MYOCARDIAL/PERICARDIAL FUNCTION AND DISEASE — BASIC

901-91 Diastolic Dysfunction During Demand Ischemia is due to a Reversible Rigor Force and is not a Calcium (Ca^{2+}) Activated Tension

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Background: Exercise-induced angina (demand ischemia (DI)) causes an acute increase in LV diastolic chamber stiffness (↑DCS), via a mechanism that may involve i) diastolic persistence of excessive cytosolic Ca^{2+} (particularly from incomplete resequestration by an energy limited sarcoplasmic reticulum (SR)) with continued cross-bridge cycling, or ii) rigor force from ATP depletion. *Aim* To determine the nature of the tension underlying ↑DCS in DI.

Methods and Results: A) Diastolic anginal physiology was created in isolated isovolumic (balloon-in-LV) blood perfused rabbit hearts. Tachyardia (T: 7 Hz) imposed during restricted coronary blood flow (30% of baseline) increased DCS (ie isovolumic LVEDP) 7–9 mmHg after 15 ± 1 min (n = 38), increased lactate production (pre-T vs post-T: 0.12 ± 0.03 vs 0.45 ± 0.03 μM/min/gL Vww, $p < 0.001$) without increasing oxygen extraction. ↑DCS was reversible on reperfusion, similar to patients with angina. B) During the state of ↑DCS, brief intracoronary (ic) infusion of saline (S, n = 7) was compared to 50 mM ammonium chloride (NH_4Cl, n = 7) and to 14 mM Ca^{2+} (n = 6). Function was similar during low-flow ischemia pre-T (LV systolic pressure (LVSP)/LVEDP S = 67/18 vs NH_4Cl 58/17 vs Ca^{2+} 67/17 mmHg, NS) and post-T (S = 38/25 vs NH_4Cl 39/26 vs Ca^{2+} 43/24 mmHg, NS). i) NH_4Cl exerted a biphasic effect on LVSP over 2.5min (LVSP maximum increase to 70 ± 4, $p < 0.001$, followed by decrease to minimum 52 ± 2mmHg, $p < 0.001$) commensurate with an action as an intracellular alkalinising and then acidifying agent, to alternately increase and decrease myofilament Ca^{2+} sensitivity. However LVEDP remained unaffected suggesting ↑DCS was not Ca^{2+} dependent. ii) Ca^{2+} increased LVSP (S vs Ca^{2+} 57 ± 3 vs 97 ± 5 mmHg, $p < 0.001$), *decreased* DCS (LVEDP S vs Ca^{2+} 25 ± 1 vs 21 ± 1 mmHg, p i 0.001), and *increased* relaxation rate (−dP/dt/P 13 ± 1 vs 10 ± 1/s, $p < 0.005$). Hence Ca^{2+} resequestration capacity during a state of ↑DCS was intact and capable of acceleration, consistent with a functional and responsive SR. C) To further investigate the nature of ↑DCS we applied a method novel to the isolated heart with a quick (0.5s) stretch-release (QSR) of 25% of intraventricular balloon volume in three groups of hearts with ↑DCS i) classic rigor with zero-flow ischemia ii) ic infusion of 5 mM caffeine and 5 mMCa^{2+} (producing Ca^{2+} activated ↑DCS) and iii) in DI. QSR instantly lysed increased diastolic tension during zero-flow ischemia (LVEDP pre-vs post-QSR 27 ± 1 vs 17 ± 1 mmHg, $p < 0.001$), and also in DI (27 ± 2 to 15 ± 1 mmHg, $p < 0.001$). By contrast, LVEDP was unaffected by QSR during Ca^{2+} activated ↑DCS (28 ± 1 to 26 ± 1 mmHg, NS). Hence, ↑DCS in DI behaved as a rigor tension with QSR.

Conclusion In DI, neither does ↑DCS behave as a Ca^{2+} activated tension nor is subcellular Ca^{2+} reuptake disabled. Rather, ↑DCS displays properties of a rigor force which may produce ischemic diastolic dysfunction in DI.

901-92 The Relationship Between Changes in Myocyte Electrical and Contractile Events with the Development of Dilated Cardiomyopathy

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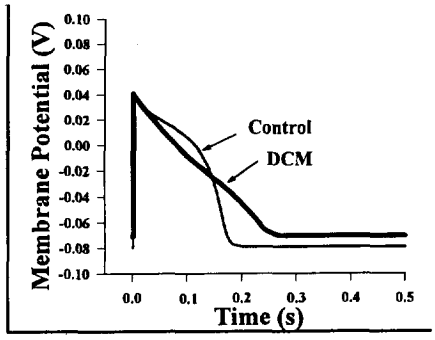
Changes in myocyte (MYO) membrane potential (MYO-MP) are major determinants in contractile processes. We hypothesized that the development of dilated cardiomyopathy (DCM) will cause specific changes in MYO-MPs and be directly associated with well defined abnormalities in MYO contractile events. Simultaneous indices of isolated MYO-MP (resting, RMP; max upstroke velocity, Vmax; time to 90% repolarization, APD_{90}) and contraction (velocities of shortening, VELSHT; and relengthening, VELLEN) were obtained in 7 pigs with DCM (pace 240bpm; 3wks) and 7 control (CON) pigs at baseline (BAS) and with β-AR stimulation (25 nM isoproterenol) using microelectrodes and high speed videomicroscopy.

	RMP(mV)	Vmax(V/s)	APD_{90}(ms)	VELSHT(μm/s)	VELLEN(μm/s)
BAS-CON	−78.4 ± 0.6	130 ± 3	169 ± 7	57 ± 3	57 ± 4
BAS-DCM	−71.5 ± 1.1*	93 ± 5*	202 ± 6*	35 ± 2*	36 ± 3*
β-AR-CON	−78.4 ± 1.3	166 ± 6#	236 ± 9#	135 ± 6#	136 ± 7#
β-AR-DCM	−74.6 ± 1.3*#	113 ± 3*#	265 ± 10*#	83 ± 6*#	68 ± 6*#

*$p < 0.05$ vs CON, #$p < 0.05$ vs Baseline

Baseline MYO-MPs recorded from a control and a DCM MYO are shown in Figure 1. MYO-MPs at peak MYO contraction and at end of MYO contraction were higher with DCM compared to CON (−48 ± 4* vs −65 ± 3 mV; and −71 ± 1* vs −78 ± 1 mV). Thus, more positive MYO-MPs were observed; particularly during active MYO relaxation. The abnormalities in the MYO-MP and MYO contractile relationships were not normalized with β-AR stimulation.



Summary: In this model of dilated cardiomyopathy, significant alterations in myocyte contractile function and action potential characteristics were observed. These alterations in the temporal relationship between myocyte electrical and mechanical events may be a fundamental contributory mechanism responsible for the contractile dysfunction observed in this model of cardiomyopathic disease.

901-93 Selective Inhibition of Epicardial Function Reduces Left Ventricular Endocardial Torsion and Principal Strain: A Magnetic Resonance Imaging Study Using Tissue Tagging

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Cardiac motion results from the complex interaction of individual muscle fibers organized into layers. Epicardial (epi) fibers are aligned with the direction of endocardial (endo) torsion and principal strain (PS) angle, suggesting an influence on endo function. Therefore, we hypothesized that selective inhibition of epi function will alter endo deformation. Twelve open chest dogs underwent continuous pericardial lavage at baseline (BL) and with heating of the lavage fluid (HT), while the blood temperature was held constant. Heating decreases contractile function. Imaging was performed at BL and at HT and included 4 short axis images with 4 radially prescribed tags and 4 long axis images with 4 parallel transverse tags. Gradient echo images were obtained at end-diastole and end-systole. The tag-endo and tag-epi intersections were located and reconstructed into 24 3-D myocardial cuboids for 3-D finite strain analysis. Torsion was measured as the apex to base difference in rotation about the cavity centroid at end-systole. Results compare the free wall (exposed to heated lavage) at BL and at HT. *Results:* Lavage temperature increased from 35.7° ± 1.2 at BL to 40.0° ± 0.7 at HT ($p < 0.001$). As a direct result of the heating, epi torsion and PS magnitude decreased from −4.1° ± 3.0 to −1.4° ± 2.4 ($p < 0.02$) and from −0.10 ± 0.03 to −0.08 ± 0.03 ($p < 0.001$), respectively. Although blood and therefore, endo temperature was constant (34.7°) at both BL and HT, endo torsion and PS magnitude decreased from −9.1° ± 6.8 to −2.5 ± 4.9 ($p = 0.002$) and from −0.29 ± 0.06 to −0.23 ± 0.10 ($p < 0.05$), respectively. Wall thickening decreased from 30.8% ± 14.3 to 18.5% ± 17.6 ($p = 0.004$). In the septum (unexposed to heated lavage) torsion, PS and thickening were unchanged. In conclusion, selective inhibition of epicardial function by augmented temperature caused a significant decline in endocardial torsion and PS magnitude, local measures of endocardial function, demonstrating the important contribution of epicardial function to endocardial deformation.

MYOCARDIAL/PERICARDIAL FUNCTION AND DISEASE — CLINICAL

901-94 The Angiotensin Converting Enzyme DD Genotype is Associated with Preserved Right Ventricular Function in Patients with Severe Primary Pulmonary Hypertension

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A polymorphic marker within the ACE gene has been found to correlate with circulating and tissue ACE activities and with the incidence of severe pulmonary hypertension (Abraham et al, JACC 1994; 23: 177A). While the association of the ACE DD genotype and pulmonary hypertension suggests

a role for angiotensin II (Ang II) in the pulmonary vasoconstriction and pulmonary vascular smooth muscle proliferation characteristic of this disorder, we hypothesize a compensatory role for Ang II in the maintenance of right ventricular (RV) function in such patients. We evaluated the frequency of the ACE DD genotype in 55 patients with severe primary pulmonary hypertension (PPH) and compared clinical severity and right heart hemodynamics at the time of presentation in 20 of these patients stratified on the basiw of their ACE genotype (DD vs non-DD, n = 10 in each group). The incidence of the ACE DD genotype was 49% in the PPH patients compared to 23% in a control population (n = 89, p = 0.0009). Mean ± SEM right heart hemodynamics, echocardiographic RV internal dimensions (RVID) and NYHA classifications for the 2 groups are shown below:

	DD	Non-DD	p value
Mean PA Pressure (mmHg)	52 ± 4	53 ± 3	0.84
PCWP (mmHg)	5 ± 1	6 ± 1	0.59
Cardiac Output (L/min)	5.12 ± 0.43	2.65 ± 0.21	0.00007
PVR (Wood Units)	10.0 ± 1.3	19.3 ± 2.4	0.004
RA Pressure (mmHg)	5 ± 1	10 ± 2	0.08
RVID (cm)	3.1 ± 0.3	3.7 ± 0.2	0.08
NYHA Class	2.2 ± 0.3	3.3 ± 0.2	0.02

Significantly, the duration of symptoms attributable to PPH was not different between the DD and non-DD groups (35 ± 19 vs 22 ± 6 months, p = 0.58). *Conclusion:* The ACE DD genotype is associated with preserved RV function in PPH patients, supporting a compensatory myocardial or inotropic role for Ang II in PPH.

901-95 Stress-induced Subendocardial Underperfusion: A Potential Mechanism of Ischemia in Hypertrophic Cardiomyopathy (HCM)

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Myocardial ischaemia is known to occur in patients with HCM, despite angiographically normal coronaries. However, the precise mechanism for this phenomenon is unknown. Preliminary work with positron emission tomography (PET) has demonstrated selective subendocardial underperfusion during stress in some patients with very thick interventricular septa. To investigate this further, we measured regional myocardial blood flow [MBF (ml/min/g)], at baseline and following infusion of dipyridamole (Dip, 0.56 mg/kg over 4 minutes), using $H_2{}^{15}O$ or $^{13}NH_3$ and PET in 22 patients with HCM, mean age 39 ± 9 years. The thickness of the interventricular septum and the left ventricular free wall were 26 ± 5 and 15 ± 5 mm respectively. Values of MBF were calculated in the subendocardial (endo), and subepicardial (epi) regions of the interventricular septum. Coronary vasodilator reserve (CVR) was calculated as Dip/baseline MBF. *Results:* At baseline endo-MBF was 0.87 ± 0.36 and epi-MBF 0.80 ± 0.34 (p = NS), resulting in an endo/epi flow ratio of 1.09 ± 0.28. Following Dip, endo-MBF was 1.13 ± 0.43 and epi-MBF 1.44 ± 0.44, resulting in an endo/epi flow ratio of 0.80 ± 0.22 (p < 0.001 vs baseline). In 13/22 patients (59%), the endo/epi ratio decreased to less than 0.80 following Dip (animal data show that normally the endo/epi ratio is close to 1 and ranges between 0.8 and 1.2, both at baseline and during maximal coronary vasodilatation). The CVR was 1.33 ± 0.53 in the endo and 1.95 ± 0.70 in the epi (p < 0.01). A linear relation (R = 0.58, p < 0.01) could be demonstrated between endo-CVR and the endo/epi ratio following Dip. *Conclusions:* 1) Dip-induced subendocardial underperfusion occurs frequently in HCM; 2) This appears to be associated with a more impaired CVR in this layer; 3) Transmural maldistribution of MBF during stress may be a mechanism of ischaemia in these patients despite normal coronaries.

901-96 Long Term Evolution of Left Ventricular Function in Patients with Syndrome X

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The long-term follow up and the evolution of left ventricular function of syndrome X (SX) have not been investigated in large and homogeneous patient populations. We followed the clinical course and the evolution of left ventricular (LV) function in 99 pts (78 women, 21 men; mean age 54.9 ± 7 years) during a mean follow-up of 6.7 ± 4 years. Patients underwent exercise testing and echocardiographic assessment of LV function at study entry and at follow up. All pts had positive exercise tests and 64 had transient ST depression on Holter monitoring. Transient myocardial ischemia was documented in 32% of pts by means other than the ECG. During follow up, no deaths or major cardiac events occurred. Exercise tests were positive at follow-up and no differences in exercise test variables were observed compared with tests at study entry. No changes in global or regional wall motion were observed. LV shortening fraction and diastolic and systolic LV diameters remained unchanged during follow-up (35.4 ± 4% *vs* 35.6 ± 3%, 49.6 ± 3 *vs* 49.4 ± 3 mm, and 32 ± 2 *vs* 31.7 ± 2 respectively). Only 1 pt developed congestive heart failure (LVEF dropped from 57% to 30%). Two patients developed conduction abnormalities and 8 systemic hypertension. During follow up 29 pts were hospitalized for a suspected MI (5 pts) or unstable angina (24 pts). Owing to chest pain 25 pts were severely limited and 7 abandoned work.

Although chest pain in syndrome X seems to be cardiac in origin and the exercise test is positive, an ischemic origin can be demonstrated in only a small proportion of pts. Cardiac mortality was not observed and a decline of LVEF is not a frequent event.

MYOCARDIAL INFARCTION — BASIC

901-97 Stroke and Long-term Anticoagulant Therapy in 3404 Post-Myocardial Infarction Patients

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In a randomized, double-blind, placebo controlled trial (ASPECT) we studied 3404 post-myocardial infarction patients who suffered a stroke during long-term anticoagulant therapy. The duration of treatment ranged from 1 day to six years. Three years following randomization, 2% of the patients on anticoagulant therapy had a stroke compared to 4% in placebo.

The incidence of stroke analyzed on "intention-to-treat" was 0.7 per 100 patient-years in the anticoagulant group and 1.2 per 100 patient-years in placebo, a hazard ratio (HR) of 0.60 with a 95% confidence interval (CI) of 0.40 to 0.90, a 40% reduction in the risk of stroke in the anticoagulated group. A total of 19 intracranial bleeding was observed. The risk of hemorrhages was 8 times greater for anticoagulated patients compared to placebo. Eight of the 17 bleedings were fatal in the anticoagulant group and no fatal hemorrhages occurred in placebo. A total of 15 cerebral infarctions occurred in the anticoagulated group and 43 in placebo. Of the 14 hemorrhagic strokes, 6 were within INR 3.0–4.0 and 8 with an INR > 4.0. Of the 7 non-hemorrhagic strokes, 2 were at INR < 2, 3 within INR 3.0–4.0, 1 at INR > 4.0, and no measurement was available in one patient. The total number of patients who died or were severely disabled as a result of cerebral stroke amounted to 13 in the anticoagulated group, compared to 18 in placebo.

Conclusion: The results of the ASPECT trial indicated that long-term anticoagulant therapy substantially reduced the risk of stroke in post-myocardial infarction patients. The increased risk of bleeding complications associated with anticoagulant therapy was offset by a marked reduction in ischemic events.

901-98 Are Indirect Markers an Accurate Measure of Free Radical Activity Following Primary Angioplasty Reperfusion in Acute Myocardial Infarction?

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Oxygen-derived free radicals (FR) have been found to be important mediators of myocardial reperfusion injury in animal studies. In man, most studies of FR measurement after reperfusion have relied on indirect markers alone. However, their accuracy and relationship to FR's has been controversial. We have therefore used primary PTCA for AMI as a model of acute reperfusion to compare *direct* FR measurement using electron paramagnetic resonance (EPR) spectroscopy and the spin trap agent α-phenyl N-tert butyl nitrone, with two of the most commonly used *indirect* markers. These were: [1] the percentage molar ratio (PMR) of the diene conjugate 9,11-octa-decadieneoic acid to the naturally-occurring isomer 9,12-linoleic acid, and [2] serum malonaldehyde (MDA).

16 patients (mean age: 56.9 yrs, range 47–66), undergoing successful primary PTCA (8 LAD, 1 Intermed, 1 LCx, 6 RCA) of less than 6 h duration (mean 3.55 h, range 2.25–5.0), had venous sampling from the base of the right atrium/coronary sinus before angioplasty (TIMI 0) and at timed intervals up to 24 h after recanalisation (TIMI 3).

Direct FR measurement using EPR showed a biphasic time-course. Relative to the pre-PTCA level, FR's increased sharply after 15 min (P < 0.05) with peak levels at 1½ and 3½ h (P < 0.001). Following a decline to 6 h a late peak was observed at 24 h which may originate from accumulating myocardial leukocyte infiltration. Indirect FR measurement using PMR showed a significant increase between 15 min and 1½ h (P < 0.01) only. MDA levels remained unchanged throughout the study.

These results demonstrate that compared to direct FR measurement using EPR, indirect markers used in this study have limited or no usefulness in assessing FR generation in AMI. Myocardial reperfusion studies in man should ideally use direct methods.