Clinical Features of Mixed Physiology of Constriction and Restriction

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Background: Patients with mixed physiology of constriction and restriction have been reported, but their long-term survival has not been well documented.

Methods: Study subjects consisted of 38 patients (57 ± 14 yrs, 8 female, 30 male) who were diagnosed as having mixed physiology based on echocardiography, MRI (or CT), cardiac catheterization, endomyocardial biopsy and/or surgical findings. We evaluated their echocardiographic, clinical features and calculated Kaplan-Meier survival curve to compare with that in patients with pure constriction.

Results: Prior radiation therapy was the most frequent (50%) cause of mixed physiology followed by coronary artery bypass graft without prior radiation and heart transplantation. The respiratory variation of peak early diastolic transmitral flow velocity was 125.3±93 vs 210.5±123, in patients with sinus rhythm, 18.1% in patients with atrial arrhythmia. Pericardial thickening was localized in 29 patients. At-cause 5-year mortality was 40% and unrelated to age, etiology, left ventricular systolic function and therapeutic course. There was a significant difference between the survival rates in patients with mixed physiology and in 133 patients with pure constriction (Figure).

Conclusions: Because of the high mortality in mixed disease, discrimination of this entity from pure constriction is important. Echocardiography is helpful in noninvasive technique in diagnosis and understanding the physiology of the patients with mixed constriction and restriction.

OCCURRENCE OF CHAGAS’ DISEASE CLONAL T-CELL-REACTOR COMPOSITION IS NOT ASSOCIATED WITH ENTEROVIRAL OR ADENOVIRAL INFECTION IN DILATED CARDIOMYOPATHY: IMPLICATIONS FOR THE PATHOGENESIS OF DILATED CARDIOMYOPATHY

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Background: Autoimmunity, resulting from molecular mimicry between viral and cardiac antigens, is postulated for the pathogenesis of dilated cardiomyopathy (DCM). Autoimmunity targeting distinct antigens evokes expansion of specifically reactive T-cell clones infiltrating the target tissue, which can also result from chronic presentation of foreign (e.g. viral) antigens.

Methods: DNA extracted from explanted DCM hearts (n=17, 1 female; 49±13 years, LVFE: 18±5%) were investigated by a family specific PCR for the VII-VIII-J8 region of the TCR gene and GeneScan analysis for clonal TCR rearrangement. Non-DCM hearts (ischaemic cardiomyopathy: n=2, septic cardiac disease: n=3, donor hearts: n=3) served as controls. The TCR-PCR-products analyzed by high-resolution fragment analysis (GeneScan), displayed a Gaussian-like distribution profiles in polyclonal and single dominant peaks in monoclonal T-cell populations. Clonal TCR-PCR-products were directly sequenced. Enteroviral and adenoviral genome was amplified by PCR.

Results: The GeneScan analysis of the TCR-V9 PCR-products demonstrated a clonal T-cell population in 9/17 (53%) of the DCM hearts. In contrast, exclusively polyclonal composition of the TCR-V7 PCR-products were obtained from the non-DCM hearts. Sequence analysis of the clonal TCR-V9 PCR-products from the n=9 DCM hearts determined V19.01 in n=6 cases (67%), and V19.01, V19.03 and V19.03-3.01 in each of the remaining cases. Clonal TCR-composition was not significantly (p>0.05) associated with PCR amplification with viral genome.

Conclusions: Clonal TCR rearrangement is exclusively present in DCM but not in further cardiomypathies. The clear predominance of V19.01 family T-cell clones in DCM indicates that these TCR clones target specific antigens. Our results are consistent with the autoimmmun hypothesis of DCM, since enterov- or adenoviral persistence are not significantly associated with a specific clonal TCR rearrangement. Eventually, a TCR-based immunotherapy in DCM (e.g. with anti-TCR antibodies or DNA vaccines) might be a feasible therapeutic option in DCM with clonal TCR-composition.

9:00 a.m.

834-C

Impaired Hyperaemic Myocardial Blood Flow Is Related to Systolic Function in Idiopathic Dilated Cardiomyopathy

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Aim: Hyperaemic myocardial blood flow is impaired in patients with idiopathic dilated cardiomyopathy (DCM). The degree of impairment is related to diastolic dysfunction and prognosis. This study was conducted to evaluate the relation between hyperaemic myocardial blood flow and systolic function in patients with DCM.

Materials & Methods: Patients with advanced stage of idiopathic dilated cardiomyopathy (NYHA III or IV, EF<30%) and healthy control subjects were studied. Myocardial blood flow (MBF) was determined by postmission emission tomography (PET) using 15O-labelled water under baseline conditions and during pharmacologically induced stress. MR tissue tagging was performed for quantification of regional myocardial function. End systolic circumferential shortening (ESCB) was calculated using the Harmonic Phase (HARP) method.

Results: Ten patients with DCM (mean age 54±10 years, 5 male) and 7 control subjects (mean age 28±3 years, 6 male) were studied. Mean rest MBF was similar for DCM and controls (0.91±0.33 vs. 0.97±0.21 ml/min/g, respectively, p>NS). Hyperemic MBF and ESCS were reduced in DCM (2.23±1.01 ml/min/g and 6.1±2.4%, respectively) compared to controls (4.09±0.80 ml/min/g and 15.2±2.1%, respectively, p<0.01). There was a significant correlation between stress MBF and ESCS in DCM (r=0.89, p<0.01). No correlation present between rest MBF and systolic function in DCM.

Conclusions: The combination of PET and MRI offers a unique opportunity to quantitatively assess global and regional perfusion function. In patients with advanced stage of DCM, the degree of impaired hyperaemic blood flow is related to systolic dysfunction.

9:15 a.m.

834-D

Coronary Vasoactivity Responses Are Impaired Independent of Nitric Oxide and Endothelial Function in Conscious Dogs With Dilated Cardiomyopathy

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Background: Dilated cardiomyopathy (DCM) has been associated with nitric oxide (NO) deficiency and endothelial dysfunction, resulting in depressed systemic and coronary vasodilator responses to endothelium-dependent challenge. However, it remains controversial as to whether endothelium-independent vasomotor function is preserved in DCM,

oxide and lower vascular smooth muscle response to NO. These alterations may play a role in precipitating and maintaining the progressive damage of myocardial microvasculature and contribute to the development and progression of the Chagasic cardiomyopathy.

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particularly in the coronary circulation. We have shown previously that intrinsic smooth muscle tone in coronary vessels in DCM is depressed, but the functional significance of this observation is as yet unknown.

Methods: We studied the responses of the systemic and coronary circulation to a variety of vasodilators in conscious dogs with pacing-induced DCM (240 min-1, 29±4 days). The dogs received graded IV infusions of the endothelium-dependent acetylcholine (ACH, 0.05-50 CBG responses, C vs DCM: ACH: 22±14% vs 160±11%, NTG: 220±17% vs 138±9%, ADO: 635±74% vs 413±65%, NIC: 388±59% vs 115±23%, ISO: 219±19% vs 87±21%. Peak CVR responses, C vs DCM: ACH: -77±1% vs -69±1%, NTG: -75±1% vs -62±2%, ADO: -88±1% vs -77±3%, NIC: -79±2% vs -63±4%, ISO: -87±2% vs -48±5%). These greater vasodilation responses persisted after controlling for heart rate differences or changes in mean arterial pressure.

Conclusions: In contrast to systemic vasodilator responses, coronary vasodilator responses in DCM is impaired to a multitude of agonists, dependent or independent of NO or second messenger mechanisms. This implies structural or distal signaling defects unique to the coronary vascular smooth muscle in DCM.

9:30 a.m.

834-5 Outcomes of Peripartum Cardiomyopathy in the Current Era of Heart Failure Management
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Background: Patients with peripartum cardiomyopathy (PPC) have a better prognosis than other forms of cardiomyopathy. However, historical studies showed that 40 to 50% of patients with PPC do not have a meaningful recovery or experienced a significant deterioration in their cardiac function. These studies were done before the current era of heart failure management. We report the University of Alabama at Birmingham’s experience with this form of cardiomyopathy.

Methods and Results: Thirty-seven patients were referred to our program with peripartum cardiomyopathy between January 1, 1990 and December 31, 2002. The data was extracted from the clinical charts. The age at diagnosis was 28±6.6 years, and on average patients were 33 days postpartum (range 60 days pre-160 days post-partum). Eighty percent of the patients had a normal mean LV EDD (79±14 mm) and mean LVESD (41±11 mm) at LPEDD (62±8.8 mm, p=0.007). Seventy-two percent of the patients had a significant improvement in the LVEF to >25%, 39% of patients had follow-up echocardiograms in our institution. Overall, the LVEF improved significantly (p=0.007). More importantly, the NYHA class improved in all but the patients who died or were transplanted. Patients were followed for an average of 28 (range 1-94) months. Four patients were transplanted, 1 died and 1 was lost to follow-up. The NYHA class improved significantly (P=0.007). More importantly, the NYHA class improved in all but the patients who died or were transplanted or lost to follow-up. Of the survivors or not transplanted or lost to follow-up, 25/31 (90%) were NYHA class I-II and none was NYHA class IV. Thirty-one patients had follow-up at 41±14 months (P=0.007). These differences do not take account of the fact that because of the greater mortality in severe DCM.

Conclusion: The prognosis of PPC appears to be better than previously reported. Transplantation or more invasive therapies should be reserved for those patients who fail medical therapy.

9:45 a.m.

834-6 Identification of Cardiac Sarcoïdosis From the Patients Presenting as Unexplained Heart Failure and Cardiomyopathies
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Background: Diagnosis of cardiac sarcoidosis (CS) is usually confirmed during the follow-up of extra-cardiac sarcoidosis. However, the diagnosis is often difficult when CS patients show heart failure as the first manifestation without evidence of involvement of other organs because endomyocardial biopsy frequently fails to reveal non-caseating epithelioid granuloma. Majority of these patients are diagnosed as idiopathic dilated cardiomyopathy (DCM). Methods: To characterize CS patients presenting as unexplained heart failure (CS-HF), we reviewed 30 consecutive CS patients diagnosed between 1987 and 2002 and identified 11 CS-HF patients. Clinical findings and outcome of the CS-HF were compared to those of 123 DCM patients diagnosed at the same period. Results: Abnormal accumulation of gallium-67 in the heart or extra-cardiac tissue was the first clue to suspect CS in 7 of the 8 CS-HF who underwent the whole body gallium-67 scan. Granulomas were confirmed from the heart in 5 patients, lymph nodes in 4, skin in 1 and skeletal muscle in 1. Eight CS-HF showed higher incidence of female (70% vs. 22%, p<0.001), complete atrioventricular block (70% vs. 0%, p<0.0001) and sustained ventricular tachycardia (40% vs. 9%, p<0.05), and lower cardiac index (2.0±0.4 mmHg/L/min vs. 2.5±0.5 mmHg/L/min, p<0.05) and left ventricular dimension (58±11 mm vs. 68±8 mm, p=0.05) as compared with DCM patients. During a mean follow-up of 80 months, 6 CS-HF died suddenly or of refractory heart failure. Although 10 of the 11 were treated with corticosteroids, survival rate was significantly worse in CS-HF than DCM (40% vs. 72%, p<0.001).

Conclusions: CS-HF had different clinical features and outcomes as compared with DCM. Understanding the comprehensive examinations including whole body gallium-67 scan and biopsies from the extra-cardiac tissue are useful for the diagnosis of CS patients presenting as unexplained heart failure and cardiomyopathies.

8:45 a.m.

835-2 Carvedilol Better Protects Against Vascular Events Than Metoprolol in Heart Failure: Results From COMET
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Background: In COMET, carvedilol (25 mg bid) was shown to reduce mortality compared to metoprolol (IR 50 mg bid) (512 deaths/1511 versus 600/1518, p=0.0017) in the treatment of heart failure with a mean follow-up of 57.9 months. Adverse events would be expected to reflect this advantageous outcome. The alpha-1 and beta-2-blocking effects of carvedilol, which possibly contributed to its survival advantage, are expected to be reflected in the adverse events profile.

Methods: 3029 patients with left ventricular systolic dysfunction and NYHA class II to IV were randomised to double-blind study therapy. Patients were seen every four months over a period of 47 to 71 months. Adverse events as reported by the investigator were recorded on the case record form and analysed centrally.

Results: Of 1511 patients allocated to carvedilol 93.6% experienced an adverse event and 73.8% a cardiovascular adverse event. Of 1518 patients allocated metoprolol the figures were 95.9% and 75.6%. Adverse event reports of sudden death (8.9% versus 12.1%), myocardial infarction (4.6% versus 6.3%), unstable angina (3.8% versus 5.1%) and stroke (3.5% versus 4.3%) were less common with carvedilol. Heart failure (42.6% versus 44.9%), dyspnoea (9.7% versus 11.2%) and peripheral oedema (2.6% versus 3.7%) occurred less frequently with carvedilol. No consistent differences existed with regard to bradycardia or heart block. Hypotension (14.2% versus 10.5%), dizziness (12.4% versus 11.7%) and syncpe 8.2% versus 6.3% were commoner with carvedilol. Diabetes (11.1% versus 12.5%) and hypokalaemia (2.0% versus 3.2%) were less common with carvedilol. The incidence of bronchospasm (0.7% versus 0.4%) and asthma (0.5% versus 0.3%) was very low in both groups. These differences do not take account of the fact that because of the greater mortality more patients in the carvedilol group were available to experience adverse events.

Conclusion: The lower number of adverse cardiovascular events with carvedilol reflects the beneficial effect on mortality. Metabolic and haemodynamic adverse events are compatible with the known different properties of these two beta-blockers.