substance P fibres, which were all observed to occur in the plexus less frequently and were less widespread, VIP and particularly substance P being localised to specific regions and chambers. Discrete PGP 9.5 immunoreactive nerve endings, representing terminals of sensory nerve fibres within the atrial endocardium and may represent baroreceptors. A close relationship between this extensive innervation and the non-vascular and endothelial component of the endocardium was demonstrated using cryostat sections of the cardiac chambers. Thus indicating a possible functional role for the endocardial plexus in overall cardiac function.
(266) POSTER

IMPAIRED CARDIAC MYOCYTE CONTRACTILITY IN ENDOTOXEMIA IS REVERSED BY INHIBITION OF NITRIC OXIDE
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Department of Cardiac Medicine, National Heart and Lung Institute, London

Endotoxic shock causes depression of myocardial contractility, the mechanism of which is poorly understood. Nitric oxide (NO) synthase can be induced within cardiac myocytes by endotoxin (lipopolysaccharide; LPS) treatment of animals. The effects of substrates and inhibitors of NO synthase on myocyte contractility were studied on isolated, contracting ventricular myocytes from normal and LPS-treated (5 mg/kg i.p. administered 4 h before sacrifice) guinea-pigs. Electrically-stimulated (0.5 Hz) contractions were recorded using videomicroscopy length-detection. Contraction amplitude was calculated as a percentage of the resting length. Baseline contraction of myocytes from LPS treated animals was 54% (n=17, p<0.001) of the baseline contraction of myocytes from normal animals. The NO synthase inhibitor, Nω-nitro-L-arginine methyl ester (L-NAME) 10^{-5}M reversibly increased contraction amplitude of myocytes from LPS treated animals by 40±6.6% (p<0.001, n=17). Another inhibitor, Nω-nomonomethyl-L-arginine gave similar results. The effect of L-NAME was reversed by coadministration of L-arginine 10^{-5}M, but not D-arginine. The guanylate cyclase inhibitor, methylene blue (MB) 5x10^{-5}M increased contraction of myocytes from LPS-treated animals by 157±27% (p<0.005, n=7) over 15 min. In normal cells MB increased contraction by 54±11% (p<0.005, n=6). In both groups MB was toxic after prolonged superfusion. Agents which prevent synthesis or the effects of NO reverse the depression of myocyte contraction seen in endotoxemia. NO production within cardiac myocytes may contribute to the contractile impairment in endotoxic heart failure.

(267) POSTER

CAN DYSPNOEA AND FATIGUE BE MEASURED REPRODUCIBLY DURING EXERCISE IN CHRONIC HEART FAILURE?
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Patients with chronic heart failure (CHF) experience dyspnoea and fatigue during their everyday activities. Quantification of these symptoms during submaximal exercise may provide a useful means of measuring patient disability and the impact of drug treatment. We have evaluated the reproducibility of 2 subjective scaling systems (SSS) administered during exercise in patients with CHF. 8 patients were studied. Each undertook 2 baseline maximal treadmill exercise tests. Submaximal tests were undertaken 1,2,4 and 8 weeks later. Each consisted of 6 mins. exercise at 3 work loads (65%, 75% & 85% of peak VO2)[table]. During each stage of the submaximal test patients recorded their symptoms of fatigue and dyspnoea using computer automated visual analogue and Borg CR10 scales (VAS and BS). Reproducibility was calculated in the standard way as the ratio of between subject variability to within subject variability (table). The higher the ratio the better the reproducibility.

<table>
<thead>
<tr>
<th>VAS/Borg</th>
<th>% peak VO2</th>
<th>Dyspnoea</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>65%</td>
<td>1.9</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>75%</td>
<td>1.3</td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td>85%</td>
<td>2.1</td>
<td>2.1</td>
<td>1.6</td>
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</table>

The SSS used were found to be as reproducible in patients with CHF as they are in treadmill familiar normal volunteers (reproducibility ratios in normals for dyspnoea are 0.8 for Borg and 1.7 for VAS during similar protocol). Reproducibility was best at higher work loads. Overall the VAS was the most reproducible SSS. SSS applied during a constant load submaximal exercise test may offer a useful means of evaluating symptoms in CHF and their response to treatment.

(268) POSTER

VENTILATION-PERFUSION MATCHING IN CHRONIC HEART FAILURE
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The shortness of breath experienced by patients with heart failure is thought to be due to mismatch between ventilation and perfusion resulting in excessive dead space ventilation. In order to assess ventilation perfusion matching, 28 patients underwent symptom limited treadmill exercise with arterial blood sampling.Expired gas analysis using argon dilution was used to determine metabolic gas exchange. Fractional dead space ventilation and the alveolar-arterial oxygen difference were derived. Twenty patients had symptomatic heart failure, and a control group of eight had asymptomatic left ventricular dysfunction. There was a fall in fractional dead space ventilation in all patients (0.43 to 0.28; p<0.001) but this was more marked in the controls (peak dead space fraction 0.19 (controls), 0.32 (patients); p=0.002). There was a rise in alveolar arterial oxygen difference in all patients (1.59 kPa to 2.55; p=0.006) with no difference between patients and controls. Arterial oxygen tension rose (12.8 kPa to 14.83 during recovery; p<0.001) and arteriovenous oxygen tension fell during exercise (4.89 kPa to 4.63; p<0.001), at the same time as pH fell (from 7.43 to 7.39; p<0.001). Dead space fraction did not correlate with maximum oxygen consumption, but fell to a greater extent in the control group than in patients (r=0.35 vs. 0.12 respectively). Thus, neither fractional dead space ventilation nor physiological shunting explains the increase in ventilation seen in heart failure. There appears to be a non-CO2 drive to excessive ventilation resulting in a fall in carbon dioxide tension during exercise. There is a reduction in dead space as a fraction of tidal volume, but fractional dead space ventilation is higher in patients. This may be compensation for the increased ventilation which would otherwise cause an extreme fall in arterial carbon dioxide tension.

(269) POSTER

RENAL EFFECTS OF LOW DOSE PRAZOSIN IN PATIENTS WITH CONGESTIVE HEART FAILURE
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Activation of the sympathetic nervous system (SNS) may contribute to the renal vasoconstriction and sodium retention seen in congestive heart failure (CHF). However, the few studies which examined the renal effects of prazosin in CHF have been disappointing. It is worth noting that relatively large doses of prazosin were employed in these studies, which by virtue of reducing systemic blood pressure caused a reduction in renal perfusion. We have examined the renal response to low non-depressor doses (0.25 mg and 0.50 mg) of prazosin in CHF patients.

Eight female patients aged 53-72y with CHF (NYHA classification II-III) were studied on 2 occasions undergoing water diuresis. Following a stabilization period, patients were randomized to receive oral tablets of placebo or prazosin (0.25 mg at 0 min, 0.50 mg at 120 min and 0.50 mg at 240 min with their usual daily diuretic requirements, mean frusemide dose of 83 ± 14 mg), Glomerular filtration rate (GFR) and effective plasma flow (ERPF) were estimated from clearances of inulin and PAH respectively. Segmental tubular function was assessed by the lithium clearance method. Compared to placebo, prazosin caused a significant increase in urinary sodium excretion (mean ± s.e. mean) from 36 ± 7 µmol/min to 92 ± 7 µmol/min, p<0.01, paralleled by significant increases in fractional excretion of sodium (p<0.05) and lithium (from 13.7 ± 2.3% to 20.7 ± 3.3%, p<0.05). GFR, ERPF, blood pressure and heart rate were not altered by prazosin treatment. Furthermore, prazosin pre-treatment did not alter any of the renal responses to their daily dose of frusemide.

In summary, our results have shown that low non-depressor doses of prazosin is natriuretic in CHF patients. It remains to be determined if these beneficial effects will be maintained over longer periods of prazosin administration.
The Renal Response to Dobutamine and Nitroprusside in Patients with Chronic Heart Failure During Frusemide Induced Diuresis.

Department of Medicine (Cardiology), Royal Postgraduate Medical School, Hammersmith Hospital, London.

Both dobutamine and sodium nitroprusside (SNP) can improve haemodynamic status in heart failure and increase renal blood flow but have opposite effects on renal perfusion pressure. The aim of the present study was to determine whether increases in renal blood flow or perfusion pressure would enhance a frusemide-induced diuresis in chronic heart failure (CHF). Sodium intake was fixed for three days prior to each study and medication was withheld on study days. Frusemide was given by hourly bolus in identical fashion on each of 3 study days. (Mean total for the 4 hours was 19mg) to maintain a constant, moderate diuresis. PAH was infused to calculate renal plasma flow (ERPF). Patients voided urine hourly for 4 hours. During the 2nd and 3rd hours, vehicle (normal saline) was infused at 30ml/hour then 60ml/hour respectively (placebo) and dobutamine or SNP added in random, single-blind fashion on 2 of the 3 study periods. Dobutamine was infused at 1μg/kg/min during the 2nd hour and then incrementally up to 10μg/kg/min for the 3rd hour. SNP was infused at 0.2μg/kg/min for the 2nd hour then incrementally up to 0.6μg/kg/min for the 3rd hour. Plasma and urinary electrolytes were measured hourly and plasma saved for measurement of ANP, catecholamines and renin. ERPF increased (174±30ml/min to 316±30ml/min, p<0.003) during high dose dobutamine infusion. During low-dose SNP infusion ERPF tended to rise, but fell towards baseline during high-dose infusion. Mean arterial pressure did not change during dobutamine infusion, but fell (87±6 to 71±5mmHg, p<0.02) during the high dose SNP infusion. Renal vascular resistance fell with both agents. Urine volume during the high-dose infusions was greater with dobutamine compared to SNP (260±87, 191±61 and 216±77ml/hour for dobutamine, SNP and vehicle respectively, p<0.02) as was sodium output (21±10, 145±5, 15±2, p<0.05). Treatment that improves central haemodynamics and reduces renal vascular resistance may impair the response to diuretics if the renal perfusion pressure is not maintained.

Does Digoxin Facilitate the Renal Response to Frusemide in Chronic Heart Failure?

Department of Medicine (Cardiology), RPMS, Hammersmith Hospital, London.

Digoxin improves quality of life and functional status in patients with chronic heart failure (CHF). With chronic heart failure, digoxin is widely prescribed. Whether digoxin has a diuretic effect has not been clearly demonstrated. We have performed HRV analysis on 24 hour ambulatory recordings (Marquette Series 8000) on 73 patients (mean age 52, range 24-75 years) with CHF (38 ischaemic heart disease and 35 idiopathic dilated cardiomyopathy) and 24 normal controls (mean age 42, range 16-68 years).

Pretreatment values for SBP (Systolic Blood Pressure) were: (controls) 131±8 and (patients) 160±11. In the CHF group, the effect of digoxin was less pronounced, only reaching significance for mRR (Shortening Fraction) (p<0.01) and exercise capacity (maximal oxygen consumption, p<0.05). No difference was observed using analysis of covariance in HRV between patients with dilated cardiomyopathy and ischaemic heart disease (p>NS). HRV in CHF patients with CHF is significantly lower than in normal patients (p<0.01). In the CHF group, patients treated with digoxin had lower HRV (mRR, SD, SDNN, TDI, TFF, LF) than in normal patients.

An Analysis of Heart Rate Variability in Patients With Chronic Congestive Heart Failure.

Cardiac Department, St George's Hospital Medical School, London.

Heart rate variability (HRV) is depressed in patients with chronic heart failure (CHF) but the important determinants of HRV and the influence of the aetiology of heart failure in these patients remains unclear. We have performed HRV analysis on 24 hour ambulatory recordings (Marquette Series 8000) on 73 patients (mean age 52, range 24-75 years) with CHF (38 ischaemic heart disease and 35 idiopathic dilated cardiomyopathy) and 24 normal controls (mean age 42, range 16-68 years).

All measured values of HRV were reduced in patients with CHF compared to normal controls (p<0.05, p<0.001). Patients with CHF secondary to dilated cardiomyopathy showed a greater reduction in HRV compared to those with ischaemic heart disease (SDR, p<0.01; SDNN, p<0.001). In the control group, parameters of HRV were highly dependent on age (R=0.5-0.6, p<0.01) with the exception of mRR, SDRR and SDNN (p>NS). In the CHF group, the effect of age was less pronounced, only reaching significance for mRR, SDRR and SDNN (p<0.05). The reduction analysis showed there was no association of HRV with CHF. HRV was markedly influenced by left ventricular systolic function (shortening fraction, p<0.01) and exercise capacity (maximal oxygen consumption, p<0.05). No difference was observed using analysis of covariance in HRV between patients with dilated cardiomyopathy and ischaemic heart disease (p>NS).
OPTIMAL ATRIOVENTRICAL INTERVAL DURING DDD PACING: RELATION TO UNDERLYING VENTRICULAR FUNCTION
A Drissas, J Joshi, S Webb, L Lewis, CM Oakley, P Nihoyannopoulos.
Dept. of Medicine, Clinical Cardiology, Hammersmith Hospital, RPMS, London.

To examine the relationship between the optimal atrioventricular interval (AVI) and left ventricular (LV) function, we used two-dimensional and Doppler echocardiography to study 24 patients (age 51+9 years) with permanent DDD pacemakers implanted due to high grade atrioventricular block. Nine (38%) patients showed normal LV function (Group A), 8 (33%) patients expressed mainly diastolic LV dysfunction (normal fractional shortening, prolonged isovolumic relaxation time, reduced ratio of early/atrial Doppler transmural flow velocities). Group B and 7 (29%) patients showed severely impaired LV systolic function (fractional shortening <20%) (Group C).

After programming of the pacemaker stroke volume was measured by Doppler during DDD pacing at different AVI (ranged from 50-250 ms) and also during VVI pacing. Heart rate was kept constant (69±5 bpm). During DDD pacing the mean optimal AVI (defined as the AVI which achieved maximal stroke volume) was longer in Group B (172±27 ms) compared with both Group A (142±17 ms) (p<0.05) and Group C (97±15 ms) (p<0.01). Percent increase in stroke volume from worst to optimal AVI was greater in Group B (194±4%) compared with both Group A (13±3%) (p<0.01) and Group C (6±5%) (p<0.05). In addition, a greater increase in stroke volume from VVI to DDD pacing at optimal AVI was seen in group B (26±2%) compared with Group A (15±4%) (p<0.01). Group C showed the least increase (7±3%) in stroke volume from VVI to DDD pacing at optimal AVI.

In conclusion, optimizing the AVI is more important in patients with impaired diastolic but preserved global LV systolic function. In addition, patients who derive significant haemodynamic benefit from an optimal AVI also derive significant benefit from DDD compared to VVI pacing. Patients with severely impaired LV systolic function derived no benefit either from optimizing AVI or from DDD compared with VVI pacing.

THE GROWING PROBLEM OF HEART FAILURE IN SCOTTISH HOSPITALS
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Northwick Park Hospital, Harrow, Middx

The incidence and prevalence of heart failure (HF) is believed to be rising in developed countries. This clearly has important implications for Health Services planning yet there is little information on the extent of the problem in the UK. The aim of this study was to ascertain the impact of HF on Scottish Hospitals. Scotland has a relatively stable population of approximately 5 million.

Scottish Hospital In-patient Statistics (SHIPS) provide a comprehensive picture of hospital utilisation, morbidity and mortality. SHIPS data on heart failure (ICD-9 428.0, 428.1, 428.9, 402, 425.5, 425.4 & 425.9) for 1980-1990 were examined. The number of discharges with HF listed as the 1st diagnosis rose steeply from 6790 in 1980 to 10778 in 1990. HF as any of 1 to 6 listed diagnoses increased from 13667 to 21590. Over this period there were approximately 1.4 discharges per individual per year. In 1980 few (1.1%) comprised 52.5% of HF discharges. 18.9% of HF discharges were in the age band 45-64 yrs, 27.0% in the band 65-74 yrs and 51.9% in the band 75+ yrs. The corresponding HF discharge rate per 1000 population in each age band was 3.2, 12.9 and 20.2. Of those discharged with a diagnosis of HF only 4% were from Cardiology wards whereas 77% came from General Medical and 19% from Geriatric Assessment wards. HF, therefore, contributed to 7.3% of all "internal medicine" (General Medicine and Cardiology) discharges and 11.6% of Geriatric discharges. The average in-patient stay was 15.7 days (p < 0.001 compared to 11.4 days). In 1990 it was 11.4, 6.8 and 28.5 days, respectively (compared to 13.9, 9.6 and 61.5 days in 1980). In 1980 HF bed occupancy alone cost the NHS in Scotland up to £13 million. In the period 1980-1990 the in-patient case fatality rate for patients dropped steadily from 24.8% to 19.3%.

HF is an increasingly common and cause of admission (and readmission) to hospital in Scotland. In-hospital mortality remains very high. Further investigation of the impact of HF on hospital resources and how this might be modified by treatment is urgently required.
MYOCARDIAL 72- and 60-KILODALTON STRESS PROTEIN CONTENT AND RESISTANCE TO HYPOXIA/REOXGENATION
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The Hatter Institute for Cardiovascular Studies, Division of Cardiology, University College Hospital, London, UK.

Heat stress pre-treatment limits myocardial damage associated with ischaemia/reperfusion and hypoxia/reoxygenation. The mechanism of such protection is unknown but may involve stress protein induction. We have attempted to address the relationship, within individual hearts, between myocardial content of the 72kDa and 60kDa stress proteins (HSP72 & HSP60) and subsequent resistance to hypoxia/reoxygenation. Stress proteins were induced by elevating rectal temperature of anaesthetised rabbits to 42°C for 15 mins (HSP, n=12). Control rabbits (C, n=12) were treated identically but without heating. The following day, right ventricular papillary muscles were mounted in a Langendorff bath, superfused with oxygenated modified Tyrode's solution at 37°C and field stimulated at 1Hz. Subsequently, remaining "sister" papillary muscles were removed for stress protein analysis. Papillary muscle stress protein content was estimated for HSP72 and HSP60 by densitometric assessment of Western blots normalising to the actin band of an identically loaded Coomassie stained gel. The superfused papillary muscles were stabilised and then subjected to 30 mins hypoxia with substrate deprivation followed by 90 mins reoxygenation and return of substrates. This study provides circumsstantial evidence that the protection associated with heat stress may be stress protein mediated.

Endothelium-dependent dilatation competes with \(\alpha_1\)-and \(\alpha_2\)-adrenergic constriction in the coronary microcirculation of the beating heart

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Microcirculation Research Institute, Texas A & M University Health Science Center, Texas, USA and Department of Cardiology, University of Wales College of Medicine, Cardiff

We hypothesised that the coronary microvascular constrictor response to \(\alpha\)-adrenergic activation may be accentuated by loss of endothelium-dependent dilatation. To test this, canine coronary microvascular diameters were measured in the beating heart by intravital microscopy and fluorescein microangiography and atherosclerotic epi-illumination during \(\alpha\)-adrenergic activation before and after inhibition of nitric oxide (NO) synthesis. Selective \(\alpha_1\)- and \(\alpha_2\)-adrenergic receptor activation was achieved by noradrenaline (0.05 and 0.2 \(\mu\)g/kg min \(^{-1}\)) in the presence of an \(\alpha_2\)-adrenergic antagonist (rauwolscine, 0.2 mg/kg, \(n=9\)) or an \(\alpha_1\)-antagonist (prazosin, 0.75 mg/kg, \(n=6\)) and \(\alpha_2\)-antagonist (propranolol, 1 mg/kg). NO synthesis was inhibited by L-arginine analogues (L-NA or L-NNAME, 30 mg/kg iv.), and systemic arterial pressure was held constant. \(\alpha_2\)-activation constricted small arteries (>100 \(\mu\)m diameter) (<4 \(\%\) and -5 \(\pm\) 1 \(\%\) for the 2 doses of N.A., p < 0.05) but not arterioles. Conversely, \(\alpha_1\)-activation constricted arterioles (>-6 \(\%\) and -3 \(\pm\) 4 \(\%\), p < 0.05 and NS), but not small arteries. Inhibition of NO synthesis constricted all microvessels (-6 \(\pm\) 2 \(\%\), p < 0.05), abolished acetylcholine-mediated dilatation, and potentiated \(\alpha_1\)- and \(\alpha_2\)-adrenergic constriction. \(\alpha_1\)-constriction was unmasked in arterioles (-7 \(\pm\) 3 \(\%\) and -10 \(\pm\) 4 \(\%\), p < 0.05) and \(\alpha_2\)-constriction was unmasked in small arteries (-8 \(\pm\) 1 \(\%\) and -6 \(\pm\) 2 \(\%\), p < 0.05). Alpha-adrenergic constriction was not accentuated by increased tone per se, since it did not occur during preconstriction with angiotensin II in separate experiments. These results indicate that \(\alpha_1\)-constriction normally predominates in small arteries and \(\alpha_2\)-constriction in arterioles. Endothelium-dependent dilatation competes with \(\alpha_1\)- and \(\alpha_2\)-adrenergic constriction throughout the coronary microcirculation. These findings may explain increased \(\alpha\)-adrenergic constriction in disease states associated with coronary microvascular endothelial impairment.

THE INFLUENCE OF LOW MOLECULAR WEIGHT HEPARIN (LMWH) ON INTIMAL ProliferATION IN CULTURED HUMAN SAPHENOUS VEIN
Dept. of Surgery, University of Leicester, Leicester.

Heparin has been proposed as a potential agent for the prevention of vein graft intimal hyperplasia. In this dose ranging study the effect of LMWH on intimal proliferation in cultured human saphenous vein was investigated. Thirty paired segments of saphenous vein were incubated at 37°C for 14 days in culture medium with 30% fetal calf serum. LMWH was added to the medium of one of the paired segments at 1, 10 and 100 \(\mu\)g/ml (5 veins each dose). 5-bromo-2-deoxyuridine (Brd-U) was used to label all proliferating cells during the final 24 hours of the culture period. Neointimal thickness was measured by 2 independent observers. The results are shown in the table:
CAPTOPRIL INHIBITS OXIDATION OF HUMAN LOW DENSITY LIPOPROTEIN CHOLESTEROL
EG Godfrey, J Stewart, HJ Dargie, JL Reid, M Dominiczak, CA Hamilton, JM McMurray. Departments of Medicine & Therapeutics, Biochemistry and Cardiology, Western Infirmary, Glasgow, Scotland, UK.

There is growing evidence that oxidation of low density lipoprotein (LDL) cholesterol is a prerequisite for macrophage uptake and initiation of atherosclerosis. We have investigated the possibility that captopril, which is both an ACE inhibitor and an antioxidant, can inhibit human LDL oxidation. Blood was collected from healthy female volunteers. LDL was isolated by sequential density gradient ultracentrifugation and dialysed for 48 hours. Oxidation was then initiated with 4μM CuCl₂. Following a lag-phase there was a rapid increase in diene conjugates which was measured spectrophotometrically at 234nm. The lag-phase was used as a standard measure of resistance to oxidation (Esterbauer et al., J. Biol. Chem., 1992, 267: 67-75).

In contrast to mechanical alternans; a contraction in the generation of regional electrical alternans; i.e. during atrial fibrillation, the generation of regional electrical alternans; i.e. during atrial fibrillation, was noted in patients (n=126±16min. Of the generation of regional electrical alternans; i.e. during atrial fibrillation, the generation of regional electrical alternans; i.e. during atrial fibrillation, is always accompanied by alternans in the generation of regional electrical alternans; i.e. during atrial fibrillation, ventricular systolic pressure ([1.4±1.0]N·m⁻²) was measured with Doppler echocardiography in neonates (age <28 days) with suspected aortic arch obstruction, image guided pulsed Doppler (PWD) recordings were obtained from the aortic arch during the obstruction, and blind continuous wave Doppler (CWD) interrogation of the descending aorta was also performed from the suprasternal notch. Associated intracardiac defects were present in 22 neonates. The diagnoses (confirmed at surgery or catheterisation) were preductal coarctation (21 patients), postductal coarctation (6 patients), interrupted arch (5 patients) and aortic arch atresia (4 patients). Using CWD, a high velocity jet (>2.2m/sec) was recorded from the suprasternal notch in 13 patients (36%). Of these, 4 had preductal, and 6 post ductal coarctation. The remaining 3 patients had arch atresia or interruption. By PWD, a prominent diastolic flow signal towards the descending aorta was recorded in the proximal arch in all patients with coarctation (pre- or postductal), representing either a diastolic pressure gradient across the obstruction, steal from collateral arteries supplying the descending aorta, or diastolic ductal steal. This diastolic signal was absent in patients with interruption or arch atresia. In conclusion, ductal patency often precludes the development of a large pressure drop across the coarctation in neonates. Alternatively, a high velocity CWD signal may be recorded from a restrictive ductal obstruction. Diastolic PWD profiles from the transverse arch permit a more meaningful assessment of the haemodynamics of obstructive lesions of the arch in neonates.
We studied the acute haemodynamic response to captopril in 15 infants with uncontrolled cardiac failure due to an intracardiac left to right shunt. The aim was to see if we can predict non-invasively those infants who will react adversely to captopril by increasing their left to right shunt as has been shown in studies involving cardiac catheterisation. The children were sedated with chloral hydrate (100 mg/kg). Baseline measurements were made of heart rate and blood pressure. Aortic and pulmonary artery diameters were determined from 2 dimensional echocardiographic images and aortic and pulmonary stroke distances from continuous wave Doppler echocardiography.

Captopril (median reduction 18%, P<0.05) although 1 infant decreased (median 50), in 2 patients. Baseline Qp/Qs ranged from 2.5 - 5.1 and following captopril decreased had an ISVR <35 units in 2 patients. Our study suggests that there is no adverse or non-invasive to captopril therapy in the long term however has not been addressed.

Myocardial ischaemia is common during haemodialysis (HD) but there have been no studies of coronary blood flow during HD. To further understand the pathophysiology of coronary insufficiency during HD we non-invasively measured haemodynamics, coronary artery dimensions and coronary blood flow in 14 patients undergoing bicarbonate HD. Patients were studied before, at 4 time points during and 45 minutes after HD. Heart rate, blood pressure and cardiac output were measured. High frequency transcutaneous echocardiography was used to image and measure coronary blood flow velocity from the distal left anterior descending coronary artery (LAD). LAD diameter was measured and instantaneous LAD blood flow calculated from area X mean velocity. Total LAD flow was calculated from area X velocity time integral X heart rate. Control readings were taken on a non-HD day.

### RESULTS

<table>
<thead>
<tr>
<th>Pre-HD</th>
<th>HD</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total LAD flow m/min</td>
<td>82.9(9.8)</td>
<td>72.9(9.0)</td>
</tr>
<tr>
<td>Instantaneous LAD flow m/s</td>
<td>3.1(2.8)</td>
<td>2.6(3.7)</td>
</tr>
<tr>
<td>Cardiac output l/min</td>
<td>4.3(0.2)</td>
<td>3.5(0.2)</td>
</tr>
</tbody>
</table>

LAD flow and cardiac output fell significantly at all points during HD, returning to baseline after HD. Heart rate, blood pressure and LAD diameter were not significantly changed during HD. LAD flow and cardiac output were stable on the control day. Conclusion: Reduction in coronary blood flow may be due to direct myocardial depression or acid/base disturbances as heart rate and blood pressure were unaltered. This study provides further understanding of coronary haemodynamics during HD. Further studies using these techniques described may guide more appropriate anti-anginal therapy in this context.
LACK OF ACUTE PULMONARY VASODILATION DOES NOT PRECLUDE SUCCESSFUL CLINICAL RESPONSE TO PROSTACYCLIN (PGI) IN SEVERE PULMONARY HYPERTENSION (SPH) 
A T Butt, T W Higginbottom, G Croanna, M Takao, C Glanville, A McMahon 
Department of Respiratory Physiology, Papworth Hospital, Cambridge

Continuous PGI infusion has produced sustained haemodynamic and symptomatic improvement in SPH (Rubin et al, Am Int Med 1990;112:485-491). Generally vasodilator therapy is recommended for those patients showing a significant reduction in pulmonary vascular resistance (PVR) to acute vasodilator challenge (Reeve et al, Am Rev Respir Dis 1986;134:342-346). We have questioned the need to perform acute vasodilator trial in SPH and report the results from 19 patients (mean age 38.9 ± 3.8 y) with SPH (Mean pulmonary artery pressure 60.3 ± 2.75 mmHg, cardiac index 1.65 ± 0.78L/min/m², right atrial pressure 12.6 ± 1.5mmHg and mixed venous oxygen saturation 71.6% ± 3.9%). Majority of patients had primary pulmonary hypertension (n=14) whereas others had SPH due to pulmonary embolism (n=5). Haemodynamics were measured at baseline and after vasodilator trial with PGI, and patients were grouped into responders (R) and non-responders (NR) depending upon the degree of fall in PVR, 20% being target value. All patients were then commenced on continuous PGI infusion and their exercise tolerance was measured at baseline and after PGI therapy (6.05 ± 7.6 weeks; mean ± SD). The results are as follows:-

<table>
<thead>
<tr>
<th>Patients</th>
<th>PVR (Wood Units)</th>
<th>% drop in PVR 12mm walk (m)</th>
<th>% rise in exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>After PGI R (n=11)</td>
<td>20.7 ± 2.9</td>
<td>14.2 ± 2.9</td>
</tr>
<tr>
<td>NR (n=8)</td>
<td>16.5 ± 1.0</td>
<td>13.9 ± 0.87</td>
<td>15.4 ± 1.2</td>
</tr>
<tr>
<td>mean values ± SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An improvement in exercise tolerance with continuous PGI infusion and their exercise tolerance was measured at baseline and after PGI therapy (6.05 ± 7.6 weeks; mean ± SD). The results are as follows:-

CATECHOLAMINE AND CIRCULATORY RESPONSE TO A STREAM OF COLD AIR AT REST AND DURING EXERCISE 
Cardiovascular Medicine, University Hospital, Nottingham, NG7 2HU

Many patients with angina complain of symptomatic deterioration on exposure to cold. The physiological mechanism explaining this phenomenon remains unclear. We have studied the effect of localised cold stimuli to the face in the presence of a constant ambient temperature. Cardiac output (CO), stroke volume (SV) and noradrenaline levels were measured at rest and during treadmill exercise in 9 healthy males under temperature controlled conditions. A stream of cold air was then directed at the face and repeat measurements performed. The results are displayed below:

<table>
<thead>
<tr>
<th>Exercise stage</th>
<th>CO (l/min)</th>
<th>SV (ml)</th>
<th>Noradrenaline (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room Cold</td>
<td>4.0(0.2)</td>
<td>4.6(0.4)</td>
<td>56.3(6.4)</td>
</tr>
<tr>
<td>Cold</td>
<td>61(8.9)</td>
<td>76(9.1)</td>
<td>97.8(8.9)</td>
</tr>
<tr>
<td>Room Cold</td>
<td>8.8(6.9)</td>
<td>9.1(6.7)</td>
<td>106(8.5)</td>
</tr>
<tr>
<td>Room</td>
<td>11.1(6.7)</td>
<td>11.5(6.0)</td>
<td>1114(7.8)</td>
</tr>
</tbody>
</table>

*p<0.001 & p<0.001
Cold exposure increased CO during early exercise but no difference was seen at rest. This stimulus significantly increased stroke volume and noradrenaline levels at rest and during exercise. These changes were noted in the absence of a significant pressor response. The increase in cardiac work as a result of these changes may explain why patients with angina notice an increase in symptoms when exposed to cold winds.

DUPLICATION HEMICYCLOTHROMY IN PATIENTS UNDERGOING MITRAL VALVE SURGERY 
S Forse, S Purkile, TB Graham, CT Lewis, PG Miller 
Departments of Cardiology & Cardiovascular Surgery, Royal London Hospital, Whitechapel, London

Mitral valve disease may have an adverse effects on liver function. Reduction in cardiac output secondary to mitral valve disease may reduce hepatic arterial perfusion whereas portal perfusion is related to right ventricular function. The aim of this study was to investigate hepatic haemodynamics before and after mitral valve surgery & De Vega tricuspid repair. Eighteen consecutive patients (6 mitral stenosis (MS), 7 regurgitation (NR) & 5 mitral & tricuspid regurgitation (MTR)) and six control patients undergoing routine coronary artery bypass surgery were investigated. Hepatic artery and portal perfusion were assessed using pulse wave Doppler positioned within the hepatic artery and portal vein to record velocities over six cardiac cycles. A suspended 2D image was used to measure mean cross sectional area of the hepatic artery and portal vein. Hepatic & portal venal flow rates (HAF & PVFR resp; mIs) and Doppler perfusion index (DPI; HAF/PVFR ratio) were calculated from time averaged velocities and averaged cross sectional areas pre-operatively (A), and 1 month post-operatively (B).

<table>
<thead>
<tr>
<th>CONTROLS</th>
<th>MS</th>
<th>MTR</th>
<th>HAF</th>
<th>PVFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A B A B A B</td>
<td>241.2 255.3 198.2</td>
<td>212.3 179.8 227.3</td>
<td>110.6 205.6</td>
<td></td>
</tr>
<tr>
<td>B A B A B</td>
<td>212.7 200.6 120.8</td>
<td>112.0 106.9 107.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPI</td>
<td>0.15 0.14 0.13</td>
<td>0.12 0.12 0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.04)</td>
<td>(0.03)</td>
<td>(0.03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(mean ± s.e.m.; * p<0.05 Student's t-test)

SKELETAL MUSCLE AND THE CONTROL OF VENTILATION ON EXERCISE: EVIDENCE FOR METABOLIC RECEPTORS. 
A Clark, M Pippoli, AJS Coats 
Department of Cardiology National Heart & Lung Institute, Dovehouse Street, London SW3 6LY

The relationship between ventilation and carbon dioxide production during exercise is linear, and it is often assumed that carbon dioxide production is the signal for increased ventilation. In chronic heart failure, the slope of this relationship is increased, but the mechanism underlying the increase is not known. Skeletal muscle is abnormal in chronic heart failure, and it is possible that a link exists between skeletal muscle and the control of ventilation. In order to see if it is possible to alter the ventilation to carbon dioxide production relationship and whether there is a signal from exercising muscle to respiratory control centres, 15 normal subjects were exercised on a treadmill using a control run and a run when cuffs were inflated to supraphysiological pressure around the thighs. Ventilation and metabolic gas exchange were measured. Compared with the control run, ventilation increased (22.53 l/min to 25.26; p<0.001) and oxygen consumption decreased (from 14.79 ml/s/kg/min to 12.75; p<0.01) during exercise when the cuffs were inflated. Carbon dioxide production remained unchanged. The net result was an increase of 25% in the ventilation/carbon dioxide production slope from 20.9 to 25.43 (p<0.001). Thus, there must be a signal to increase ventilation on exercise from exercising muscle that is enhanced by the effects of altering the muscle from the circulation. This by definition cannot be a blood borne factor released by muscle. This experiment provides evidence for a metabolic receptor communicating via a neural signal, possibly representing an action of the known muscle efferent receptors. Excessive activity of this reflex may be an explanation for the increased ventilation/carbon dioxide production slope seen in chronic heart failure.

Compared with controls (*), patients with MR, NS & MTR had significantly reduced HAF. MTR was also associated with a significantly reduced PVFR. DPI was significantly reduced in MS & MTR, but not MR. Following surgery, relative improvements were noted in most patients but especially in patients with MTR (*).
(294) POSTER

CO-ORDINATED ATRIAL CONTRACTION IS NECESSARY FOR THE RELEASE OF ATRIAL Natriuretic PEPTIDE DURING EXERCISE IN PATIENTS WITH COMPLETE HEART BLOCK

Department of Cardiology, General Infirmary at Leeds, Leeds

Previous studies have demonstrated that plasma atrial natriuretic peptide (ANP) levels in patients with impaired atrial function are within the normal range. Peripheral ANP was measured during exercise in 12 patients with complete heart block (CHB) and permanent rate responsive pacemakers (mean age 57.6 ± 8.7 yrs, 7 males).

7 patients had co-ordinated atrial contraction (AC) (determined by echocardiography and the presence of P waves on the resting electrocardiogram). 5 patients had chronic atrial fibrillation (AF). All had good left ventricular (LV) function, (LV ejection fraction >50%). Each patient performed 3 treadmill exercise tests with a 60 minute rest period between each. Maximal inspired oxygen volume (VO2 max) was determined during test 1. Tests 2 and 3 were performed to 70% VO2 max in a single-blind crossover, the pacemaker being programmed to either VVI (fixed rate, 70 bpm) or VVIR (rate response, upper rate 130 ppm). Blood samples were taken at rest and at 3 minute intervals during exercise. Plasma ANP was measured using a two-site immuno-radiometric assay.

Results: Median [ANP] BASAL

<table>
<thead>
<tr>
<th>Test</th>
<th>ANP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>63 p=NS</td>
</tr>
<tr>
<td>AC</td>
<td>85 p&lt;0.05</td>
</tr>
<tr>
<td>VVI</td>
<td>61 p=NS 53</td>
</tr>
<tr>
<td>VVI</td>
<td>226 p=NS 182</td>
</tr>
</tbody>
</table>

There was a significant increase in plasma [ANP] during exercise in patients with AC which was independent of ventricular rate.

Conclusions: It has previously been suggested that ANP release by non-functioning atria is normal. For the first time, we have shown that the presence of co-ordinated atrial contraction is required for the release of ANP during exercise in patients with CHB, and that this appears to be independent of ventricular rate.

(295) POSTER

ACUTE DISSECTION OF THORACIC AORTA: EFFECT ON BLOOD PRESSURE IN THE ARMS

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Departments of Cardiology and Cardiothoracic Surgery, Northern General Hospital, Sheffield

It is held that in acute dissection of the thoracic aorta there is marked disparity in BP between the arms. Precise figures are lacking. We therefore audited the records of the last 50 cases from our centre. 35 were male, mean age was 59 (SD 14) years. 29 were Type A, 21 Type B. In only 23/50 were records of BP in both arms made. Of these, 14 were Type A and 9 Type B. Overall mean BP was 122/65 (SD 45/24) mmHg. This did not significantly differ from a 'control' group of patients presenting with chest pain: mean 119/69 (SD 19/12) mmHg. When the higher of each pair of readings was taken (reflecting systemic pressure), the dissection group's mean was 130/72 (SD 38/20) mmHg, the chest pain group's 126/70 (SD 19/12) mmHg, p=NS. Mean L-R disparity was +40/24 (SD 66/38) mmHg for Type A and -11/0 (SD 18/5) mmHg for Type B (p<0.02). The only absent pulses were in 4 Type A patients. When they were excluded, Type A mean disparity fell to 0/4 (SD 29/23) mmHg, not significantly different from Type B or the chest pain controls.

So in dissection of the thoracic aorta, BP tends to be lower in the R arm in a Type A dissection, and (to a lesser extent) lower in the L arm in a Type B dissection. But the magnitude of BP disparity between the arms is relatively unhelpful, not least because middle aged patients with chest pain may have a L-R or R-L disparity of up to 10/5 in 35% of cases. An absent pulse is the only reliable sign in the peripheral circulation of a dissection. In our series, an absent radial with Type A dissection was the only absent pulse recorded.

(296) POSTER

ASSESSMENT OF REGIONAL LONG AXIS MYOCARDIAL VELOCITY DURING DOBUTAMINE STRESS USING MAGNETIC RESONANCE VELOCITY MAPPING: A COMPARISON OF NORMAL CONTROLS AND PATIENTS WITH ISCHAEMIC HEART DISEASE

Stefan P Karpawtowski, Sandy M Forbat, Raad Mohiddin, Guang Z Yang, David N Firmin, Richard Underwood, Donald Longmore, Royal Brompton National Heart and Lung, London

Abnormalities of ventricular wall motion may be present at rest in ischaemic heart disease (IHD). Stress may exacerbate existing abnormalities and provoke new ones. We have used symptom limited dobutamine stress and imaging with magnetic resonance velocity mapping (MRV) to study regional ventricular long axis function. Nineteen patients with IHD (7 with prior infarction, 3 female, age 30-69) and 8 normal subjects were studied. MRV cine velocity maps were acquired through a basal short axis plane, divided into 32 sectors to provide regional long axis myocardial velocity. Following a resting study dobutamine was infused at 5, 10, 15μg/kg/min if tolerated and the study repeated. Early diastolic long axis velocity was standardised to the peak circumferential value to permit comparison. Compared with baseline, controls showed an increase in peak long axis velocity (p=0.0002) and a decreased time to peak velocity (p=0.0036) at heart rates below 100 during stress. The increase varied around the ventricle, lateral wall increased by 32% of baseline values, inferior by 15%, septum by 12% and anterior by 20%. At rest all 8 patients with prior infarction and 3 without had impaired long axis function. All patients showed increased absolute long axis velocity during stress in at least one segment. Eleven developed velocity of reduced relative velocity during stress, two showed no change. Two developed global reductions in velocity despite increases in the rate-pressure product. One showed an increase in velocity in an area abnormal at rest. The patient with triple vessel disease had the greatest change during stress. Comparing baseline velocity measurements with those at the first level of stress, controls had a mean of 32 with an increased velocity over baseline by 35μg/kg/min dobutamine, patients had a mean of 20 sectors out of 32 with increased velocity at the first level of dobutamine, p=0.013. All patients tolerated the procedure well. Low dose dobutamine stress provoked alterations in relative regional velocity in both controls and patients. The most common response in patients was to develop a region of reduced velocity.

(297) POSTER

MAGNETIC RESONANCE CORONARY ANGIOGRAPHY: TECHNIQUES AND PRELIMINARY RESULTS


Magnetic resonance imaging (MRI) of the coronary arteries faces formidable problems because of their small size and tortuosity combined with respiratory and cardiac motion. Rapid imaging techniques with diastolic imaging over the period of a breath-hold greatly reduces motion artefact and may overcome many of the problems. A 1.5T magnet was used with a gradient echo sequence and 8 phase encoding steps per cardiac cycle over 120ms of late diastole. Total acquisition time was 16 heart beats, with a pixel size of 1.6 x1.6mm and slice thickness 4mm. To enhance the contrast between arteries and surrounding fat, fat suppression using selective pre-excitation was used. This employs the principle of chemical shift, whereby protons in fat resonate at a higher frequency than protons in water. We studied 20 subjects, 10 normals and 10 with coronary artery disease. After a rapid learning phase, the proximal coronary arteries were identified in 15 subjects by imaging of the coronary sinuses in the transaxial plane. A surface coil was used in the last 10 studies resulting in improved imaging with increased signal to noise. Lower transaxial imaging located the midportion of the arteries in the atriocaval and interventricular sulci. Oblique imaging in planes defined from the proximal and mid portions of the arteries allowed imaging of significant lengths of the arteries. Overlapping contiguous slices were acquired to show the transition of the arteries through the oblique planes. Cine loops of these slices allowed easier interpretation of the anatomy. We have demonstrated the potential of MR to image coronary anatomy noninvasively. Breath-hold multislice imaging using subsecond echo-planar imaging is expected to provide further improvements.
IDENTIFICATION OF PATIENTS AT RISK OF THE FAT EMBOLISM SYNDROME USING TRANSOEOSOPHAGEAL ECHOCARDIOGRAPHY
ACH Pell, JF Keating, J Christie, GR Sutherland
Departments of Cardiology and Orthopaedic Surgery, Royal Infirmary, Edinburgh.

The fat embolism syndrome (FES) is an important cause of pulmonary, neurological and cardiac dysfunction following skeletal trauma. Its pathophysiology remains poorly defined and there is no reliable method to identify those patients most at risk of FES. Transoesophageal echocardiography (TEE) was performed in 24 patients with traumatic injuries (mean injury severity score 9; range 4-24) to investigate its role in predicting patients at risk of FES. Echogenic material was embolized within the right atrium and ventricle in patients undergoing operative treatment. In 14 patients embolism was minimal or absent (Group 1). Moderate embolism with small (1-10 mm diameter) echogenic masses occurred in 6 pts (Group 2), and severe embolism with numerous small and large echogenic masses (1-6 cm diameter) in 4 pts (Group 3). There was no correlation between severity of embolism and age, fracture type or time since injury. The postoperative course in 21 pts was uncomplicated. However 3 pts in Group 3 developed clinical evidence of FES (hypoxia, neurological dysfunction, petechial rash). Massive intraoperative embolism was observed in 1 pt, with the development of right ventricular dilatation and severe tricuspid incompetence that precipitated paradoxical embolism across a patent foramen ovale. Systemic FES developed postoperatively and subsequently multigorgan microvascular fat embolism was demonstrated at autopsy in Group 3 pts. Conclusions: These results provide new information on the pathophysiology of FES and suggest that TEE might be a useful technique to identify patients at risk of FES following surgical treatment of traumatic injuries. Paradoxical embolism of fat through a patent foramen ovale is a possible mechanism for the systemic features of FES.

COLOUR DOPPLER VELOCITY MAPPING - IN VITRO STUDIES TO DEVELOP A NEW MYOCARDIAL IMAGING TECHNIQUE
A Fleming, W.N. McDicken, G.R. Sutherland, M.J. Stewart
Departments of Medical Physics and Cardiology, University of Edinburgh, Edinburgh.

Colour Doppler ultrasound imaging has proven a useful technique in observing blood pool motion. Theoretically the same technology, with suitable modification, should be capable of imaging wall motion abnormalities. Moreover, information may be available on the movement of fibre groups within the tissue, thus providing additional information on both myocardial structure and function. The development of the system software for lower velocities (0-3 cm s\(^{-1}\)) to be displayed with high resolution, and (iii) reducing the number of samples taken from each ultrasound line so that the frame rate is increased. Velocities are encoded in the usual way, with red indicating movement towards the transducer and blue indicating motion away. Further software modification enabled the imaging of myocardial acceleration and velocity-variance in addition to velocity. A series of in vitro phantom studies, using both rehydrated foam and a gel/agar mixture as tissue equivalent materials, have been performed. These were used to test: (1) Resolution of the velocity estimator, (2) Resolution of the colour-rejector, (3) Effect of signal strength on the velocity display, and (4) Accuracy of the velocity encoding. Similar studies examined resolution of the acceleration and variance modalities. Results: (1) Resolution of the colour-rejector has been shown to be 3 mm, indicating that structures 3 mm could be observed using this technique. (2) Resolution of the velocity estimator has also been shown to be 3 mm, suggesting this estimation of velocity without the need for blood-pool will be possible. (3) Spatial resolution of colour Doppler images was slightly lower than that of pulse-echo imaging, but with the additional information available from velocity encoding. Conclusion: This series of phantom experiments has shown that modification of a standard colour Doppler imaging system can allow myocardial imaging with resolution adequate for the study of both overall wall motion and intramural blood motion. With further modification improved tissue edge detection should be possible and this technique may allow both improved recognition and quantification of wall motion abnormalities.

MAGNETIC RESONANCE IMAGING IN THE EVALUATION OF INTERMEDIATE TERM RESULTS OF COARCTATION BALLOON ANGIOPLASTY IN ADULTS
ME Fawzy, A Rifai, WN von Sinner, O Galal, B Dunn, MF El-Deeb
Department of Cardiovascular Diseases, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Twenty-three consecutive adult patients (pts) with a mean age of 25 years, who underwent balloon angioplasty for congenital native coarctation, were restudied by catheterization and nuclear magnetic resonance imaging (MRI) at a mean follow-up of 21 months after dilation. Both studies were performed between 1 and 180 days (mean 40 days). The diameter of the aorta at the site of the previous coarctation was measured on angiogram and MRI, each by two independent observers. The results were compared using linear regression analysis. Results: 1) The gradient across the previous coarctation ranged from 0 to 20 (mean 7.8±3.3) mm Hg. 2) The diameter of the aorta measured at the previous coarctation site on angiogram was 13.7±3.7 mm, with an excellent correlation with MRI measured at MRI (13.5±3.7 mm with r = 0.96, SEE = 0.91, P < 0.001) in the pts with 0-15 mmHg residual gradient across decoarctation site measured ≥ 11 mm on MRI. Two pts had small aneurysms 2 cm in diameter, demonstrated by angiography and MRI which had not increased in size at follow-up 2 years later. 4) Two pts developed restenosis diagnosis correctly by both catheterization and MRI. Conclusion: 1) MRI provides excellent visualization of the anatomy of coarctation of the aorta and is a noninvasive method for follow-up of patients undergoing balloon coarctation angioplasty and invasive restudy is not necessary. 2) Intermediate term results of coarctation balloon angioplasty is encouraging.

RAPID ASSESSMENT OF LEFT VENTRICULAR VOLUME BY SHORT AXIS CINE MAGNETIC RESONANCE IMAGING

We have previously established the accuracy of left and right ventricular volumes measured by summing chamber areas in multiple contiguous slices. The method can be impractical however, requiring up to 45 minutes of data acquisition. We have therefore compared the technique with measurements made from cine acquisitions of short and long axis planes with a total acquisition time of 15 minutes. We studied 20 patients (mean age 52, range 34 to 73, 15 male) six months after myocardial infarction (CAD) and 10 normal subjects (mean age 41, range 27 to 50 years, all males). Cine acquisitions were made in midslice vertical and horizontal long axis planes and in the two short axis planes which divided the long axis into three equal parts. Volume was calculated assuming the ventricle to be composed of a cylinder, a truncated cone, and a cone. There was good agreement between the two methods at end diastole (LVEDV) but less good agreement at end systole (LVESV). There was no correlation between the discrepancy of volume measurement and either the volume itself or the extent of wall motion abnormality.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>9.1 (2.55)</td>
<td>105 (51)</td>
</tr>
<tr>
<td>Diff (SD)</td>
<td>1.3 (18.3)</td>
<td>25.2 (13.7)</td>
</tr>
</tbody>
</table>

We conclude that rapid measurements of end diastolic volume are more accurate than those of end systolic volume and hence ejection fraction, but that the rapid technique is sufficient for routine clinical use in both normal and abnormal ventricles providing the potential error is recognised.

<table>
<thead>
<tr>
<th></th>
<th>LVEDV (ml)</th>
<th>LVESV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>142 (23)</td>
<td>155 (51)</td>
</tr>
<tr>
<td>Diff (SD)</td>
<td>25.2 (13.7)</td>
<td>25.9 (16.2)</td>
</tr>
</tbody>
</table>

We conclude that rapid measurements of end diastolic volume are more accurate than those of end systolic volume and hence ejection fraction, but that the rapid technique is sufficient for routine clinical use in both normal and abnormal ventricles providing the potential error is recognised.
TO EVALUATE FOLLOWING INTRA-VENOUS INJECTION COLOUR

Moreover, of stable, transpulmonary myocardial Stewart, have therefore adapted ventricle was selectively image perfused myocardium. Intra-venous imaging after myocardial signal strength suitable subsequent Marwick, with (CAD). Dobutamine NIBI p-0.02), have cardiography DE (71% vs. 51%) using (99/110, PAC). Percentage changes into separate low-PROB groups, and the absence of disease in the low-PROB group was 76% (120/159 36%) and MIBI-SPECT (99/110, 30%). Conclusions have similar sensitivities for the prediction of CAD. DE is more effectively classifies pts into groups with high- or low-probability of CAD.

COLOUR DOPPLER IMAGING OF THE MYOCARDIUM FOLLOWING INTRA-VENOUS INJECTION OF A TRANS-PULMONARY CONTRAST AGENT - A NEW TECHNIQUE TO EVALUATE REGIONAL MYOCARDIAL PERFUSION?

Myocardial two-dimensional contrast echocardiography using direct intra-coronary injection of optimized contrast media offers the potential for myocardial perfusion imaging following intra-venous injection, initial results have been disappointing due to 2-D image ultrasound attenuation. By comparison, colour Doppler flow detection is less influenced by intervening tissues. Moreover, colour Doppler signal strength is enhanced by the presence of contrast material within the insonated region of interest. We have therefore adapted a standard ultrasound machine, changing the colour Doppler software to preferentially image myocardial motion. Two colour maps were specifically developed for image acquisition from contrast enhanced myocardium: (i) Velocity, (ii) Energy. Initial animal experiments were performed in 4 open-chest anaesthetised pigs. Colour Doppler imaging after direct intra-aortic injection of SHU 508A, a new saccharide based transpulmonary contrast agent, before and after ligation of the left anterior descending coronary artery, confirmed the ability of these maps to selectively image perfused myocardium. Contrast enhancement following intra-venous injection was less apparent due to impaired visualisation of the left ventricle from right ventricular myocardial opacification. However, by imaging the left ventricle posteriorly, contrast enhancement in the left ventricle was evident. Clinical studies were then carried out in 16 patients with cardiac lesions but no ischaemic heart disease. Multiphase imaging of the left ventricular myocardium was performed using 2-D, colour Doppler and M-mode colour Doppler modalities. Images were acquired immediately before and for 10 minutes after the intra-venous injection of 3.2 G of SHU 508A, recording both on video tape and on digital quad screen format to allow subsequent side by side comparison. A visually appreciable effect on myocardial signal strength was apparent in 6/16 studies. Conclusion: With suitable modification of standard Doppler equipment an increase in Doppler signal strength can be detected in perfused left ventricular myocardium following intra-venous injection of SHU 508A. These initial studies suggest that this new technique may have the potential to allow the non-invasive assessment of regional myocardial perfusion.

THE MANAGEMENT OF TRICUSPID REGURGITATION AT THE TIME OF MITRAL VALVE REPLACEMENT - THE SURGEON’S DILEMMA

Late tricuspid regurgitation (TR) following mitral valve replacement (MVR) is associated with dilatation of the tricuspid annulus and a poor functional outcome. Tricuspid valve (TV) repair is therefore sometimes undertaken at the time of initial surgery in an attempt to prevent the development of late TR. We surveyed 127 surgeons throughout the UK regarding their current practices in assessing and correcting TR in patients undergoing MVR. Late TR is perceived to be an important (91%) but uncommon (82%) problem by those who replied (101/127 [79%]). The TV is assessed routinely by 64% of surgeons pre-operatively, 50% per-operatively, 48% both and 25% not at all. The following methods of assessment of TR are routinely undertaken; haemodynamic (51%), right ventriculography (11%), pre-operative echocardiography (69%), per-operative digital palpation of the TV (67%) and per-operative echocardiography (18%). The majority of surgeons (87%) perform TV repair only when TR is considered severe and the minority when it is mild or moderate (16%). The favoured method of repair includes Carpentier ring annuloplasty (37%), De Vega annuloplasty (31%), TV replacement (13%) and tricuspid bicuspidization (5%). Thus, although most surgeons assess the TV in patients undergoing MVR, the optimal methods of doing so remain open to question. Per-operative echocardiography with colour Doppler has been shown to be a simple and accurate means of assessing the severity of TR in patients with rheumatic mitral valve disease and yet is undertaken in only the minority of cases. The failure of more widespread usage of such an approach when TR is considered mild or moderate may explain the continuing appearance of TR in the late post-operative period.
ULTRASOUND-GUIDED COMPRESSION OF FEMORAL ARTERY PSEUDANEUROYSMS FOLLOWING CARDIAC CATHETERISATION

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The use of ultrasound-guided compression in the treatment of femoral artery pseudoaneurysm following coronary angiography or coronary angioplasty was studied over an 18 month period. Colour flow Doppler ultrasound imaging was performed if a pseudoaneurysm was suspected clinically (and expulsive haematura). Following catheterisation of 2448 patients, a femoral pseudoaneurysm was identified in 14 (0.6%). These lesions were 21 - 58 mm (mean 35 mm) in diameter. One complex rapidly expanding lesion was deemed unsuitable for compression therapy and was surgically repaired. The remaining 13 were treated by compression over the neck of the lesion with the ultrasound probe for 20 - 90 mins (mean 42 mins). The procedure was generally well-tolerated with sedative premedication. Success was defined as closure of the track from the femoral artery to the pseudoaneurysm cavity. Eleven (85%) patients were successfully treated and none of these lesions had recurred when reviewed. Two failures occurred; one case, not diagnosed after catheterisation, was a chronic lesion diagnosed 2 months later and the other failed to occlude after 30 mins compression but had spontaneously thrombosed when reviewed 2 months later. If compression therapy is to succeed, lesions should be treated within one week of formation. In a group of 106 consecutive patients over a 6 month period undergoing coronary angioplasty or atherectomy (8F-11F sheaths), only two (1.9%) femoral pseudoaneurysms were identified (both 8F sheaths) and both were successfully treated. Ultrasound-guided compression is the technique of choice for the primary management of femoral artery pseudoaneurysm formation.

THE EFFECT OF CHOICE OF BLOOD PUMP ON PLATELET AGGREGABILITY.

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Platelet dysfunction is a well recognised complication of cardiopulmonary bypass (CPB) which contributes significantly to morbidity and mortality. We investigated the effect of 2 types of blood pump used for CPB on platelet function. 22 patients undergoing routine coronary artery bypass surgery were randomised into either Group 1:St. Jude Lifesystem Centrifugal Pump (n=10) or Group 2:Roller Pump (n=12). Perfusion pressure were maintained between 60 to 80 mmHg and flow rate was 2.1 l/min/m². Platelet aggregation studies were performed pre-operatively, 4 and 24 hours post CPB using the Born method in platelet rich plasma to 50 μmol/l adenosine 5’ diphosphate (ADP). Parameters measured were 1) time to maximal aggregation in seconds (tmax), 2) slope of initial aggregation (Sagg) and 3) % change in aggregation (% agg). Statistical analysis were performed using the Wilcoxon Matched Pairs Test and the Mann-Whitney U Test.

Results

<table>
<thead>
<tr>
<th>Group</th>
<th>tmax Pre op</th>
<th>tmax 4 hrs</th>
<th>tmax 24 hrs</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>10±20 sec</td>
<td>12±5*</td>
<td>16±2 4**</td>
<td>* p=NS</td>
</tr>
<tr>
<td></td>
<td>(mean±SEM)</td>
<td>(mean±SEM)</td>
<td>(mean±SEM)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Group 2</td>
<td>10±5 14</td>
<td>17±2</td>
<td>23±6 16**</td>
<td>* p=0.009</td>
</tr>
<tr>
<td></td>
<td>(mean±SEM)</td>
<td>(mean±SEM)</td>
<td>(mean±SEM)</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

* and ** compared to pre op, 1 compared to 4 hours

The increase in tmax was significantly greater in Group 2 compared to Group 1 (p=0.04). Platelet aggregation induced with 50 μmol/l ADP showed no significant changes in Sagg in either group but with 100 μmol/l ADP, Sagg fell significantly in Group 2 (p<0.05). % agg remained unchanged post CPB in both groups. This study confirmed that CPB adversely affects platelet aggregability and the degree of damage appears to be reduced using a centrifugal blood pump.

CRYOCARDIAC DENERVATION: A NOVEL TECHNIQUE APPLIED TO INTRACTABLE CHEST PAIN IN CARDIOMYOPATHY

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A 35 year old woman presented with a two year history of intractable chest pain associated with a predominantly apical hypertrophic obstructive cardiomyopathy refractory to maximal medical therapy. Coronary angiography revealed normal epicardial coronary arteries but assessment of maximal coronary vasodilator reserve with intraarterial adenosine disclosed severe impairment, suggestive of small vessel coronary artery disease. Unwilling to expose her to the long term complications of cardiac allografting, we elected to perform cryocardiac denervation using a technique previously employed in an experimental study. The technique is simpler than cardiac transplantation and, we believe, safer. Right ventricular endomyocardial biopsies, performed before and after denervation, were subjected to quantitative immunohistochemical analysis using a computer assisted image analysis system. An indirect immunofluorescence technique was employed using antisera to the general neural marker PGP 9.5 (see table) and neuropeptide Y (NPY). The density of nerve cell populations are expressed as mean % fluorescent area with 95% confidence intervals (95% CI). The total nerve cell population (as determined by the density of nerves displaying PGP 9.5-like immunoreactivity) fell from 6.2±2.1 to 0.4±0.6, a fall of 94% suggesting complete extrinsic denervation. The total nerve cell population (as determined by the density of nerves displaying PGP 9.5-like immunoreactivity) fell from 6.2±2.1 to 0.4±0.6, a fall of 94% suggesting complete extrinsic denervation. This pattern was similar to that seen following transplantation. We believe this to be the first occasion on which such a technique has been used therapeutically. The patient has experienced a dramatic improvement in her symptoms and this has been associated with quantitative immunohistochemical evidence of complete extrinsic denervation.
Measurements of radiation dose incident at various body sites were received during diagnostic and interventional cardiac catheterisation using thermoluminescent and film badge systems. All procedures were performed from the femoral approach using a Siemens Cardoskop U system. Operator protection was afforded by a 0.3mm Pb apron. The data showed that a conventional film badge worn at the waist beneath the apron regularly recorded unquantifiable monthly doses (<0.2mSv) and failed to reflect total body dose. Dosimeters at other body sites consistently recorded high doses. Relative to the dose at the waist, doses incident at other sites were greater by factors of 7.4 at head, 7.5 at neck, 15.3 at left shoulder, 6.8 at left hand, 2.2 at right hand, 17.5 at left thigh (beneath apron) and 26.2 at left knee. Greatest operator dose was due to backscatter from lateral cineangiography when the source was on the same side of the patient as the operator. Total dose for diagnostic coronary angiography was reduced by 30% when the 2 lateral runs (right and left coronary) were performed with the source on the opposite side to the operator. Standing approximately 2 feet further from the source reduced the dose at most sites by a factor of 3–4. An equipment service reduced operator dose by 40% (compared to procedures pre- and post-service). Comparison with other data suggests that dose reduction by a factor of about 10 can be obtained with lead and lead-glass screens. Similar dose reductions were obtained in this study by the expedient of standing behind someone else.

The object of this study was to investigate the feasibility of obtaining endovascular biopsies of the pulmonary artery from a transvenous approach. Nine sheep underwent pulmonary artery biopsy using a 7 French gauge bioptome introduced via the pulmonary artery. In the first three sheep the bioptome was introduced through a purse string incision in the main pulmonary artery at thoracotomy. In the subsequent 6 sheep the internal jugular venous approach was used with a long curved 7 French gauge sheath manipulated over a wire supported end hole catheter. The bioptome was advanced under fluoroscopic control until resistance could be felt and multiple biopsies (1–4) were taken. The samples obtained were studied histologically and the lungs examined with 1 cm serial sections for evidence of serious haemorrhage, contusion or pleural perforation. Biopsies were obtained in all animals. A total of 26 specimens were obtained in 44 attempts (yield 59%). Arterial wall was found in all but one specimen (96%). Lung parenchyma was present in 8 (31%). One sheep had a modest myocardial stain of the right ventricular outflow tract during positioning of the long biopsy sheath with no haemodynamic deterioration. There was no evidence of pneumothorax on fluoroscopy and major haemorrhage was not seen at postmortem examination in any sheep. These results demonstrate that endovascular biopsy of the pulmonary artery can be performed without significant complications. Biopsy material is small by conventional standards and may be of value in the ultrastructural assessment of pulmonary vascular pathology. Method and yield will be demonstrated.

A novel cardiac myofilament desensitising agent released by endocardial endothelial cells

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Endocardial endothelial cells (EEC) modulate myocardial contractile function and diffuse an inhibitor of NO generation which generally influence the onset of relaxation. We studied the nature and intracellular mechanisms of these agents. Cultured sheep EEC were superfused with Heps-buffer (1 mM Ca2+) and the effluent used to isolated sheep myocardium. The subsequent relaxation elicited by NO donors was inhibited by anendothelin specific antiserum. Myocyte cell length (CL) was monitored by a photodiode array and simultaneous [Ca2+]i by the ratio (R) of 410:490 nm ind-1 fluorescence emission. A transient negative followed by a positive inotropic effect was noted. When the number of EEC was increased, a large sustained negative inotropic effect was seen. Twitch amplitude and time to peak shortening decreased rapidly (25:4.3 ± 7.7:1.2 %; p<0.05) and resting CL increased (+1.0±0.2 μm; p<0.01). These effects were rapidly reversible. EEC effluent kept at 37 °C for several hours or at 4 °C for 48 h had the same effects. In indo-1 loaded myocytes (n=7), there were no significant changes in systolic or diastolic R+0.0±0.3 %; -0.4±0.6 %; p>ns). Effects similar to EEC were seen with cultured sheep vascular endothelial cells (VEC). EEC effluent effects were not inhibited by indomethacin (30 μM), nitric oxide synthase inhibitors or by endothelin specific anti-serum. We have noted similar effects with cyclic GMP. However, KT5823, a specific inhibitor of cGMP inotropic effect by NO donor had no inhibitory effect and EEC effluent caused no change in myocyte cGMP content. In myocytes loaded with the fluorescent pH probe SNARF-1 (n=5), no significant change in pH was seen after adding EEC effluent. Thus both EEC and VEC tonically release a novel unidentified agent which induces potent, rapidly reversible cardiac myofilament calcium desensitisation and thus an earlier onset of relaxation. This substance may modulate short-term contraction-relaxation coupling in the heart. (AMS was supported by the BHF).

DISTENSIBILITY OF LARGE ARTERRIES IS INCREASED BY ENDOThELiUM-DERIVED RELAXING FACTOR (EDRF) IN NORMAL SUBJECTS.

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A fundamental property of large arteries is their elasticity, which converts pulsatile cardiac ejection to continuous tissue perfusion and thus minimises cardiac work. The elastic properties of the arterial wall are determined by their structure, transmural pressure and vasomotor tone. They are described by the distensibility, which is inversely related to pulse wave velocity (PWV). Arterial distensibility is reduced in atherosclerosis and hypertension, conditions associated with reduced EDRF activity as well as structural changes. Whether endothelium-mediated dilatation influences distensibility (an effect that may be independent of changes in arterial diameter) has not been established. 5 healthy subjects (mean age 49y) were studied. PWV was calculated from the time delay of a pressure wave arriving at transducers mounted 5 cm apart on a catheter positioned in the right common iliac artery (RCIA). The pressure signals were analysed in real-time using a transputer-based system (resolution <0.1 ms). Acalcyloline (ACH) infused into the proximal RCIA (10−7, 10−6 and 10−5 M) caused dose-dependent reductions in PWV (-5 %, -14 % and -17 %, mean respective changes from baseline 9.87 m/s, p<0.05 for the 2 higher doses), indicating increased distensibility. It caused associated changes in mean RCIA pressure (2-%, -9% and -12% from baseline 121 mmHg, p<0.05 for the 2 higher doses) and heart rate (+6%, +10%, +19% from 68 bpm, p<0.05 for the highest dose). The experiment was therefore repeated, but ACH was infused distal to the arterial segment whose distensibility was being measured. ACH induced the same changes in blood pressure and heart rate but no changes in PWV (-2%, +4%, +12%, N.S.). Thus, PWV was decreased by the local action of ACh and not by any associated systemic effect. These data show that EDRF increases arterial distensibility.
ENDOTHELIAL ADHESION MOLECULE EXPRESSION AND LOW DENSITY LIPOPROTEINS

Objective. Modified low density lipoprotein (LDL) has been implicated in atherogenesis. This study compares monocyte adhesion to the endothelium in LDL preparations and subsequent foam cell formation by mechanisms not yet fully elucidated. This study investigated the effect of native, minimally modified (mm-LDL) and oxidatively modified LDL (o-LDL) on the leucocyte adhesion molecules VCAM-1, ICAM-1 (vascular cell and intercellular adhesion molecule, respectively) and E-selectin (E). Interactions between different cell types of the vessel wall were also investigated by incubation of LDL with human coronary artery smooth muscle cells (SMC). Methods. LDL was isolated from healthy volunteers by ultracentrifugation (NVT 65, Beckman) in the presence of 1 mM EDTA. Both native and modified LDL were used. Leucocytes were isolated by density gradient centrifugation and cultured on a cultures of SMC. Before sacrifice, the excised arteries were harvested and their selection of LDL was either copper oxidized, minimally modified by prolonged storage, or used in its native state. Determination of LDL preparations was assessed by electrophoresis, formation of conjugated dienes and malondialdehyde content. Primary cultures of human coronary artery and umbilical vein EC, and human coronary artery SMC were assessed for purity by morphological appearance and by von Willebrand factor and α-actin expression, respectively. No cytotoxicity was observed by chromium release or morphological changes with any form of LDL for the concentrations and time course described below. EC were transferred to 96 well plates and allowed to reach confluence. They were incubated for 4 hours in Medium 199 (plus 10% foetal calf serum alone, or with additions of LDL, 0.001 to 100 μg/ml, or the positive control, interleukin-1 100 μg/ml). In some experiments, test media underwent 18 hours pre-incubation with the SMC, before being applied to the EC. AM expression was quantified by an enzyme linked immunosorbent assay (monoclonal antibodies provided by Dr. A. D. Haskard, Royal Postgraduate Medical School).

Results. No induction of VCAM-1, ICAM-1 or E-selectin or expression was observed in either coronary artery or umbilical vein EC following stimulation with native, mm- or o-LDL. In addition, pre-incubation of native or modified LDL with SMC did not induce endothelial AM expression. Conclusions. The mechanism by which o-LDL and mm-LDL enhance monocyte adhesion to the endothelium does not involve the direct induction of VCAM-1, ICAM-1 or E-selectin. In addition, modified LDL does not induce expression of these endothelial AMs via an indirect action on vascular SMC.

EDRF PROMOTES METABOLIC CORONARY DILATION BY AUTOREGULATORY SHIFT OF RESISTANCE INTO ARTERIOLES SENSITIVE TO ADENOSINE
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Recent reports have shown that inhibition of endogenous nitric oxide (NO) synthesis attenuates coronary vasodilation by the myocardial metabolite, adenosine triphosphate (ATP). To evaluate this hypothesis, we measured coronary microvascular diameters in the beating canine heart using intravascular microscopy with stroboscopic ep-illumination during ADO (10 μg/kg i.e. infusion) before and after inhibition of NO synthesis by N0-nitro-L-arginine methyl ester (L-NAME; 30 μg/kg i.e.). Epicardial coronary blood flow (CBF) was measured by Doppler ultrasonad. Animals were β-blocked with propranolol (1 μg/kg i.e.). Before L-NAMe, ADO increased coronary blood flow (CBF) by 118±25% mean ± SEM; p<0.05, n=13) by dilating arterioles (30-100 μm) by 26±5% (diameter) and small arteries (100-300 μm) by 76±3% (both p<0.05). L-NAME constricted small arteries by 31±1% (p<0.05) while arterioles dilated by +112±3% (p<0.05). There was no change in CBF, suggesting that the arteriolar dilation was autoregulatory. After L-NAMe, the increase in CBF caused by acetylcholine was abolished, indicating loss of endothelium-dependent dilatation. Also after L-NAMe, ADO failed to dilate arterioles and small arteries (diameters 0.25-2 mm, NS v. control p<0.05 v. change without L-NAMe) and did not change CBF (+6±7%, NS, p<0.05 v. change without L-NAMe). The direct influence of L-NAMe (10-8 to 10-4 M) was also evaluated in isolated canine coronary arterioles (63±2 mm, NS) cannulated and pressurised before L-NAMe. L-NAMe did not change arteriolar tone or the dose-dependent dilatation by ADO (log M) E0=6.5, further supporting the importance of autoregulatory influences on arteriolar tone in vivo. Thus, inhibition of NO synthesis by L-NAMe constricts small arteries, and stimulates autoregulatory dilation of arterioles in the intact myocardium. These dilated arterioles fail to dilate further with ADO. These results imply that EDRF normally dilates small arteries, and maintains metabolic vasodilator reserve through an autoregulatory shift in the major site of resistance to arterioles which are sensitive to ADO.

INCREASING CORONARY VASCULAR RESISTANCE AND UP-REGULATION OF ENDOTHELIN RECEPTORS IN DERENATURED BOVINE CORONARY ARTERIES
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The effects of extrinsic cardiac denervation on endothelin-(ET) activity in isolated coronary arteries were assessed using a technique of cryoablation. Nine calves underwent cryodenervation 2-4 weeks before sacrifice. The excised hearts were compared with those of nine control animals using quantitative autoradiography to determine the density of the ET B1 and ET B2 binding sites, and with proximal and distal anterior descending coronary artery (LAD) were studied. Specific ET binding was significantly increased in proximal (21.3±3.4 μS.E.M. vs 34±4.5 μM/mm², p<0.05) and distal (39.3±6.2 vs. 85±7.6 μM/mm², p<0.001) LAD. A further 12 animals were randomized to undergo cryodenervation (D) or sham thoracotomy (C). Re-study 23±6 days later involved ET infusion into the left atrium at doses of 2-1000 pg/kg/min. At rest and after ET infusion, coronary sinus blood flow was significantly lower and coronary vascular resistance was significantly higher in denervated animals.

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