### ANNUAL MEETING AT WEMBLEY 18–21 MAY 1993: PROGRAMME

#### Tuesday 18 May

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.00</td>
<td>Officers' Meeting</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>10.00</td>
<td>Council Meeting</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>11.00</td>
<td>Registration</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>12.00</td>
<td>Snack lunch and coffee – Exhibition Hall</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>1.20</td>
<td>Welcome by the President Dr D A Chamberlain</td>
<td></td>
</tr>
<tr>
<td>1.30–3.00</td>
<td>Papers 1–6 Atheroma Removal Cardiacomyopathy</td>
<td>Grand Hall</td>
</tr>
<tr>
<td></td>
<td>Papers 7–12 Dilated</td>
<td>Avon I</td>
</tr>
<tr>
<td>3.00–5.00</td>
<td>Papers 13–18 Arrhythmias</td>
<td>Severn I</td>
</tr>
<tr>
<td></td>
<td>Papers 19–24 Myocardial Biology British Society of</td>
<td>Severn II</td>
</tr>
<tr>
<td></td>
<td>Echocardiography British Paediatric Cardiac Association</td>
<td>Avon II</td>
</tr>
<tr>
<td>6.30</td>
<td>Council Dinner</td>
<td>HQS Wellington</td>
</tr>
</tbody>
</table>

#### Wednesday 19 May

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.15</td>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>9.00–9.30</td>
<td>Coffee – Exhibition Hall</td>
<td>Grand Hall</td>
</tr>
<tr>
<td>10.30–11.15</td>
<td>Coffee and Posters – Exhibition Hall</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>11.15–12.45</td>
<td>Papers 55–59 Stents</td>
<td>Avon II</td>
</tr>
<tr>
<td></td>
<td>Pathophysiology, Basic/General Interventions</td>
<td>Avon III</td>
</tr>
<tr>
<td>12.45–2.15</td>
<td>Lunch and Postcards</td>
<td>Severn I &amp; II</td>
</tr>
<tr>
<td>2.15–2.15</td>
<td>Working Party on Grown Up</td>
<td>Canterbury Suite</td>
</tr>
<tr>
<td>2.15–2.15</td>
<td>Press Conference</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>1.00–2.00</td>
<td>Moderated Posters (145–158)</td>
<td>Exhibition Hall</td>
</tr>
<tr>
<td>2.15–3.45</td>
<td>British Nuclear Cardiology Group Papers 78–83 Arrhythmias</td>
<td>Avon I</td>
</tr>
<tr>
<td></td>
<td>VT/VF</td>
<td>Grand Hall</td>
</tr>
<tr>
<td>3.45–4.30</td>
<td>Tea and Posters – Exhibition Hall</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>4.30–5.30</td>
<td>Keith Jefferson Lecture – Myocardial Perfusion</td>
<td>Grand Hall</td>
</tr>
<tr>
<td>5.30–6.30</td>
<td>British Cardiac Society Annual General Meeting</td>
<td>Grand Hall</td>
</tr>
</tbody>
</table>

#### Thursday 20 May

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.15</td>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>8.45–10.30</td>
<td>Young Research Workers Prize Final Final</td>
<td>Grand Hall</td>
</tr>
<tr>
<td></td>
<td>Finalists: P J Keeling, S H Francis, A J B Brady, M R Bennett</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Judges: Prof M J Davies (chairman), Prof W J Remme, Dr P Weissberg and Prof S Cobbe</td>
<td></td>
</tr>
<tr>
<td>9.30–10.30</td>
<td>NURSES’ DAY (Coffee – 8.30 in Exhibition Hall)</td>
<td>Avon I &amp; II</td>
</tr>
<tr>
<td>10.30–11.15</td>
<td>Coffee &amp; Posters – Exhibition Hall</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>11.15–12.15</td>
<td>Papers 108–111 Arrhythmias</td>
<td>Avon III</td>
</tr>
<tr>
<td></td>
<td>Papers 112–115 Hyperrophic Cardiacomyopathy</td>
<td></td>
</tr>
<tr>
<td>11.15–12.30</td>
<td>Papers 116–120 Nuclear Cardiology; Magnetic Resonance Imaging</td>
<td>Severn I &amp; II</td>
</tr>
<tr>
<td>12.15–2.00</td>
<td>Lunch and Posters (239–317) – Exhibition Hall</td>
<td>Whitehall Suite</td>
</tr>
<tr>
<td>2.00–4.00</td>
<td>Practical Cardiology – Dr A McLeod, Prof R Vincent, Prof R W F Campbell, Prof J Petrie</td>
<td>Grand Hall</td>
</tr>
<tr>
<td>2.00–3.30</td>
<td>Paper Nos 121–126 Coronary Flow Syndrome X</td>
<td>Avon III</td>
</tr>
<tr>
<td>4.00–6.00</td>
<td>Ethical &amp; Legal Committee</td>
<td>Canterbury Suite</td>
</tr>
<tr>
<td>3.30–4.30</td>
<td>Tea and Posters – Exhibition Hall</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>4.30–6.30</td>
<td>RITA I and II Nurses’ Meeting – Clinical value of assessment of diastolic ventricular function</td>
<td>Whitehall Suite</td>
</tr>
<tr>
<td>4.30–5.30</td>
<td>Strickland Goodall Lecture – Emergency.valves</td>
<td>Grand Hall</td>
</tr>
<tr>
<td>7.30 for 8.00</td>
<td>Annual Dinner – Natural History Museum</td>
<td></td>
</tr>
</tbody>
</table>

#### Friday 21 May

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.15</td>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>9.00–10.30</td>
<td>Plenary Session – Ventricular architecture and heart failure</td>
<td>Grand Hall</td>
</tr>
<tr>
<td></td>
<td>Professor M Noble (Chelsea and Westminster Hospital), Dr M St John Sutton (Royal Brompton),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Professor S Ball (St James Hospital, Leeds) and Dr K Swedburg (Gothenburg, Sweden)</td>
<td></td>
</tr>
<tr>
<td>9.30–10.00</td>
<td>TECHNICIANS’ DAY</td>
<td>Avon I &amp; II</td>
</tr>
<tr>
<td>10.30–11.15</td>
<td>Coffee – Exhibition Hall – Sundry Posters – Read codes, Data on access and availability of CABG and PTCA, Technicians</td>
<td>Avon I &amp; II</td>
</tr>
<tr>
<td>11.15–12.45</td>
<td>British Cardiovascular Intervention Society</td>
<td>Grand Hall</td>
</tr>
<tr>
<td></td>
<td>Papers 133–138 Coronary Artery Surgery</td>
<td>Avon I &amp; II</td>
</tr>
<tr>
<td>11.15–12.45</td>
<td>British Cardiovascular Intervention Society</td>
<td>Avon I &amp; II</td>
</tr>
<tr>
<td></td>
<td>Papers 139–144 Valve Disease</td>
<td>Severn I &amp; II</td>
</tr>
<tr>
<td>12.45–2.00</td>
<td>Technicians’ Meeting</td>
<td>Canterbury Suite</td>
</tr>
<tr>
<td>12.45–2.00</td>
<td>Lunch – Exhibition Hall – sundry posters (as during coffee break)</td>
<td>Chaucer Suite</td>
</tr>
<tr>
<td>15TH ANNIVERSARY CELEBRATION OF MAJOR EXHIBITION</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complimentary wine and snacks available to all delegates

---

*Br Heart J. first published as 10.1136/hrt.69.5.Suppl.P3 on 1 May 1993. Downloaded from http://heart.bmj.com on September 16, 2023 by guest. Protected by copyright.*
**TUESDAY 18 MAY 1993**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>from 11.00</td>
<td>Registration. Coffee and snack lunch facilities available in the Exhibition Hall from 12.00</td>
</tr>
<tr>
<td>12.00</td>
<td>Exhibition open</td>
</tr>
<tr>
<td>1.20</td>
<td>Welcome by the President: Dr D A Chamberlain</td>
</tr>
</tbody>
</table>
| 1.30–3.00 | **Grand Hall**  
Atheroma Removal  
(chairman: Dr M F Shiu)  
Papers 1–6 |
| 1.30–5.00 | **Avon I**  
Dilated Cardiomyopathy  
(chairman: Dr Celia Oakley)  
Papers 7–12 |
| 1.30–5.00 | **Avon II**  
British Society of Echocardiography  
Quantification in Echo/Doppler  
(chairmen: M Monaghan and L M Shapiro)  
1.30–1.50 Aortic regurgitation (P Wilde)  
1.50–2.10 Right ventricular function  
(M Connelly)  
2.10–2.30 Systolic left ventricular function  
(K Gray)  
2.30–3.00 Diastolic left ventricular function  
(M Monaghan)  
3.00–3.30 Tea  
3.30–4.00 Mitral valve repair: the echo/surgical interface (F Wells and A Kenny)  
4.00–5.00 Annual General Meeting |
| 1.30–5.00 | **Avon III**  
British Paediatric Cardiac Association  
Therapeutic Controversies. Closure of the arterial duct  
(chairman: M Godman)  
2.00–2.20 Transcatheter technique is the best treatment (M Tynan)  
2.30–2.40 Thoracoscopic surgery is treatment of choice (F Laborde)  
2.40–3.10 Discussion  
3.10–3.30 Tea |
| 3.00–3.30 Tea – Exhibition Hall |
| 3.30–5.30 | **Grand Hall**  
Unstable Angina  
(chairman: Dr R H Swanton)  
Papers 25–30 |
| 3.30–5.30 | **Severn I**  
Arrhythmias  
(chairman: Dr D Wyn Davies)  
Papers 13–18 |
| 3.30–5.30 | **Severn II**  
Myocardial Biology  
(chairman: Prof P Poole-Wilson)  
Papers 19–24 |
| 3.30–5.00 | Round-table discussion |
| 3.30–5.00 | **Severn III**  
Myocardial and Vascular Biology  
(chairman: Dr M Noble)  
Papers 31–36 |
| 3.30–5.00 | **Severn IV**  
Heart Failure CVS Physiology  
(chairman: Dr H J Dargie)  
Papers 37–42 |
| Continuing Debates in Cardiac Surgery  
Dealing with the left AV valve in atrioventricular septal defect  
(chairman: S Hunter)  
3.30–3.45 Is the valve really a mitral valve?  
(R H Anderson)  
3.45–4.00 Echocardiographic assessment  
(M Rigby)  
4.00–4.20 Traditional surgical approaches  
(J Stark)  
4.20–4.40 Individualised treatment based on measurement (Ej Ebels)  
4.40–5.00 Round-table discussion  
5.00–6.00 AGM–Election of Officers and installation of new President  
1.30–3.00 | **Severn I**  
Arrhythmias  
(chairman: Dr D Wyn Davies)  
Papers 13–18  
3.30–5.30 | **Severn II**  
Myocardial Biology  
(chairman: Prof P Poole-Wilson)  
Papers 19–24  
3.00–3.30 Tea – Exhibition Hall  
3.30–5.30 | **Grand Hall**  
Unstable Angina  
(chairman: Dr R H Swanton)  
Papers 25–30  
3.30–5.00 | Round-table discussion  
3.30–5.00 | **Severn III**  
Myocardial and Vascular Biology  
(chairman: Dr M Noble)  
Papers 31–36  
3.30–5.00 | **Severn IV**  
Heart Failure CVS Physiology  
(chairman: Dr H J Dargie)  
Papers 37–42  
5.00–6.00 AGM–Election of Officers and installation of new President |
The success of percutaneous transluminal coronary balloon angioplasty (PTCA) is limited by lesion morphology, and position, plaque instability and restenosis. Lesion debulking with mechanical devices may improve primary success rates with fewer acute complications. On an intention-to-treat basis we elected to perform directional coronary atherectomy (DCA) in 26 pts using the Simpson AtheroCath (Devices for Vascular Intervention), and percutaneous transluminal coronary rotablation (PTCR) in 23 pts using the Rotablator (Heart Technology). Three pts were not treated as planned because of progression of disease whilst on the waiting list; the procedure was not possible in a further 7 pts (failure to engage the guide catheter - 1, failure to cross lesion with the guide wire - 6). Mechanical atherectomy was therefore attempted in 39 pts (22 DCA, 17 PTCRA), 21 (54%) of whom had had recent unstable angina or myocardial infarction (MI). All pts except one had AHA/ACC types B or C lesions. DCA was used predominantly for proximal or mid-vessel eccentric lesions. PTCA was used for long, irregular, spiralling, calcified, tapered or bifurcation lesions. After successful guidewire positioning, procedural success was 92% overall (36/39), 91% for DCA (20/22) and 94% for PTCRA (16/17). Adjunctive PTCA was used in 18% of DCA and 71% of PTCRA periprocedural occlusion occurred in 2 pts - 1 DCA (treated with PTCRA) and 1 PTCRA pts at 24 hours (treated medially) and 1 on day 4 (treated with thrombolysis). Small local dissections were seen in 1 DCA and 2 PTCRA cases (no adverse sequelae), but left mainstem dissection occurred in 1 DCA pt (treated with CABG). No deaths occurred; 3 pts (7.7%) suffered a Q-wave MI and minor elevation of creatine kinase occurred in 2 pts (5.1%). Drawbacks of the DCA device include its bulk and rigidity, and the major problems with PTCRA are poor torque transmission of the guide wire and the need for adjunctive PTCA. In spite of these problems, appropriate selection of DCA and PTCRA for complex lesions results in a high procedural success rate with an acceptably low complication rate. These complimentary devices enhance the primary success rate of complex procedures, increasing the scope for intervention, and may lead to a reduction in early and late complications.

**MECHANICAL CORONARY ATERECTOMY IN COMPLEX AND RECENTLY UNSTABLE LESIONS**

MA de Belder, TA Millane, MA Anderson, CW Punphrey, DE Ward.
Regional Cardiothoracic Unit, St George's Hospital, London.

### EARLY EXPERIENCE OF DIRECTIONAL CORONARY ATERECTOMY IN A UK CENTRE

C M Bellamy, E D Grech, R K Aggarwal, M T Ashworth, M W Myskow, D R Ramsdale
The Cardiothoracic Centre, Liverpool

We performed directional coronary atherectomy (DCA) using the Simpson device on 25 occasions. Patients were selected for DCA if they had a bulky or eccentric symptomatic stenosis in a proximal or mid-segment of a non-tortuous coronary artery. 29 lesions were treated, 23 de novo, 6 for restenosis. 26 lesions were in the left anterior descending, 2 in the right, and one in the circumflex coronary artery. The lesion was pre-dilated with a 2.0 or 2.5 mm angioplasty balloon in 16 cases. A 6F atherectomy device was used in all but 3 cases. In 13 cases the atherectomy site was dilated following DCA by percutaneous transluminal coronary angioplasty (PTCA) to optimise angiographic appearance. In 3 patients further distal lesions were treated by PTCA. The mean percentage diameter stenosis was reduced from 87.9% to 3.5%. 23 patients became asymptomatic immediately following DCA. In one patient occlusive dissection of a circumflex artery required emergency coronary artery bypass surgery. In another patient closure of a right coronary artery seven hours after an initially successful DCA procedure was successfully treated by thrombolysis and PTCA. The mean number of specimens removed per case was 5.8. Intima was retrieved in 100%, internal elastic lamina in 48%, media in 48% and adventitia in 12%. Microscopic calcification was found in 60%, neointimal hyperplasia in 44% and thrombus in 44%. Fibrous plaque was present in 100% and showed ulceration in 28%. Our initial series shows that directional coronary atherectomy is an effective and safe procedure for the treatment of obstructive coronary artery disease in selected patients. The technique is particularly effective for morphologically complex lesions that are unfavourable for PTCA. The procedure is unlike PTCA and requires additional training if complications are to be kept low and success high. The requirement, in most cases, for pre- and post-dilation using PTCA makes DCA a more expensive treatment than PTCA alone.

### INITIAL EXPERIENCE OF PROCEDURAL OUTCOME OF DIRECTIONAL CORONARY ATERECTOMY FOR THE TREATMENT OF COMPLEX CORONARY ARTERY LESIONS

Regional Medical Cardiology Centre, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BB.

Directional Coronary Atherectomy (DCA) is a new percutaneous transluminal technique particularly suitable for eccentric bulky lesions in large coronary arteries. We have performed Directional Coronary Atherectomy (DCA) via the femoral artery in 32 patients (26 male). Mean age 58 (± 10 SD). The site of the lesions were, Left Anterior Descending (LAD) 21, Right Coronary Artery (RCA) 10, Circumflex (Cx) 1. Lesion characteristics were type B1 24, B2 6 and 2 type C. Device was 5F in seven, 6F in twenty and 7F in five. The mean volume of contrast was 278 ± 120 mls. In six cases pre dilatation was required to facilitate advancement of the device. A mean of 5.1 ± 2 cuts (range 2-10) and a mean of 2.6 (2-6) pieces of atheroma was obtained. The procedure was successful with residual stenosis less than 50% vessel diameter in twenty-seven patients (84%) including one where DCA was performed as an emergency rescue procedure after failed balloon angioplasty. There were four failures (2 elective DCA and 2 attempted rescue procedures) requiring emergency surgery. In one patient DCA could not be performed because of guide catheter failure but balloon angioplasty was successful. The mean pre procedure diameter stenosis was 79% ± 10. The mean residual stenosis post procedure was 12 ± 5%. Light microscopy of retrieved tissue showed atheromatous plaque in 26 patients, media in 5 patients including 2 with rescue angioplasty. Two patients developed transient side branch occlusion, and in 2 spasm distally and at the site of lesion occurred. There were no deaths and no femoral artery complications.

In conclusion, Directional Coronary Atherectomy (DCA) appears to have a high success rate in complex eccentric coronary artery lesions.

### CORONARY SMOOTH MUSCLE CELLS IN CULTURE AFTER DIRECTIONAL ATERECTOMY. DO THEY REFLECT OR PREDICT RESTENOSIS?

DC MacLeod, VA Uman, M de Jong, J Escan, PJ de Feyter, PW Serruya. Thoraxcenter, Rotterdam, The Netherlands.

The behaviour of smooth muscle cells (SMC) cultured from directional coronary atherectomy (DCA) may differ for primary atherosclerotic (P) and restenotic (R) lesions. In 67 patients who had DCA (67 lesions: 48 P, 19 R), we related the growth of SMC in culture to (a) source: P or R and also to (b) restenosis at 6 months post-DCA.

**Methods.** Tissue explants were placed in culture. SMC outgrowth in primary culture and successive secondary culture (sustained passage of SMC) were documented. For SMC in secondary culture, growth curves were constructed and population doubling times derived. Coronary angiograms at DCA and at control post-DCA (6 months: 67 patients) were quantitatively analysed off-line.

**Results.** (a) Lesion type did not influence the outgrowth (n=28) or successful sustained (n=77) passage of SMC (‡) test but R SMC showed accelerated growth in secondary culture with a shorter derived doubling time (hours, means and 95% CI). These data are in Table 1.

<table>
<thead>
<tr>
<th>Primary</th>
<th>Outgrowth Sustained</th>
<th>Doubling time</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>18/48</td>
<td>8/28</td>
</tr>
<tr>
<td>P</td>
<td>71 (62-83)</td>
<td></td>
</tr>
<tr>
<td>Restenotic</td>
<td>10/19</td>
<td>4/19</td>
</tr>
<tr>
<td>R</td>
<td>52(48-58)</td>
<td></td>
</tr>
</tbody>
</table>

(b) Culture results in relation to categorical restenosis 6 months post-DCA (‡) test, continuous diameter (%) stenosis and cross sectional minimal luminal diameter (‡AML, mm) are in Table 2. The groups did not differ significantly (‡) test, Kruskal-Wallis test: medians and 95% CI. And of SMC.

<table>
<thead>
<tr>
<th>Primary</th>
<th>No growth Sustained</th>
<th>Outgrowth</th>
<th>Stenosis</th>
<th>% stenosis</th>
<th>&gt;45 (‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>12/39</td>
<td>8/28</td>
<td>72%</td>
<td>3(27-65)</td>
<td>45 (5-44)</td>
</tr>
<tr>
<td>P</td>
<td>34(18-61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion.** SMC from restenotic lesions demonstrated accelerated growth in secondary culture. Otherwise, the success of primary and secondary SMC culture after DCA did not reflect or predict restenosis.
SINGLE CENTRE, SINGLE OPERATOR EXPERIENCE WITH EXCIMER LASER CORONARY ANGIOPLASTY
JT Stewart, LDR Smith, DS Thomson, BS Jenkins, DJ Colart, MM Webb-Peploe
Department of Cardiology, St. Thomas’ Hospital, London.

Procedural success in complex coronary angioplasty (PTCA) may be enhanced by technological improvements in the hardware. We have attempted excimer laser coronary angioplasty (ELCA) of 168 coronary lesions in 121 patients, as ELCA alone (101 lesions) or ELCA plus ballooning. 65 lesions: 2 lesions were not crossed with a guide wire. Of the 121 patients, 83% were male; mean age was 55 (range 26-78) years, and mean left ventricular ejection fraction was 57 (27-84)%. Most (85%) were in Canadian Cardiovascular Society classes 2 to 4, and 52% had multivessel coronary disease. Indications for ELCA included: restenosis after PTCA (26%), diffuse disease (32%), ostial disease (7%), side branch involvement (24%), and total occlusion (8%); 70% of lesions treated were > 5 mm in length. Procedural success was obtained in 110 (91%). There were 6 deaths (5%), 4 due to a complication of ELCA, and 1 patient (0.8%) underwent emergency coronary surgery. Other complications of ELCA were: coronary perforation 2 (1.2%), occlusive dissection 4 (2.4%), thrombus formation 4 (2.4%), and distal emboli 3 (1.8%). Follow-up angiography at 6 months in 59 patients after stand alone ELCA, showed a good long term result in 33 lesions and restenosis (>50% residual stenosis) in 26 (restenosis rate 44%), and in 34 patients after ELCA plus PTCA, showed a good long term result in 23 lesions and restenosis in 11 (restenosis rate 32%).

ELCA improves the procedural success rate in the transluminal treatment of complex coronary lesions, but the incidence of procedural complications and restenosis remains high. Our results suggest that restenosis is related to post-procedural residual stenosis and that adjunctive PTCA after ELCA improves long term outcome by reducing residual stenosis.

ABNORMAL CREATINE KINASE MB SUBFORM RATIOS AS MARKERS OF MYOCARDIAL DAMAGE IN DILATED CARDIOMYOPATHY: THEIR RELATION WITH ORGAN-SPECIFIC CARDIAC ANTIBODIES
ALP Caforio, M Hossein-Nia, PJ Keeling, PK Johnson, P Brown, GF Bottazzo, D W Holt, WI McKenna, London and St George’s Hospital Medical School, London.

Analysis of creatine kinase MB (CK-MB) tissue/pulmonary subform ratio (MB2/MB1) offers a sensitive measure of myocardial damage in dilated cardiomyopathy (DCM), which can be abnormal when the overall CK-MB plasma levels are normal. Disease and organ-specific (o-s) cardiac antibodies (Abs) are found in 20-30% of patients with dilated cardiomyopathy (DCM); this suggests that in these patients there is chronic myocardial damage, due to underlying autoimmune disease. To provide evidence for ongoing myocardial damage in DCM and to evaluate whether this is associated with the presence of o-s cardiac Abs, we determined antibody status and total CK, CK isoforms and MB2/MB1 ratios in 110 (43 male, 11 female, aged 44±15 yrs, 28 in NYHA class I/II and 18 in class III/IV). o-s cardiac Abs were detected by immunofluorescence on normal human heart; skeletal muscle was used to detect cross-reacting Abs. Plasma levels for total CK and CK isoforms (MM=heart and skeletal; MB=heart) were measured by immunoenzymatic methods, using CK-NAC substrate reagent. MB2/MB1 was determined by high resolution agarose gel electrophoresis and by densitometer scanning. O-s cardiac Abs were found in 10 (22%) pts and cross-reactive Abs in 13 (28%); the remaining 23 patients were antibody negative. Mean plasma levels of total CK (UI) and CK-MM (UI) and CK-MB (ng/ml) were within the normal range in DCM patients and with and without Abs, but tended to be higher in patients with o-s cardiac Abs than in those who were antibody negative (175±10 vs 128±7, 1.5±2 vs 1±1, 1.5±4.1 vs 0.9±1.4, respectively). A sizeable proportion (26%) of all DCM patients had abnormal MB2/MB1 ratios (>1); this tended to be more common among patients with o-s cardiac Abs than in those who were antibody negative (4/10, 40% vs 5/23, 22%, p=NS).

The finding of abnormal MB2/MB1 ratios is a marker for subtle on-going myocardial damage in DCM; its association with cardiac Abs would be consistent with autoimmune pathogenesis and should be further assessed. It remains to be established whether tissue damage is mediated by the Abs or by T cells.

NITRIC OXIDE SYNTHASE ACTIVITIES IN HUMAN MYOCARDIUM
de Belder1, L A, Radomski, M, Why1, H, Richardson1, P, Bucknall1, C, Salas, E, Marttila2, J, Mondaca, J
Departments of Cardiology1 and Medicine2, King’s College Hospital, London, Welcombe Res. Labs, Beckenham, Kent, UK.

Nitric oxide (NO) is synthesized from L-arginine by two enzymes, the constitutive and inducible NO synthases (CNOS and INOS, respectively). CNOS is expressed in target tissues only after stimulation with endotoxin and some cytokines. We have investigated the hypothesis that induction of this enzyme may explain the specific cardiac dysfunction seen in dilated cardiomyopathy (DCM), a condition in which cytokines have been implicated. Right ventricular endomyocardial biopsies were obtained from 17 patients with DCM. These were freeze-crushed and homogenized, then centrifuged and the resultant soluble fraction used for measurement of NO synthase activity. The constitutive and inducible NO synthase activities were measured either by using enzyme immunoassay for cyclic GMP (Amersham, n=10) or by conversion of L-14C-arginine to L-14C-citrulline (n=7). Heart tissue from patients with DCM showed significant activity of INOS (13.7±3 pmol citrulline/mg/min and 26.0±10.3 fmol cyclic GMP/mg/min). In contrast, the CNOS activity was 10-11 fold lower when measured by citrulline formation (1.2±0.3 pmol citrulline/mg/min) or not detectable when cyclic GMP was measured. A further study examined atrial tissue taken from patients undergoing coronary bypass surgery who had normal sized hearts. These are not a matched group, but the results show a clear predominance of CNOS - the activity of CNOS was 15.4±2 pmol citrulline/mg/min and 30.4±2.4 fmol cyclic GMP/mg/min, and that of INOS was very low (2.5±0.6 pmol citrulline/mg/min) or not detectable when measured. These data suggest a physiological as well as a pathological role of NO in the myocardium.
PERIPHERAL RESISTENCE TO ANP ACTIVITY IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY
S Berri, G Iervasi, A Clerico, A Pilo, C Palmieri, S Turchi, R Bonini, S Pugliese, G Trianni, A Bigianni, L Donato
C R Clinical Physiology Institute, University of Pisa, Italy

ANP seems to play a key role in sodium-water balance particularly in heart failure. Although plasma ANP levels are often elevated, patients with heart failure exhibit evidence of volume overload, suggesting a peripheral resistance to ANP biological action. In 7 normal subjects and in 5 pts with idiopathic dilated cardiomyopathy (IDCM) with different degrees of ventricular dysfunction, we studied the in vivo ANP kinetics (production rate, metabolic clearance and tissue distribution from plasma disappearance curve of 1 ANP) after iv bolus injection, in order to assess if a peripheral resistance to ANP activity could be documented. A strong relationship between Na excretion and ANP clearance was documented by preliminary studies. We suggest, therefore, that ANP may play a role in the pathophysiology of heart failure in such pts.

CLINICAL AND PROGNOSTIC SIGNIFICANCE OF CREATINE KINASE (CK) MB ISOFORMS IN IDIOPATHIC DILATED CARDIOMYOPATHY
M Hossein-Nia, P J Keeling, P Brown, S Bent, D W Holt, W J McKenna
Department of Cardiological Sciences, St George's Hospital Medical School, London, SW17 ORG

The identification of patients with idiopathic dilated cardiomyopathy (DCM) who will deteriorate due to progressive heart failure remains difficult. Analysis of creatine kinase (CK) MB isoforms has been found to be a sensitive indicator of myocardial damage. To determine if alterations in CK-MB isoforms are associated with clinical or prognostic features in patients with DCM, we measured total CK and CK-MB activities, and CK-MB isoform ratios in 66 consecutive patients (47 male and 19 female median age 45 years, range 18-74) with clinical DCM (WHO criteria). Patients had been symptomatic for 31 months (range 0.5-158) with 27 in NYHA functional Class I, 13 in Class II, 16 in Class III, and 10 in Class IV. Of 38 patients who underwent endomyocardial biopsy, 2 had myocarditis and 22 established fibrosis. No association was found between total CK and CK-MB activities and any clinical feature, marker of left ventricular function or biopsy feature. However, a significantly higher MB2/MB1 ratio was present in patients with increasing left ventricular dilatation (p<0.02) and in a greater proportion of patients with endomyocardial fibrosis (p=0.02). There was, however, no association between MB2/MB1 ratio and clinical status or any parameters of ventricular function. During follow-up, 16 patients had progressive heart failure (group I), 2 patients died from sudden death (group II) and the remaining 48 patients were clinically stable (group III). MB2/MB1 ratio was significantly higher in group I compared to group III (1.3±0.6 vs 0.9±0.7, p<0.05). Conclusion: In DCM patients, analysis of CK-MB isoforms is an indicator of myocardial damage and may aid with identification of those patients at risk.

THE NATURAL HISTORY OF DILATED CARDIOMYOPATHY IN BRITISH CHILDREN
M Burch, S Siddiqi, J Deanfield, C Bull. The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH

The natural history of dilated cardiomyopathy (DCM) in British children is unknown, and North American studies have conflicting conclusions; particularly with regard to the effect of age on the frequency of late sudden death. Therefore we retrospectively analysed the outcome of all 61 children with DCM presenting with echocardiographic shortening fraction <20% and end diastolic dimension >95th centile to our unit from 1979-1992; median age of diagnosis was 12 months (range 1 day to 14 years); and median follow up 19 months (range 1 day to 15 years). Actuarial survival from presentation was 79% at 1 year and 61% at 5 years. However, 3 month survival was 95% in those <2 years but only 73% in those >2 years. Age >2 and presence of mural thrombus were predictive of death within 1 year, but only young age was a predictor with multivariate analysis (p=0.003). None of the 6 with documented left ventricular end diastolic pressures (LVEDP) >20mmHg survived without transplantation. Of the 21 deaths 7 were sudden and occurred at a median 8 months from presentation (range 5 months-8 years), no late deaths occurred in the 11 in whom echocardiographic dimensions returned to normal 91% of whom were <2 years at presentation. Thus, we recommend early (<3 months) recourse to transplantation assessment in children with DCM with persistent cardiac failure if >2 years of age; particularly if mural thrombus or LVEDP >20mmHg are present. Survivors with persistent left ventricular dysfunction remain at risk of sudden death.

INCREASED FREQUENCY OF ORGAN-SPECIFIC CARDIAC ANTIBODIES IN HEALTHY RELATIVES OF PATIENTS WITH DILATED CARDIOMYOPATHY: EVIDENCE FOR AUTOIMMUNE PATHOGENESIS

Familial occurrence is a feature of autoimmune disease; organ and disease-specific autoantibodies are found in patients and in their relatives at a higher frequency compared to normals. Such antibodies can be detected years before clinical symptoms and may identify asymptomatic relatives at risk. Organ-specific cardiac antibodies (o-s cardiac Abs) are markers of autoimmunity in patients with dilated cardiomyopathy (DCM). To assess the frequency of these antibodies among DCM relatives, and to identify individuals at risk, we studied 255 healthy DCM relatives. Of these 118 were from 28 families with more than 1 affected member (multiplex) and 137 from 26 families with only 1 affected member (simplex). The 28 multiplex pedigrees were identified at 4 different Institutions, including our own. The 26 simplex pedigrees were from a consecutive patient series seen at our Institution. All 255 relatives (129 male, 126 female, aged 34 ± 17 yrs) were screened with electrocardiography and 2 dimensional echocardiography. O-s cardiac Abs were detected by immunofluoresence on human heart; skeletal muscle was used to identify cross-reacting antibodies. All sera were tested blindly from clinical data. The frequency of o-s cardiac Abs is low among normals (7/200, 3.5%) and in heart failure not due to DCM (2/249, 1%). O-s cardiac Abs were more common in DCM relatives than in normals (35/255 vs 7/200, p=0.0001) and than in heart failure controls (35/255 vs 1/249, p=0.0001). The frequency of o-s cardiac Abs tended to be higher among relatives of multiplex compared with those from simplex pedigrees (21/118, 18% vs 14/137, 10%, p=NS). These findings are in keeping with those reported in other autoimmune diseases, such as insulin-dependent diabetes mellitus, and provide strong support to the involvement of autoimmunity in DCM. Antibody positive first degree relatives of DCM patients may be at risk of developing disease; follow-up studies are in progress.
They were divided into three groups according to symptoms. Group 1 presenting with syncope, Group 2 presenting with palpitations, and Group 3 presenting with non-invasive investigation (ECG, 48 Hour Tape, Echo and Exercise Testing). All had had Hospital admissions and outpatient attendances. EPS was performed using 3 leads via the R femoral vein. Group 1 (23 pts) consisted of 8 patients with no documented arrhythmias, 5 with suspected bradycardia, and 10 had suspected ventricular arrhythmias. In those with no arrhythmias 4 had proven ventricular tachycardia (VT), 3 now controlled on drugs, 1 receiving an AIocD, 5 with suspected bradycardia, and 2 had proven VTs, now suppressed medically. In the 10 with suspected VT/FF this was proven in all 2 going on to AIoCs. EPS was used to guide drug therapy in all. Group 2 patients consisted of 19 with SVT and 12 with VT, 9 had no documented arrhythmias. In those with SVT, identification of accessory pathway anatomy was made in all. In 13 pts drug therapy (guided by EPS) was successful. In 4, EPS proved drug ineffective and radio frequency ablation was performed successfully. In 12 pts with VT and palpitation, 7 had drugs changed following EPS, and VT was suppressed. In 5 EPS showed VT was unsuppressed and they were referred for surgery or AIoCs. In 9 with no proven arrhythmias EPS identified significant arrhythmias in 4.

There were no complications. This study confirms that diagnostic EPS can safely and effectively be performed in a DGH. These are especially effective in investigating patients with syncope, and in providing a proper strategy for drug management. This reduced OP attendances, stopped Hospital admissions and should be cost effective.

Changes in Ventricular Excitability During Pharmacological Unloading of the Failing Heart: contrasting effects of sodium nitroprusside and captopril.


Patients with impaired left ventricular (LV) function are susceptible to ventricular arrhythmias and sudden death. During long-term therapy of cardiac failure, ACE inhibitors have been shown to reduce the incidence of sudden death compared to controls; however, the effects of these agents on the electrophysiology of the failing heart are unknown. We compared the changes in cardiac excitability produced by sodium nitroprusside (SNP) and captopril (CAPT) in 8 patients with impaired LV function (ejection fraction < 40%) in a randomized crossover study with a 48-72 hrs washout period. A Franz combination catheter was used to record a monophasic action potential (MAP) signal from the interventricular septum during constant atrial pacing; ventricular refractoriness (VERP) and latency were determined by a single extrastimulus technique. SNP or CAPT were administered intravenously with dose-adjustment to achieve a stable reduction in peak systolic pressures of approximately 15%. Steady-state electrophysiological measurements were made before and after pharmacological unloading. Results are given as mean (SEM) change from baseline with corresponding p-value.

<table>
<thead>
<tr>
<th></th>
<th>CAPT p value</th>
<th>SNP p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Systolic Pressure (mmHg)</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>MAP Duration (ms)</td>
<td>5 (4)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>VERP (ms)</td>
<td>6 (2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>-2 (3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

In summary, despite producing equivalent reductions in loading, captopril prolonged whereas nitroprusside shortened ventricular refractoriness (VERP). Neither drug altered latency. This difference may reflect a complex interplay of mechatronic, neuro-hormonal and direct electrophysiologic actions.

Fourty six members of a family with the Romano Ward Syndrome were studied. Three families had died suddenly before the age of 20, following emotional or physical stress.

Nine subjects had resting QTc prolongation (>440ms). Two patients had normal resting QTc intervals but had had documented syncope. Two grandparents and 4 parents of affected individuals had normal QTc intervals at rest. Three of these subjects had QTc shortening on exercise. The remaining 3 lengthened their QTc intervals with exercise. Two prolonged their QTc interval to such an extent that the T wave fused with the preceding P wave even at modestly increased heart rates, a feature shared by one of their cousins. Eight of the 16 sufferers and carriers of the Romano Ward syndrome (50%) had marked QTc dispersion (defined as Max QTc-Min QTc, measured from a 12 lead electrocardiogram) of more than 0.10s compared with 2 of the 30 normal subjects (6.6%).

Families carrying the Romano Ward gene can show a wide variety of electrophysiologic abnormalities both at rest and on exercise. Parents with normal resting QTc intervals can have children with the Romano Ward Syndrome. Appropriately assessed members of a Romano family cannot be based on resting QTc interval alone and should include exercise testing signal averaged electrocardiographic abnormalities at both rest and on exercise. Parental QTc intervals may predict cardiac arrhythmia in the offspring.

QTC Dispersion, late potentials and exercise electrocardiography in a large family with the Romano Ward Syndrome.

J EHD, DH Bennett. The Regional Cardiothoracic Centre, Wythenshawe, Manchester.

Digoxin is commonly prescribed for paroxysmal atrial fibrillation (PAF), despite suggestions that it may increase the frequency and duration of episodes of atrial fibrillation (AF). The CRAFT-I trial was undertaken to determine the effects of digoxin in PAF.

Eighty patients with symptomatic PAF, recruited from 10 UK centres, were issued with patient-activated electrocardiograph recorders and entered a drug-free screening period of one month. Those who transmitted an episode of AF were randomized into a double-blind crossover trial of digoxin. Dosing was initially based on estimated creatinine clearance and subsequently adjusted according to blood levels without loss of blind. Each monitoring period commenced when a satisfactory blood level was achieved after a loading/washout phase, and continued for two months, or until two episodes of PAF were transmitted. The mean digoxin dose was 375 μg/day, and the mean blood level was 1.02 μg/l.

The treatment effect was estimated to be a 1.71-fold increase in the interval between attacks (95% CI, 1.07-2.81) and a lowering of heart rate during attacks by 15.4 (95% CI, 5.0-26.5) beats/min.

We conclude that digoxin does reduce the frequency of symptomatic attacks of PAF, though by a small factor. It is unclear whether this is due to a true antiarrhythmic action, or a lessening of symptoms because of a reduced heart rate.
Very early left ventricular mechanical activity in dilated cardiomyopathy - evidence for "concealed activation"

HB Xiao, C Roy, SJ Brecker, D Gibson. Royal Brompton National Heart and Lung Hospital, London.

To study the relation between abnormal left ventricular (LV) activation and mechanical events in dilated cardiomyopathy (DCM), we studied 48 patients (pts) (age 58±10 years) and 15 normal controls (age 49±20 years). Twelve lead electrocardiogram (ECG) and cross-sectionally guided multiple M-mode and Doppler echocardiograms were recorded. Signal averaged ECGs (SAECG) were obtained in 10 of the pts. All pts had functional mitral regurgitation (MR). Computed PR interval (183±30 ms vs 150±15, p<0.005) and QRSD duration (QRSD; 125±25 ms vs 90±10, p<0.005) were longer than normal. In DCM, the earliest LV mechanical activity involved transverse (42 pts) or longitudinal (6 pts) septal shortening, occurred 40±15 ms after the onset of the Q wave, much earlier than normal (75±15 ms, p<0.01). The onset of MR followed that of earliest wall motion by 10±15 ms, regardless of site. The electromechanical delay (Q wave to MR onset) (47±15 ms) correlated inversely with PR interval (r=-0.73, p<0.01) and QRSD (r=-0.67, p<0.05). The SAECG detected early potentials (amplitude <40 μV), whose duration (30±12 ms) correlated directly with PR interval (r=0.75, p<0.01). Once these early potentials were taken into account, electromechanical delay and PR interval were both normalised and the correlation between them disappeared.

Thus: Very early LV activation regularly occurs in pts with DCM, especially when QRSD is increased and has clear mechanical consequences. It cannot be detected on 12 lead ECG which only significantly underestimates the QRSD duration. Apparent prolongation of PR interval in such pts appears to be a sensitive marker of its presence.

Contrastility of human and guinea pig cardiac ventricular myocytes is modified by mechanisms involving nitric oxide

AJB Brady, JB Warren, SE Harding, PA Poole-Wilson. Department of Cardiac Medicine, National Heart and Lung Institute, London.

Coronary microvascular closure lies in close proximity to cardiac muscle. Contractility of cardiac myocytes can be attenuated by factors released by stimulated endothelium. In the present study the effect of nitric oxide (NO) in solution was tested on isolated contracting myocytes from guinea pig (GP), and the effects of sodium nitroprusside (SNP, a NO donor) and 8-bromo-cyclic GMP (8b-cGMP), a stable analogue of the intracellular second messenger of NO were studied on isolated ventricular myocytes from patients with heart failure (HF). NO and cGMP in solution lengthened the action potential and velocity of shortening of electrically-stimulated myocytes were recorded using videomicroscopy length-detection. Contracture amplitude was calculated as a percentage of the resting length. Superfusion with 10^(-5) M NO solution reduced GP myocyte contraction by 24±9% (n=5, p<0.05). 10^(-5) M nitric oxide solution reduced contractility by 26±9% (n=5, p<0.05). Concentration of NO in solutions was therefore confirmed using chemiluminescence. NO solution had no effect on myocyte contraction, so the effect of NO solution was not due to hypoxia. SNP had a dose-related effect, maximally reducing contraction amplitude of human myocytes by 27±7% at 10(-5) M (n=3, p<0.05) and GP myocytes by 23±5% at 3x10^(-5) M (n=9, p<0.03). 8b-cGMP reduced contractility of GP cells in a concentration-dependent manner (by 20±6% at 3x10^(-5) M, n=6, p<0.025). Thus NO attenuates cardiac myocyte contractility, either when superfused directly, or when metabolised from SNP, mediated by cGMP production within myocytes. These findings support a role of NO in the modulation of myocardial contractile function.

Adenosine-dependent accessory pathway conduction following apparently successful radiofrequency catheter ablation: a new electrophysiological action?


Adenosine is increasingly used to assess the success of radiofrequency (RF) catheter ablation of accessory pathways (APs), based on its property of inhibiting atrioventricular (AV) nodal conduction. In this study a direct effect on AP conduction apart from slight shortening of refractoriness. We describe a new phenomenon of adenosine-induced pre-excitation due to a direct action of adenosine on AP conduction following RF ablation. Ninety-three patients with Wolff-Parkinson-White syndrome and stable pre-excitation underwent successful RF ablation: there were no evidence of artegrade or retrograde AP conduction at follow-up electrophysiologic studies (2-6 weeks post-procedure). All patients received IV adenosine (0.1-0.3mg/kg) during sinus rhythm. In 86/93 adenosine induced transient AV block with no pre-excitation. In 3/93 adenosine failed to induce AV block or pre-excitation. In the remaining 4/93 patients, adenosine reproducibly induced transient AV block followed by pre-excitation. Pre-excitation persisted for longer than 60s in three cases and 180s in two. Adenosine-induced pre-excitation was still demonstrable during atrial pacing at cycle lengths up to 500ms both before and after IV propranolol 0.2mg/kg. However, in 2/4 patients with VA block, adenosine failed to restore 1:1 VA conduction. During follow-up, pre-excitation has recurred in 3/4 patients after 3-6 months. In conclusion, (1) Adenosine-dependent antegrade AP conduction may be observed occasionally after apparently successful RF ablation; and is associated with a high probability of recurrence; (2) The phenomenon does not represent latent pre-excitation; (3) The slow onset and delayed offset are strikingly different to the normal time-course of electrophysiologic actions following IV adenosine; (4) The mechanism does not depend on sinus bradycardia, reflex sympathetic stimulation or shortening of AP refractoriness, but could involve alterations in concealed conduction or a direct effect on the pathway itself.

8-bromo cyclic GMP prevents impaired relaxation at reoxygenation following brief hypoxia in isolated single cardiac myocytes

AM Shah, HS Silverman, EG Lakatta. *Dept. Cardiology, UWCM, Cardiff, CS/NIA, NIH & Johns Hopkins Medical Institutions, Baltimore, USA.

A return to normoxia / normal perfusion after brief hypoxia / ischaemia is associated with impaired myocardial relaxation in vitro and in vivo, contributing eg. to diastolic heart failure. We recently showed that 8-bromo cyclic GMP (8b-cGMP) hastens the onset of myocyte relaxation (ie. decreases time to peak shortening, TPS) by decreasing myocardial Ca2+ sensitivity. We therefore studied the effects of 8b-cGMP on posthypoxic relaxation in a new model where isolated, single rat cardiac myocytes (0.2 Hz, glucose-free Hepes buffer, 23°C) were made hypoxic (pO2 <0.02 mmHg) by a laminar counterflow of argon in a custom-designed chamber (PNAS 1988;85:6954). Myocyte cell length (CL) was monitored by a photodiode array and simultaneous [Ca2+]i by the ratio (F) of 410/490 nm indo-1 fluorescence emission. After 10 min hypoxia in urethane myocytes, reoxygenation resulted in a longer IPS (+32±12.8%) and a longer time from peak to 50% relaxation (RT50; +59±11.7%), and a decreased resting CL (1±3±0.5 μm; n=5; all p<0.05 cf. pre-hypoxic values). These changes were reversed slowly over 10-20 min. In myocytes treated with 8b-cGMP (50 μM for 10 min pre-hypoxia), after reoxygenation IPS and RT50 were briefer than pre-hypoxic, post-8b-cGMP values (+10.3±3.6%; -8.5±2.8%; +29.4%; +49.9%; +20.5%; +24.9%; +19.4%; +45.4%; +29.8%; +26.8%; +32.6%) and resting CL was unchanged (+0.2±0.1 μm). No change in amplitude or time course of the Ca2+ transient was seen in either group. These data indicate that (a) impaired posthypoxic relaxation in this model is a result of a change in intracellular calcium kinetics and possibly a transient enhancement of calcium sensitivity, (b) 8b-cGMP inhibits these abnormalities by altering cardiac myofilament properties. Cyclic GMP-elevating interventions may have direct myocardial actions (in addition to vasodilator activity) which improve posthypoxic relaxation with potentially beneficial consequences. (AMS was supported by the BHF.)
ATTENUATION OF CARDIOMYOCYTE PROTEIN SYNTHESIS BY PROTEIN KINASE C INHIBITION
K Jenkins, DH Maclver, J E Pritchard, MD Gammage, S D Logan. Departments of Cardiovascular Medicine and Physiology*, University of Birmingham, UK.

The presence of cardiac hypertrophy is a major risk factor in hypertension, although the mechanisms of heart muscle growth remain ill defined. Angiotein II and noradrenaline have been implicated in the genesis of cardiomyocyte hypertrophy both in vitro and in vivo. Both hormones stimulate phosphoinositide (PI) hydrolysis, a second messenger system in control of cell growth. We investigated the effect of these agonists on PI hydrolysis and protein synthesis in cardiomyocytes.

Cardiac myocytes derived from 1-4 day old Wistar rats were cultured in DMEM containing initially 10% fetal calf serum (FCS), supplemented with antibiotics and plated at a density of 10^5 cells per well on collagen-coated plates. Noradrenaline and angiotensin II stimulated phosphoinositide hydrolysis in a dose-dependent manner (EC50 1μM and 56 nM respectively). Their effect was inhibited by prazosin (1μM) and saralasin (0.1μM) respectively.

Using serum free medium, 10μM noradrenaline increased the rate of incorporation of [3H]-phenylalanine ([3H]Phe) into myocytes (mean±SEM, DPW/10^6 cells, n=4) (23742±577 vs 24945±577, p<0.001). [3H]Phe incorporation was inhibited by the specific PKC inhibitor chelerythrin (10μM) (27552±797 vs 32745±550, p<0.001). Angiotensin II (10μM) also stimulated the incorporation of [3H]Phe into cardiomyocytes (29494±317 vs 24945±577, p<0.001) and this effect was inhibited by chelerythrin (10μM) (23004±2086 vs 29494±317, p<0.001).

These data show that chelerythrin significantly attenuates the protein synthesis produced by noradrenaline and angiotensin II in cardiomyocytes and that protein kinase C is likely to mediate the trophic response of these hormones.

DETECTION OF MAP KINASE ACTIVATION IN CULTURED NEONATAL RAT CARDIOMYOCYTES EXPOSED TO ENDOTHELIUM
P E Glennon, M A Bogoyevitch, P H Sugden. Department of Cardiac Medicine, National Heart & Lung Institute, Dovehouse Street, London, UK.

Mitogen activated protein kinases (MAPK) are a group of enzymes which are activated by a large number of extracellular growth factors and which play a central role in signal transduction from cell membrane to nucleus. We are interested in the involvement of MAPK in cardiac cell hypertrophy. The cultured neonatal rat cardiomyocyte model displays many of the changes in phenotype typical of pathological hypertrophy in adult cardiomyocytes. We used myelin binding protein (MBP) as a substrate in an assay to detect MAPK activity after exposing these cells to two agents known to induce hypertrophy, namely endothelin-1 and 12-O-tetradecanoyl phorbol acetate (TPA, a powerful and specific activator of protein kinase C). Fast protein liquid chromatography of the cytosolic component using a Mono-Q anion exchange column and a linear NaCl gradient revealed two peaks of MBP kinase activity. The salt concentrations at which these peaks eluted strongly suggested they be MAPK. This was confirmed by sodium dodecyl sulphate polyacrylamide gel electrophoresis and labelling with MAPK-specific antisera which revealed two discrete bands of Mr 43 and 44 kilodaltons. Specificity of the kinase activity was demonstrated by the absence of significant phosphorylation of histone or protamine when these were used as alternative assay substrates. The dose response characteristics for endothelin-1 were determined and the ED50 found to be 10^-9 M. Chronic (24 hours) TPA stimulation of cells resulted in partial downregulation of the response suggesting protein kinase C has an intermediary role in MAPK activation.

These experiments have demonstrated an important new component of the intracellular signalling pathway leading to cardiac cell hypertrophy.

SODIUM NITROPRUSSIDE (SNP) DIRECTLY INCREASES RELAXATION RATE IN THE INTACT HEART
R Crockett-Mason, M J Lewis*, AM Shah. Departments of Cardiology and Pharmacology & Therapeutics, University of Wales College of Medicine, Cardiff.

SNP is generally regarded as a 'pure vasodilator'. We have recently shown that raising cyclic GMP in isolated myocytes or papillary muscle (e.g. with SNP or nitric oxide released by endocardial endothelium) induces the novel effect of hastening myocardial relaxation by reducing myocardial Ca^2+ responsiveness. In this study, we measured the effects of SNP on left ventricular relaxation and pump function in isolated ejecting guinea pig hearts perfused with Krebs buffer (37°C; constant loading and heart rate). High-fidelity micromanometer LV pressure (LVP) and dP/dt were obtained via an apical 2F catheter. LVP decay was biphasic: (i) an early mono-exponential decay to the point of inflexion on the LVP trace, described by a time-constant TE (control range 50±14 ms; n=9; 62 ±); and (ii) a late mono-exponential decay corresponding to isovolumic relaxation, described by the time-constant tau (control range 48.5±0.7 ms; n=9; 113). SNP induced premature and faster early decline of LVP. After 12 mins TE was reduced by 17.5±1.6% with SNP 1μM (n=4) and 15.4±3.1% with 10μM (n=6; both p<0.05) with no change in GMP (n=3). Peak SNP, LVP, and diastolic LV, dP/dt or stroke volume. The effects on TE were similar at both SNP concentrations despite significant differences in coronary flow (CF) (7.2±3.1% and +48.7±12% respectively p<0.05). The GMP-independent vasodilator nicardipine (1μM) increased CF to a similar degree (+31.4±4.1%; n=5; p<0.01) with no effect on TE. These data show that (i) SNP has a direct lusitropic action in the whole heart, consistent with the action of GMP in myocardium and is not a 'pure vasodilator'. (ii) This action is not due to the mechanical effects of increased CF. (Supported by the BHF and MRC)

CYCLIC GMP DECREASES MYOFILAMENT CALCIUM RESPONSIVENESS IN ISOLATED CARDIAC MYOCYTES
AM Shah*, HA Spiroge, EG Lakatta. Dept. Cardiology, University of Wales College of Medicine, Cardiff, L&CS/NIH, National Institutes of Health, Baltimore, USA.

Nitric oxide (NO) released by endocardial endothelial cells raises myocardial cyclic GMP content and has the novel effect of hastening the onset of myocardial relaxation. The mechanism of action of cGMP in the heart remains unclear. We studied the effect of 8-bromo cGMP (8bcGMP, 1-100 μM) on myocyte cell length (CL, measured by a photodiode array) and simultaneous indo-1 fluorescence (410:490 nm emission ratio, O) in adult rat ventricular myocytes (0.5 Hz, 25°C, Heps buffer, 1 mM Ca^2+). 8bcGMP (50 μM) reduced the time shortening by 17.1±3.3% (mean±S.E.M.) and contraction amplitude by 17.3±5.8% and increased steady-state diastolic CL by 0.4±0.4 μm (all p<0.05; n=7; bold lines, fig.), effects similar to those of endocardial NO. There was no significant change in diastolic peak systolic R or time to peak R. In the CL vs. [Ca2+] phase-plane diagram, 8bcGMP shifted the terminal trajectory during twitch relaxation to the right, indicating myofilaament calcium desensitisation (J Physiol 1992;447: 83-102). Similar effects were noted at 35°C and 2 Hz. 8bcGMP effects were inhibited by KT5823 (1 μM), which inhibits cGMP protein kinase (PKG), or in the presence of isoprorenaline (3 μM). 8bcGMP had no effect on pH in cells loaded with the fluorescent pH probe SNARF-1 (n=4). These results indicate that 8bcGMP reduces the relative cardiac myofilament response to calcium, probably via PKG. This action is independent of pH but may involve a cyclic AMP-sensitive mechanism. The novel actions of endocardial NO likely involve a cyclic GMP-mediated modulation of cardiac myofilament calcium sensitivity. (AMS was supported by the BHF).
The effect of heparin on transient myocardial ischaemia and in-hospital prognosis in unstable angina

Dr Holdright, D Patel, JL Sparrow, CA Wright, M Wicks, H Purcell, W Hubbard, R Thomas, GC Sutton, WG Hendry, KM Ford, Royal Brompton National Heart & Lung Hospital, LONDON, UK.

Because intracoronary thrombus formation is associated with the development of unstable angina, heparin may be beneficial. Since continuing myocardial ischaemia identifies patients at greater risk of subsequent cardiac events, the effect of heparin therapy was assessed by ST Holter monitoring in a single blind, randomised multicentre study. 273 patients with unstable angina were randomised to intravenous heparin plus conventional therapy (beta blockers, diiltiazem, nitrates and aspirin) or conventional therapy alone (H-). 146 patients (28 female), age 50.3±0.8 yrs (mean ± SEM), received heparin (H+) and 127 patients (25 female), age 60.6±0.8 yrs, received conventional therapy (H-). Heparin was infused continuously for the first 48 hrs following admission, during which time ST segment Holter monitoring was performed. The admission ECG showed ST changes in 67.1% H+ and 71.8% H- patients (p=0.01). 11,244.3 hrs of monitoring yielded 231 episodes of transient myocardial ischaemia (TIMI) of total duration 7441 min. There were no statistically significant differences between the number of patients with a positive Holter (17.8% H+ vs 23.6% H-), the number of episodes of TIMI (92 H+ vs 139 H-) or the total duration of ischaemia (2783 min H+ vs 4655 min H-). The incidence of in-hospital non-fatal myocardial infarction or death was significantly higher in patients with a positive tape compared with patients with a negative tape (53.7% vs 22.2% respectively, p<0.000005). All deaths occurred in patients with a positive tape. The addition of heparin was not associated with a significant reduction in infarction and death (25.5% H+ vs 30.2% H-). In unstable angina TIMI was associated with an adverse prognosis which is not altered by the addition of intravenous heparin to conventional therapy.


table

Patient characteristics, electrocardiographic findings and prognosis of suspected myocardial infarction patients who present with ST depression

| H S Lee, S J Cross*, J M Rawls**, K P Jennings* | Department of Cardiology*, Aberdeen Royal Infirmary, and University of Aberdeen**, Aberdeen |

Patients recruited into GISSI and ISIS-2 trials who presented with ST depression (ST+) had a high mortality (16-19%) which was not reduced by thrombolytic therapy. To determine the reasons for this and the diagnostic and prognostic value of the presenting electrocardiogram (ECG), we reviewed the case notes of all patients with suspected acute myocardial infarction (AMI) who presented with ST+ during 1990. Of the 136 patients (84 male, mean age (SD) 58 (11) yrs), 74 (54.4%, 48 male, age 68 (11) years) had confirmed infarction. Previous MI had occurred in 73 (53.7%) patients. The severity (SEV) and the number of leads (L-dep) showing ST+ were helpful in diagnosing AMI (Sensitivity, Specificity):

<table>
<thead>
<tr>
<th>SEV</th>
<th>Spec</th>
<th>Sen</th>
<th>Spec</th>
<th>Sen</th>
<th>Spec</th>
<th>Sen</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
<td>&gt;3mm</td>
</tr>
<tr>
<td>41</td>
<td>90</td>
<td>20</td>
<td>97</td>
<td>12</td>
<td>98</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>L-dep</td>
<td>24 leads</td>
<td>26 leads</td>
<td>27 leads</td>
<td>28 leads</td>
<td>74</td>
<td>52</td>
<td>85</td>
</tr>
</tbody>
</table>

Nine month’s mortality: 22.7% for those with SEV >3mm and 28.4% for those with confirmed infarction (71.4% had previous infarction). For presenting ECG: ST+ of 1mm = 8/72 (11%) >2mm = 22/344 (6%) died, x² = 10.0; P<0.01; number of leads showing ST+ <2 leads = 2/28 (7%) died, >3 leads = 28/108 (26%) died, x² = 4.6; P<0.05. Patients with AMI subsequently excluded had a surprisingly high mortality of 15% (48% had previous MI). Conclusion: Patients with suspected AMI who presented with ST+ had a high mean age, a high incidence of previous MI and a poor prognosis. ST+ of >3mm or in ≥7 leads is highly specific for the subsequent diagnosis of AMI. Patients with ST+ of ≥2mm or in ≥3 leads have a very poor prognosis.

Refractory unstable angina is associated with persistently elevated plasma levels of endothelin

I Wieczorek,* KAA Fox*, CA Ludlam**, WG Haynes***, DJ Webb**

*Cardiovascular Research Unit, University of Edinburgh, **Haematology Department, Royal Infirmary of Edinburgh, ***Department of Medicine, Western General Hospital, Edinburgh

Endothelin (ET) is an endothelium-derived peptide that is a potent vasoconstrictor and affects both systemic and coronary vascular tone. ET levels are increased in healthy controls, congestive heart failure and acute myocardial infarction (AMI). In contrast, in chronic stable angina, ET has been found to be normal. Elevated ET levels in acute coronary symptoms are associated with markers of a hypercoagulable state. We have measured ET levels in 14 patients presenting with refractory unstable angina (ECG change, unresponsive to heparin, ASA, nitrates) and in 17 healthy controls. Nine patients developed cardiac events (AMI, recurrent angina or PTCA/CABG) during 9 weeks of follow-up, while 5 remained event free. Presentation ET levels were significantly elevated in the patients compared with controls (7.80±0.29 pg/ml vs 5.29±0.29 pg/ml, p<0.001) and remained elevated at 9 weeks (8.35±0.68 vs 5.29±0.29 pg/ml, p<0.001). Levels of ET in those who subsequently developed cardiac events were significantly higher both at presentation (6.52±0.45 vs 8.01±0.29, p<0.05) and at 9 weeks (5.90±0.33 vs 8.72±0.78, p<0.01). This study demonstrated persistently elevated levels of ET in patients with unstable angina. This may support the concept of endothelial activation in this condition. The finding that ET levels were elevated in patients who developed cardiac events may provide means of identifying individuals who are at greater risk.
IMMEDIATE PTCA IN THE MANAGEMENT OF UNSTABLE ANGINA: SAFE AND EFFECTIVE THERAPY
KD Dawkins, IHI Gray, IA Simpson, N Conway. Wessex Cardiac Unit, Southampton General Hospital.

The timing of PTCA in the patient with unstable angina remains controversial because of the concern over possible increased morbidity in this subset of patients.

Over a 2.5 year period we have studied prospectively a group of 248 consecutive patients presenting with unstable angina treated with intravenous heparin and nitrates who underwent diagnostic coronary arteriography followed by immediate PTCA.

Average age for the series was 57.2 (range 32-82) years, 186/248 pts (75%) were male. Patients undergoing redo PTCA for restenosis were excluded. Previous CABG had been undertaken in 52 pts (21%).

Data were analysed on an intention to treat basis. A total of 408 lesions were dilated in the 248 pts (mean 1.7, range 1-6 lesions/patient). Single vessel PTCA was performed in 187 (75.4%) pts, of these 25 of the target vessels were occluded (TIMI grade 0). Multivessel PTCA was undertaken in 61 (24.6%) pts. Primary angiographic success of all lesions attempted was achieved in 205 (82.7%) pts, partial success (dilatation of some, but not all lesions attempted) in 21 (9.3%) pts, and failure in 20 pts (8.1%).

The early complication rate was low with an in-hospital mortality of 0.8% (2/248), Q-wave myocardial infarction in 0.4% (1), non-Q wave infarction in 1.6% (4). Emergency coronary artery bypass grafting (<24 hrs after failed PTCA) was required in 4 pts (1.6%). Patients in whom PTCA was uncomplicated were discharged home 24-48 hours after the procedure.

Thus, in patients with unstable angina requiring intravenous therapy, immediate PTCA results in an acceptable primary angiographic success rate in association with a low morbidity and mortality. This strategy allows this group of patients to be treated effectively, mobilised and discharged from hospital promptly.

PRECONDITIONING PROTECTS ISOLATED RABBIT PAPILLARY MUSCLES AGAINST HYPOXIC INJURY
DM Walker, JM Walker, MS Marber, and DM Yellon. The Hatter Institute for Cardiovascular Studies, Division of Cardiology, University College Hospital, London.

A brief period of ischaemia with reperfusion protects the myocardium from subsequent more prolonged ischaemia (‘ischaemic preconditioning’, PC). Previously this has only been demonstrated in the intact heart. Our aim was to develop a new model of preconditioning in isolated, superfused, isometrically contracting, rabbit right ventricular papillary muscle.

Right papillary muscles were suspended in an organ bath, superfused with oxygenated modified Tyrode’s solution and field stimulated at 1Hz. On stabilisation, initial functional parameters were recorded and muscles were assigned to either control or PC groups. Preconditioning was induced with 3 minutes rapid pacing (3Hz) with substrate-free, hypoxic buffer and 15 minutes reoxygenation with substrate. Subsequently both groups were exposed to 45 minutes of substrate-free hypoxia followed by 120 minutes reoxygenation with substrate.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Control</th>
<th>PC</th>
<th>PC+ SPT</th>
<th>SPT</th>
<th>R-PIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>% recovery of force at 120 min reoxygenation (mean ± SE)</td>
<td>27.4 ± 4.2</td>
<td>50.6 ± 6.7</td>
<td>30.9 ± 2.8</td>
<td>27.1 ± 49.5 ±</td>
<td>5.5</td>
</tr>
</tbody>
</table>

PC protected the myocardium, with better recovery of developed force (p<0.01). We were able to block this effect with 8-sulphophenyl-theophylline (SPT), an adenosine antagonist, and similarly protect with R-phenyl-isopropyl adenosine (R-PIA), an adenosine (A1) agonist. We conclude that PC does not depend on coronary perfusion and is likely to involve activation of adenosine receptors at a cellular level. With this model we intend to examine further the mechanisms underlying preconditioning and to investigate its role in human myocardium.

CORONARY ANGIOGRAPHY FINDINGS IN UNSTABLE AND POST-INFARCTION ANGINA PECTORIS.

Although coronary angiography (CA) may be useful in studying acute coronary syndromes and in particularising the therapeutic approach, the description of visual findings is frequently biased by a subjective translation to pathological terms. We compared the CA findings in 19 patients presenting with either unstable (n=11) or post-myocardial infarction (n=8) angina (UAP and post-MI respectively) using an objective classification of visual observations. Methods: CA of the culprit lesion was performed using a 4.5 Fr over-the-wire flexible angioscope. Angiographic and CA information was recorded simultaneously using a videotape and later analysed by two cardiologists. Lesions were classified according to morphological and clinical characteristics. A pathological interpretation of CA findings was only attempted when concomitant histological evidence (atherectomy specimens) was available. Unpaired Student’s t and chi-square (with Yates’ correction) tests were used to compare variables as required. Results: Optimal CA visualization of the stenosis and proximal vessel was obtained in all cases without complications. Tabled are some morphological and clinical data:

<table>
<thead>
<tr>
<th>UAP</th>
<th>Post-MI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset syndrome to CA (days)</td>
<td>14±5</td>
<td>21±21</td>
</tr>
<tr>
<td>Red surfaces / bodies</td>
<td>3 (27%)</td>
<td>7 (85%)</td>
</tr>
<tr>
<td>Pink surfaces / bodies</td>
<td>9 (90%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Yellow surfaces / bodies</td>
<td>0</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>White-greyish bodies</td>
<td>4 (40%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

Post-MI was associated more frequently to red and yellow material than UAP. In two post-MI stenosis showing both red and yellow structures histological evidence of fresh thrombus and cholesterol crystal clefts was obtained. Pink areas were more frequent in UAP than in post-MI although no selective atherectomy of these areas was performed. Conclusions: Angiography revealed significant differences in the chromatic and morphological characteristics of culprit stenoses of UAP and post-MI that may be related to differences in their pathological substrate. The concomitant use of directional atherectomy may facilitate the translation of these visual findings to pathological terms and to a better understanding of the natural history of both syndromes.

FREE RADICALS DO NOT INCREASE CALCIUM ENTRY VIA SARCOSOMAL VOLTAGE GATED CALCIUM CHANNELS
JS Gill, F Lu, WU McKenna, AJ Camm. Cardiological Sciences, St George's Hospital Medical School, London.

Background: Free radical induced damage to cardiac cells may be important in the development of reperfusion-induced arrhythmias and cell death. The mechanism of arrhythmogenesis has been proposed to be cellular calcium overload. This study examines whether free radical mediated cellular calcium overload occurred by increased entry of Ca2+ via voltage gated sarcosomal calcium channels (ICa).

Methods: Single guinea-pig ventricular myocytes were studied using the whole-cell clamp method. Potassium and sodium currents were suppressed by intracellular caesium and a 100 ms prepulse from a holding potential of -80 mV to -40 mV respectively. ICa was elicited by a 300 ms depolarisation from -40 mV to 0 mV at 0.18 Hz. After measurement of ICa in the control state, solutions containing cumene hydroperoxide (CH) or an oxygen-derived free radical generating system (pure nitrogen xanthine oxidase) were perfused at 1.5 mlimin. Results: ICa was reduced from 546±553 pA to 685±444 pA (n=7, p<0.05) in the presence of 100 mM CH and from 708±157 pA to 457±163 pA (n=5, p<0.001) in the presence of 500 mM CH. There was a significant difference in the reduction if ICa by the two concentrations of CH used (22.75% vs. 36.8%, p<0.05). ICa was decreased from 1303±560 pA to 968±390 pA in the presence of the free radical generating system (2.3 mM purne with 20 Ul xanthine oxidase). The decreased ICa could not be recovered by washing for up to 5 minutes with fresh recording solution suggesting irreversible damage to the sarcosomal voltage gated Ca2+ channels. Conclusions: We conclude that ICa decreases in the presence of free radicals derived from CH and the free radical generating system. It therefore appears unlikely that cellular calcium overload induced by free radicals is a result of Ca2+ entry via sarcosomal voltage sensitive calcium channels. The data suggest that free radicals may irreversibly damage the sarcosomal voltage-gated calcium channel.
COMPARISON OF ELECTROPORATION AND LIPOSOME-MEDIATED TRANSFECTION OF CARDIAC MYOCYTES IN PRIMARY CULTURE.

N. Green, K. Jenkins, J. Flarke, H. Kawai, H. Thompson, and M. O. Smith.
Department of Cardiovascular Physiology, University of Manchester, UK.

Transfection of cultured cells allows study of gene regulation and the functions of specific gene products. Transfection methods for transformed cell lines are well established, but little is known regarding methods for induction of heterologous gene expression in cells in primary culture, especially cardiac myocytes. We have compared electroporation and liposome-mediated transfection to introduce RSV-CAT containing plasmids into neonatal rat ventricular myocytes. Myocytes were isolated from 1-2 day old rats; cells (10^6/culture) were placed in an electroporation cuvette, DNA added and the cells subjected to a high voltage pulse. Cells were grown for 48-72 h to allow expression of the transfected chloramphenicol acetyltransferase (CAT) gene. The parameters needed to be optimised for successful transfection are the voltage and capacitance settings. We examined a range of voltage (150-300V) and capacitance settings (125-960μF); the optimal voltage and capacitance settings were 200V, 960μF (150V 960μF, 77.0; 170V 960μF, 89.0; 200V 960μF, 103.6; 300V 960μF, 103.1; 420V 200μF, 63.1; 200V 960μF, 103.0). Green fluorescent protein (GFP) expression was detectable in 1-2 days in culture. GFP expression was compared with RSV-CAT expression by fluorescence and immunolabelling microscopy. The results show that electroporation is more efficient than liposome-mediated transfection for transfection of neonatal rat ventricular myocytes. This method offers a valuable tool for examining the function of specific genes involved in cardiac hypertrophy.

IS VENULAR CONSTRUCTION THE PRIMARY RESPONSE TO α-ADRENERGIC ACTIVATION IN THE CORONARY MICROCIRCULATION?

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

Alpha- and beta-adrenergic receptor activation (α-ARA) on exercise increases coronary resistance and limits coronary vasodilator reserve. The mechanisms of constriction of coronary microvessels are poorly understood. We therefore evaluated the responses to α-ARA of isolated coronary arterioles (110 ± 12 μm, meanSEM; n = 35) and venules (98 ± 7 μm; n = 9). The microvessels were carefully dissected from freshly excised canine hearts (n = 20), cannulated with glass micropipettes (tip diameter ~60 μm), pressurised at 60 mmHg without flow and imaged by video microscopy. All vessels developed spontaneous tone, indicating myogenic viability. α-ARA was achieved by graded doses of noradrenaline (10^-10 to 10^-4 M) with β-adrenergic blockade by aprenolol (10^-4 M). α-ARA did not constrict coronary arterioles, even in the presence of arginine vasopressin, angiotensin II, endothelin and neuropeptide Y (which promote adrenergic constriction in other vascular preparations). Arteriolar constriction was not promoted by inhibition of nitric oxide or prostagland synthesis (N^O-monomethyl-L-arginine or indomethacin respectively, both 10^-5 M). By contrast, canine skeletal (gracilis) muscle arterioles, similarly isolated, were constricted by up to 80 ± 4% by NA (n = 3). By further contrast, α-ARA did constrict coronary venules dependently (maximum diameter change -27 ± 3%, p < 0.05 for doses of NA above 10^-10 M). This response was inhibited similarly by the α1 and α2-adrenergic receptor antagonists, prazosin and yohimbine (both at 10^-6 M, p < 0.05), indicating an increased proportion of α2-inhibitory tone in coronary venules. Thus, α-ARA does not cause constriction isolated coronary arterioles. In contrast, α-ARA constricts isolated coronary venules, due to the presence of both α1- and α2-adrenergic receptors. These results imply that the primary coronary microvascular response to α-ARA is venular constriction.

EXTRACELLULAR MATRIX SYNTHESIS OF HUMAN VASCULAR SMOOTH MUSCLE CELLS IN CULTURE.


The ability to produce extracellular matrix is a property of vascular smooth muscle cells (SMC) in intimal lesion formation which may assume particular importance in restenosis post-intervention. We studied the synthesis in vitro of sulphated-glycosaminoglycans (S-GAGs) and of collagen by SMC cultured from the following sources: coronary primary atherosclerotic (P) and restenotic (R) lesions excised at directional atherectomy, carotid plaques (C) and left internal mammary artery media (LIMA) obtained at surgery, and human umbilical artery media (U).

Methods. SMC were cultured from tissue explants. In secondary culture, the synthesis of S-GAGs was assessed by the incorporation of 35S-sulphate and of collagen 3H-proline.

Results. SMC were more active than P SMC, and U SMC less active than all other SMC, in matrix synthesis (Table 1, mean±s.e.m., mmol isoate µg total protein^-1). R and P SMC synthesised more S-GAGs than other atherosclerotic and healthy adult SMC. Surprisingly, R SMC, but not P SMC, synthesised significantly more collagen to SMC - cells derived from old consolidated lesions.

<table>
<thead>
<tr>
<th>Table 1: SMC</th>
<th>S-GAGs</th>
<th>collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSMC</td>
<td>7.49±0.38</td>
<td>0.03±0.005</td>
</tr>
<tr>
<td>PSMC</td>
<td>7.11±0.48</td>
<td>0.02±0.001</td>
</tr>
<tr>
<td>CSMC</td>
<td>3.51±0.26</td>
<td>0.03±0.001</td>
</tr>
<tr>
<td>LIMA</td>
<td>2.76±0.13</td>
<td>0.02±0.001</td>
</tr>
<tr>
<td>UMC</td>
<td>1.82±0.10</td>
<td>0.02±0.001</td>
</tr>
</tbody>
</table>

Conclusion. The capacity of SMC from restenotic lesions to synthesise S-GAGs and collagen in vitro supports the role of extracellular matrix synthesis in the restenosis process.

ANGIOTENSIN II STIMULATES THE SODIUM-HYDROGEN ANTIPORT IN PERFUSED HEART.

Department of Biochemistry and Medicine, University of Cambridge.

Angiotensin II (ANG II) stimulates the sodium hydrogen (Na^+H^-) antiport in many non cardiac mammalian preparations. In view of the potential importance of both the Na^+H^-antiport and ANG II in myocardial physiology and pathophysiology we have investigated the effects of ANG II on the Na^+H^-antiport in the perfused heart. Intracellular acidification was induced using the Na^+Cl^-exchange blocker, 5-(N-ethyl-N-isopropyl)-amiloride (10^-3 M, 10min) in the isovolumic Langendorff-perfused ferret heart. Hearts, paced at 1Hz, were perfused in a 9.4T NMR spectrometer at constant flow (5.1L/min) with nominally HCO^-3-free solution (composition: mM: NaCl, 119; HEPES, 20; KCl, 4; KHPO_4, 1.2; MgCl_2, 1.2; CaCl_2, 1.8; glucose, 10; Na pyruvate, 5; equilibrated with 100%O_2 at 30°C; pH 7.42-7.44). Intracellular pH (pHi) was estimated from the chemical shift of the 31P-NMR signal of DOG-S-Po_4. All in the concentration range 10^-10 to 10^-7 M was added directly to buffer solutions. Net acid efflux rates (J_AH, mmol L^-1 min^-1) at pHi 7.48 were calculated: J_AH=ρ_H/dt (ρ_H, intracellular intracellular buffering capacity calculated as Δ[H^+/(pH)^3]; ρ_H (HEPES) = 37±2nmol L^-1 / pHi d/dt calculated from exponential fit of pH recovery data.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Baseline pH</th>
<th>J_AH stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.0±0.01</td>
<td>1.2±0.08</td>
</tr>
<tr>
<td>10^-10 (4)</td>
<td>7.02±0.01</td>
<td>1.32±0.05</td>
</tr>
<tr>
<td>10^-8 (4)</td>
<td>7.02±0.01</td>
<td>1.60±0.12</td>
</tr>
<tr>
<td>10^-7 (6)</td>
<td>7.02±0.01</td>
<td>1.89±0.17</td>
</tr>
<tr>
<td>10^-6 (10)</td>
<td>7.02±0.01</td>
<td>1.93±0.17</td>
</tr>
</tbody>
</table>

The effects of ANG II were inhibited by both the Na^+H^- antiport blocker, 5-(N-ethyl-N-isopropyl)-amiloride and in zero sodium solution confirming mediation by the Na^+H^- antiport. The effect was also inhibited using the specific ANG II receptor inhibitor DUP753 indicating receptor mediation. That Na^+H^- antiport stimulation occurs in the physiological range of ANG II concentrations suggests that in clinical states associated with high circulating ANG II concentrations pharmacological modification of these processes may have therapeutic benefits.
MECHANISMS OF NOCTURNAL HYPOXIC EPISODES IN SEVERE CHRONIC LEFT HEART FAILURE

SW Davies, G Meacham-Jones, LME John, DP Lipkin, R Balcon, JA Wedzicha.
The London Chest Hospital & Royal Free Hospital, London.

Previous studies have demonstrated abnormalities of ventilation and of blood gases during sleep in patients with chronic heart failure. In many cases the oxygen saturation (SaO2) shows dips, defined as abrupt falls in SaO2 by >4% from a stable baseline and which last >30secs. In some cases these are associated with episodes of arrhythmia, but the mechanisms of the dips are not known.

Sleep studies were performed in 9 patients aged 46-67 years with severe but clinically stable heart failure (NYHA grades III and IV) in whom there was no evidence of pulmonary disease. No patients were obese or receiving alcohol or sedatives at the time of their study. During sleep mean SaO2 fell from 96.0 ± 1.7% awake to 91.5 ± 1.5% asleep (p<0.001). In 6 patients there were dips, usually in clusters of 4-12 dips over 12-30 min. Most dips were associated with a sinus bradycardia of 45-55 bpm, with acceleration to 75-110 bpm as SaO2 recovered, and the EEG indicated arousal and sometimes awakening as SaO2 recovered. In 2 patients some dips were accompanied by non-sustained ventricular tachycardia, and in 1 patient by transient fast atrial fibrillation. Recordings of nasal airflow and of chest wall and abdominal movement indicated that the episodes of desaturation were predominantly cyclical hypventilation rather than upper airway obstruction.

Thus episodes resembling Cheynes-Stokes respiration are common in severe chronic heart failure, even when apparently clinically stable. It is possible that these act as triggers to arrhythmias in the failing heart, and may relate to the high incidence of sudden death in severe chronic heart failure.

INCREASED ALVEOLAR-CAPILLARY MEMBRANE RESISTANCE TO GAS EXCHANGE IN CONGESTIVE CARDIAC FAILURE

D P Moore, S Parli, A R Weston, C M Oakley, J M B Hughes, J G F Cleland.
Department of Medicine (Cardiology), Royal Postgraduate Medical School, Hammersmith Hospital, London.

Although a reduced diffusing capacity for carbon monoxide is well recognised in patients with acute pulmonary oedema, it has generally been assumed that pulmonary congestion, leading to an increase in pulmonary blood volume and prolonged transit time, compensates for any functional impairment of gas transfer, thereby preventing significant impairment of pulmonary gas exchange. We have measured diffusing capacity for carbon monoxide (DLco), alveolar-capillary conductance for carbon monoxide (Dm), and pulmonary capillary blood volume (VC) using a single breath technique at different inspired oxygen concentrations in 15 male patients with varying degrees of stable congestive heart failure (CHF) of more than 6 months duration (age 55 ± 12 years, ejection fraction 27.4 ± 11.0 %). All were upon optimum medical treatment in the form of diuretics and angiotensin converting enzyme inhibitors. Results were compared with 10 sex matched control subjects (age 47 ± 15 years) without evidence of cardio-respiratory disease.

\[
\begin{array}{llllll}
\text{CHF} & 5.9 \pm 1.2 & 65 \pm 12 & 8.1 \pm 2.5 & 79 \pm 39 \\
\text{Ctrl} & 9.5 \pm 0.7 & 94 \pm 12 & 15.2 \pm 4.6 & 77 \pm 19 \\
\end{array}
\]

\[
\text{Dm (mmol/min/kPa) } \times 10^{-3} \text{ predicted } \text{DLco (mmol/min/kPa mL/m}^2\text{)}
\]

\[
p = 0.0001 \quad 0.0001 \quad 0.0001 \quad 0.0001
\]

The significant reduction of Dm in CHF patients indicates increased alveolar-capillary resistance to gas exchange. VC was similar in both groups, despite the presence of severely impaired ventilatory function. These data confirm reports of impaired diffusing capacity in CHF, identifying increased alveolar-capillary resistance as the main contributory factor, and suggesting that prolonged pulmonary venous hypertension impairs alveolar-capillary membrane function.

SKELETAL MUSCLE BLOOD FLOW IN HEART FAILURE: VALIDATION OF MEASUREMENT BY ULTRAFAST COMPUTED TOMOGRAPHY

P F Ludman, M Volterrani, S Rees, P A Poole-Wilson, A J S Coats Royal Brompton National Heart and Lung Hospital, London.

Blood flow to skeletal muscle is an important factor in determining the symptomatic limitation of patients with chronic heart failure. Current methods for measuring skeletal muscle flow are unable to distinguish flow in different muscle groups, do not allow simultaneous measurement of muscle bulk. Ultrafast computed tomography (UFCT) may be able to overcome some of these limitations. The aim was to determine the accuracy with which skeletal muscle blood flow could be measured by UFCT.

Leg blood flow measured by venous occlusion plethysmography (VOP) was compared with skeletal muscle blood flow by UFCT. Fourteen patients with chronic heart failure (age 51 to 76 years, 13 male, peak VO2 13.7 to 35.6 ml/min/kg) were investigated. VOP and UFCT measurements were performed at rest and during hyperaemic flow induced by bicycle exercise followed by 5 minutes of leg ischaemia. The UFCT measurements were made by analysing the opacification of the blood pool and muscle following a 60 ml i.v. bolus of non-ionic contrast.

Flow ranged from 1.5 to 38.1 ml/min/100ml. The slope of the line relating the two methods for all measurements was 1.1 (95% CI was 0.91 to 1.31), and the mean (± 95% limits of agreement) of the differences between the two methods was 2.5 ± 10.6 ml/min/100ml.

For the measurements performed at rest, the slope of the regression was 1.3 ml/min/100ml (95% CI was 0.16 to 2.45 ml/min/100ml), and the mean of the differences between the methods was 1.0 ml/min/100ml (with the 95% limits of agreement ± 3.2 ml/min/100ml/min). For the measurement performed during hyperaemia, the slope was 1.0 ml/min/100ml (95% CI was 0.5 to 1.5 ml/min/100ml). The mean of the differences between the methods was 4.2 ml/min/100ml (95% limits of agreement ± 14.8 ml/min/100ml). Both at rest and during hyperaemia, UFCT derived flow tended to be higher than flow derived from VOP.

UFCT is a useful tool in the measurement of skeletal muscle perfusion in man and, by planimetry of the high resolution tomograms, may also be used to assess muscle mass.

EFFECTS OF EARLY CAPTOPRIL ADMINISTRATION FOLLOWING MYOCARDIAL INFARCTION ON LEFT AND RIGHT VENTRICULAR EJECTION FRACTIONS AND VENTRICULAR VOLUMES

Departments of Cardiology, Western and Royal Infirmary, Glasgow, Scotland.

The beneficial effects of ACE inhibitors (ACE I) on remodelling after acute myocardial infarction (AMI) have largely been demonstrated by echocardiographic investigations. However, the use of radionuclide ventriculography in this context which enabled us also to assess the effects of ACE I on the right as well as the left ventricle.

In a double-blind study, 99 patients (83% male, age 40-75 years) were randomly assigned to receive either captopril or placebo within 24 hours of admission. All patients were recruited 6 hours or more following the onset of pain and none were given thrombolytic therapy. Subsequently, 56 patients developed anterior and 30 patients inferior Q-waves. Serial 99m-Tc Technetium radionuclide blood-pool scans were performed at admission, at 10 days, at 2 months and at 1 year. Median left ventricular ejection fraction (LVEF) values were 25.0 and 24.1 and at one year 28.0 and 23.6 for the captopril and placebo groups respectively. For anterior MI the figures were 23.3 and 19.9 initially vs 25.7 and 20.1 at 1 year. Median LV volumes (assessed geometrically) had increased by 10 and 14 units at one year. For anterior MIs these increases were 12 and 25 units respectively (p<0.03). A similar trend was seen for right ventricular (RV) volumes which increased by 9 and 23 units respectively.

This is the first controlled radionuclide study to confirm previous echocardiographic data showing that captopril, as compared with placebo, attenuates ventricular remodelling after AMI. While this effect was most marked in the case of anterior myocardial infarction, a beneficial trend on RV structure also was noted which has not previously been reported.
DETERMINANTS OF THE RENAL AND BLOOD PRESSURE RESPONSES TO CAPTOPRIL IN MODERATE CHRONIC HEART FAILURE

JG Motwani, AD Struthers.
Department of Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee, DD1 9SY, Scotland, UK.

While angiotensin converting enzyme inhibitors are now indicated for all grades of chronic heart failure, the two side effects which limit use of these drugs are systemic hypotension and renal dysfunction. We studied 36 patients with stable, moderate chronic heart failure in double blind placebo-controlled crossover fashion to evaluate, by multiple discriminate regression analysis, the pathophysiological determinants of changes in blood pressure, glomerular filtration rate and urinary sodium excretion following initial converting enzyme inhibition with captopril 25 mg.

Captopril-mediated fall in mean arterial pressure was predicted ($r^2 = 0.74$) by fall in serum angiotensin II (F ratio = 10, $p = 0.01$), fall in plasma noradrenaline ($F = 6, p = 0.02$) and inversely by pretreatment mean arterial pressure ($F = 5.6, p = 0.04$), patients with higher initial values exhibiting greater falls in response to captopril. Captopril-mediated decline in glomerular filtration rate, determined by radioisotope elimination was predicted ($r^2 = 0.67$) by fall in renal plasma flow ($F = 58.6, p = 0.001$), low pretreatment glomerular filtration rate ($F = 11, p = 0.007$) and low absolute post-treatment serum angiotensin II ($F = 5, p = 0.04$). Change in urinary sodium excretion was related directly to change in glomerular filtration rate ($F = 30, p = 0.001$) and inversely to change in angiotensin II level ($F=4.7, p = 0.03$) in response to captopril ($r^2 = 0.73$).

These findings emphasise the central role of circulating angiotensin II in chronic heart failure as the modifiable factor which mediates a potent antinatriuretic action while simultaneously playing a part in maintaining systemic blood pressure and independently, in maintaining glomerular filtration rate.

THE DELETERIOUS EFFECT OF ENOXIMONE ON SURVIVAL BUT BENEFICIAL EFFECT ON QUALITY OF LIFE IN PATIENTS WITH SEVERE END-STAGE CHRONIC HEART FAILURE

A J Cowley. Cardiovascular Medicine, University Hospital, Nottingham, NG7 2UH (on behalf of the Enoximone Investigators).

The medical treatment of severe heart failure is depressing. Although angiotensin converting enzyme inhibitors improve survival and well being, a considerable number of patients remain severely incapacitated. The purpose of this study was to investigate the effects of the addition of the orally active, cyclic adenosine monophosphate phosphodiesterase inhibitor, enoximone, on survival and quality of life in patients with severe heart failure. The study was started before the results of the PROMISE trial became known. Patients were randomly allocated to either placebo or enoximone treatment in a double-blind manner in addition to all other anti-heart failure medication. The trial was stopped prematurely by the Ethical Committee after 152 out of a planned 200 patients had been recruited from 16 centres in the United Kingdom. There was an excess death rate of 27 patients on enoximone, compared with 18 on placebo, ($p=0.0153$ (95% confidence intervals 0.157 - 0.821)). However, as distinct to PROMISE there was an improvement in quality of life measured with disease specific questionnaire ($p=0.0065$). Enoximone therefore appears to be associated with a worse prognosis in these very ill patients although it does improve their quality of life.