1032-121 **Utility of B-Type Natriuretic Peptide Assay in the Assessment of Symptomatic State in Hypertrophic Cardiomyopathy**

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Background. Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disease with a diverse clinical spectrum which often includes functional disability due to progressive heart failure symptoms at any age. Assessment of symptom severity may be highly subjective and encumbered by the heterogenous clinical presentation of HCM. Plasma B-type natriuretic peptide (BNP) has been used widely as an objective marker for the severity of heart failure and clinical outcome predominantly in coronary heart disease with ventricular dilatation and systolic dysfunction. We considered the possibility that BNP would be an accurate and independent predictor of heart failure severity in HCM, a disease characterized by intact ventricular function in the absence of chamber dilatation.
Methods. We prospectively assessed plasma BNP as a quantitative clinical marker of heart failure severity in 107 consecutive HCM patients.
Results. BNP showed a statistically significant relationship to the magnitude of functional limitation assessed by New York Heart Association (NYHA) functional class: I: 136 ± 159 pg/ml; II: 338 ± 439 pg/ml; III/IV: 481 ± 334 pg/ml ($p < 0.001$). Multivariable analysis showed BNP was independently related to NYHA functional class ($p = 0.003$), as well as age ($p = 0.0001$) and left ventricular wall thickness ($p = 0.0001$). BNP power was considerable both in distinguishing patients with and without heart failure symptoms, or for differentiating between no (or only mild) symptoms and severe symptoms (area under receiver opearting curve = 0.75 and 0.83, respectively). A BNP cut-off value ≥ 200 pg/ml was the most reliable predictor of heart failure symptoms with positive and negative predictive values of 65% and 79%, respectively.
Conclusions. Plasma BNP is independently related to the presence and magnitude of heart failure-related symptoms in patients with HCM. The clinical power of BNP as a marker for heart failure in HCM is, however, restricted by the overlap in BNP values between symptom-related subgroups, due largely to the important confounding variables of advancing age and substantial left ventricular wall thickness characteristic of this heterogeneous disease.

1032-122 **Comprehensive Mutational Analysis of Myosin Binding Protein C in 389 Unrelated Patients With Hypertrophic Cardiomyopathy**

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Background: Mutations in myosin binding protein C (MYBPC3) represent the most common genetic cause of hypertrophic cardiomyopathy (HCM). MYBPC3-HCM has been associated with late onset of disease and benign course. Here, we determine the frequency, spectrum, and phenotype associated with MYBPC3-HCM in a cohort of unrelated patients evaluated at a single tertiary outpatient center.
Methods: DNA was obtained from 389 unrelated HCM patients and analyzed for mutations in all 34 protein coding exons of MYBPC3 using polymerase chain reaction, denaturing high performance liquid chromatography, and direct DNA sequencing. Clinical data were extracted from patient records blinded to genotype.
Results: Seventy-six patients (19.5%) were identified with 49 MYBPC3 mutations: 24 missense, 15 frameshift, 6 premature stop, 3 splice-site, and 1 in-frame deletion. Mutation type did not influence the clinical phenotype. Compared to patients without MYBPC3 mutations, patients with MYBPC3-HCM were younger at diagnosis (35.4 ± 15 years vs 42.7 ± 19 years, $p = 0.002$), more often had a family history of HCM (44.7% vs 27.2%, $p = 0.004$), and more often received an ICD (26.3% vs 12.8%, $p = 0.003$). When comparing patients with single MYBPC3 mutations (n=67) to those with single mutations involving either the beta myosin heavy chain (MYH7) or the light chains comprising the thick filament (n=60), there was no difference in age, symptoms at presentation, or degree of hypertrophy. However, patients with MYBPC3 mutations were less likely to undergo surgical myectomy than patients with thick filament mutations (34% vs 55%, $p = 0.02$).
Conclusion: This study represents a comprehensive mutational analysis of the most common HCM-causing gene, MYBPC3, in the largest cohort of unrelated patients. Nearly 1 in 5 patients presenting to this tertiary HCM center had MYBPC3 mutations. Contrary to genotype-phenotype correlations derived from family studies, unrelated patients with MYBPC3-HCM were diagnosed at a younger age than those patients with no MYBPC3 mutation. Moreover, the only difference in phenotypic expression between MYBPC3-HCM and thick filament-HCM was likelihood of surgical myectomy.

1032-123 **Mechanisms for Left Ventricular Outflow Tract Obstruction After Initial Septal Myectomy for Obstructive Hypertrophic Cardiomyopathy**

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Objectives; Septal myectomy provides excellent outcomes for most patients with severe obstructive hypertrophic cardiomyopathy (HCM). However, in a few patients, left ventricular outflow tract obstruction (LVOTO) may recur or persist after myectomy, requiring repeat myectomy. We reviewed this subset to assess the mechanisms for recurrence or persistence of LVOTO.
Methods; From 1975 to July 2003, 610 septal myectomies were performed by the authors for obstructive HCM; 13 of these were repeat myectomies for recurrent or persistent LVOTO after myectomies performed at our institution (n=6) or elsewhere (n=7). Six patients were age 16 years or younger at the reoperation. The mean interval between initial myectomy and repeat myectomy was 5.0+/-3.7 years.
Results; At reoperation, mechanisms for obstruction included septal hypertrophy at mid-ventricular level (n=8), anomalous papillary muscles (n=3), and incomplete subaortic resection at the initial operation (n=11). Mean intraoperative peak systolic pressure gradients decreased from 68+/-34 to 6.9+/-5.1 mmHg after repeat myectomy. No mitral valve replacement was performed. An iatrogenic ventricular septal defect in one patient was successfully repaired. Mean follow-up was 5.8 years. There were no early deaths; one patient died 11 years after repeat myectomy at age 81. All surviving patients were in NYHA functional class I or II and free of significant LVOTO.
Conclusions; Dynamic LVOTO may recur or persist after classic septal myectomy in a small number of patients. Repeat myectomy can be performed with excellent outcomes. Need for reoperation may be reduced with current surgical approaches which include a more extended resection of the mid-ventricular septum, relief of papillary muscle anomalies, and routine use of intraoperative transesophageal echocardiography.

1032-124 **Coronary Microvascular Dysfunction and Long-Term Left Ventricular Remodeling in Hypertrophic Cardiomyopathy**

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Background. Left ventricular (LV) remodeling in adult patients with hypertrophic cardiomyopathy (HCM) is characterized by cavity enlargement, systolic dysfunction and wall thinning, occasionally progressing to overt systolic heart failure. To ascertain whether LV remodeling is related to coronary microvascular dysfunction, we assessed the relationship between absolute myocardial blood flow (MBF) and long-term echocardiographic changes in HCM patients. Methods. Fifty-one HCM patients (NYHA class I-II) were followed for 8.1±2.1 years following a baseline echocardiogram and PET for measurement of resting and dypiridamole MBF (Dip-MBF). Twelve controls were assessed for comparison. LV remodeling was defined by >1 of three previously published criteria: end-diastolic dimension >52 mm, fractional shortening 5 mm. The "End-stage" phase was defined as LV remodeling associated with clinical deterioration to NYHA class III-IV. Results. Resting MBF did not differ between patients and controls (0.84±0.31 vs. 1.00±0.23 ml/min/g; p=0.10) whereas Dip-MBF was severely blunted in patients (1.50±0.69 versus 2.71±0.94 ml/min/g; p<0.001). At the end of follow-up, 18 patients (35%), showed evidence of LV remodeling, including 7 in end-stage (14%; with 2 heart failure deaths and 2 patients evaluated for transplant). LV remodeling occurred 2.5-fold more frequently in the lowest tertile of Dip-MBF (0.59-1.11 ml/min/g) as compared to each other tertile (p=0.09 at survival analysis); moreover, 6 out of 7 end-stage patients were in this lowest tertile (p=0.005). At multivariate analysis, the two independent predictors of end-stage progression were Dip-MBF in the lowest tertile (OR 17.3, 95% CI: 1.7-177.1; p=0.016) and end-diastolic LV dimensions >45 mm (OR 13.5, 95% CI: 1.3-140.7; p=0.029). Conclusions. Severe microvascular dysfunction was strongly associated with long-term end stage progression in HCM patients, particularly when associated with initial evidence of LV dilatation. Conversely, patients with milder degrees of LV remodeling showed a weaker association with Dip-MBF impairment, suggesting a role for other pathophysiological triggers.

1032-125 **Electrocardiographic Pattern of Giant Negative T Wave in Hypertrophic Cardiomyopathy: Is It a Specific Feature of "Apical" Hypertrophic Cardiomyopathy ?**

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Background: Striking electrocardiographic (ECG) pattern of "giant negative T wave (GNT)" defined as >10mm deep in the left precordial leads was reported as a hallmark of apical form of hypertrophic cardiomyopathy (HCM), in which hypertrophy is confined to the most distal region of the left ventricular (LV) apex. However, the prevalence of GNT in apical HCM varies in Japan and Western countries. It can also be found in patients with typical HCM with asymmetric septal hypertrophy (ASH).
Purpose: To clarify the morphological characteristics of HCM patients with GNT, and to elucidate the relationship between apical HCM and GNT.
Methods and Results: Among 147 HCM patients, we identified 43 patients with GNT. Echocardiography revealed three distinct morphologic pattern of LV hypertrophy. (1) Hypertrophy is confined to the apex below papillary muscle level. (apical HCM: pure form) (n=14) (2) Apical hypertrophy is extended to ventricular septum, without basal septal hypertrophy. (mixed form) (n=5) (3) Typical HCM presenting ASH. (ASH) (n=24) Comparison among these three groups is shown on the table. The prevalence of GNT was 64% (14/22) in pure apical HCM, and 23% (29/125) in HCM after excluding apical HCM of pure form.
Conclusion: HCM patients with ECG pattern of GNT consist of morphologically heterogeneous subgroups (pure apical HCM, mixed form, ASH), and GNT is not a specific feature of pure apical HCM. Patients with apical HCM may have milder clinical presentation, different from those with mixed form or ASH with GNT.