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 heterogeneous 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 disorder characterized by distinct ventricular functional abnormalities due to 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 impairment among patients with NYHA functional class (r = 0.136 vs. 0.359; p < 0.002). Multivariable analysis showed BNP was independently related to NYHA functional class (p = 0.003), as well as age (p = 0.001). Left ventricular wall thickness (p = 0.001). BNP power was considering high-density lipoprotein cholesterol, and direct heart failure symptoms, or for differentiating between no (or only mild) symptoms and severe symptoms (area under receiver operating curve = 0.75 and 0.83, respectively). A BNP cut-off value > 70 pg/ml showed BNP was independently related to NYHA functional class (p = 0.003), as well as age (p = 0.001) and left ventricular wall thickness (p = 0.001). BNP power was considering high-density lipoprotein cholesterol, and direct heart failure symptoms, or for differentiating between no (or only mild) symptoms and severe symptoms (area under receiver operating 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 66% 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 symptomatic-related subgroups, due largely to the important confounding variables of advancing age and substantial left ventricular wall thickness characteristic of this heterogeneous disease.

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, 1 splice-site, and 1 in-frame deletion. Mutations in MYBPC3 were present in 18 patients (4.6%) of 389 unrelated HCM patients. MYBPC3 mutations were present in 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. 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 = 0.001). Among patients with MYBPC3 mutations, only 25% underwent reoperation for obstructive LVOTO. MYBPC3 mutation carriers were less likely to undergo surgical myectomy than patients with thick filament mutations (34% vs 55%, p = 0.02).

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 angiographic 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 end-diastolic and systolic 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 0.50, and the “End-stage” phase was defined as LV remodeling associated with clinical deterioration to NYHA class III-IV. Results. Resting MBF and MBF during dipyridamole infusion (0.88±0.31 vs. 1.00±0.23 ml/min/g; p<0.01) 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 on transplantation). 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 17.7; 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 lower degrees of LV remodeling showed a weaker association with Dip-MBF impairment, suggesting a role for other pathophysiological triggers.

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 >10 mm deep in the left precordial leads was reported as a hallmark of hypertrophic cardiomyopathy (HCM). However, whether the GNT is a specific feature in apical form of hypertrophic cardiomyopathy (HCM), in which hypertrophy is confined to the inferolateral wall, remains elusive. We evaluated the clinical significance of GNT in HCM patients presenting with apical hypertrophy.

Methods and Results: Among 147 HCM patients, we identified 43 patients with GNT. Three distinct ECG patterns of HCM were found: 32 patients fit ASH (apical hypertrophy with GNT), 8 patients fit pure apical form, and 3 patients fit mixed form of HCM. GNT was more frequently observed in patients with ASH (37% vs. 4% and 3%, respectively) whereas Dip-MBF was severely blunted in patients (1.50±0.69 vs. 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 on transplantation). 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 17.7; 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 lower degrees of LV remodeling showed a weaker association with Dip-MBF impairment, suggesting a role for other pathophysiological triggers.