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B-Type Natriuretic Peptide and Survival in Hypertrophic Cardiomyopathy

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Objectives The aim of this study was to determine the relationship between B-type natriuretic peptide (BNP) and survival in patients with hypertrophic cardiomyopathy.

Background Natriuretic peptides are released in response to neurohormonal activation, myocardial stretch, and wall tension and therefore reflect hemodynamic derangements.

Methods A total of 772 patients with hypertrophic cardiomyopathy had BNP obtained in conjunction with echocardiography and clinical evaluation, inclusive of cardiopulmonary exercise evaluation in 429 patients (56%).

Results Survival free of all-cause mortality was lower across increasing levels of BNP (log-rank test, $p = 0.002$). Three-year survival by tertile was 99.2% (95% confidence interval: 94.3% to 99.9%; BNP level $\leq$98 pg/ml), 94.8% (95% confidence interval: 88.2% to 97.8%; BNP level, >98 to <298 pg/ml), and 89.9% (95% confidence interval: 82.0% to 94.5%; BNP level $\geq$298 pg/ml). Compared with patients in the first tertile, the hazard ratios for death in the second and third tertiles were 4.88 ($p = 0.006$) and 6.98 ($p = 0.0003$), respectively. This relationship persisted in patients without resting obstructive physiology ($n = 497$, $p = 0.01$). BNP levels were related to New York Heart Association functional status ($p < 0.0001$) and the subsequent need for septal reduction therapy in follow-up ($p = 0.04$).

Conclusions In this large cohort of patients with hypertrophic cardiomyopathy, BNP was an independent predictor of morbidity and mortality. (J Am Coll Cardiol 2013;61:2456–60) © 2013 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is characterized by cardiomyocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis, resulting in regional and global abnormal generation of contractile force and hindered relaxation (1). Although the vast majority of patients have normal longevity, progressive and drug-refractory heart failure can develop in others. Given this varied clinical spectrum, symptom assessment and prognostication can be challenging in these patients.

B-type natriuretic peptide (BNP) is a biologically active peptide synthesized and released primarily from cardiac myocytes as a response to neurohormonal activation, myocardial stretch, and wall tension (2). Circulating plasma BNP levels are elevated in numerous cardiac pathologies in the presence of hemodynamic overload and increased cardiac fibrosis (3–5). The use of natriuretic peptides is a well-established tool in the diagnosis, prognosis, and management of patients with systolic dysfunction (6,7). However, there is a paucity of data on the clinical significance, particularly with regard to survival, of these biomarkers in patients with HCM (8).

Accordingly, the objective of the present investigation was to determine the prognostic utility of BNP in patients with HCM.

Methods

Patient selection. The study population consisted of 772 patients with HCM evaluated at the Mayo Clinic (Rochester, Minnesota) between January 2006 and May 2009. The diagnosis of HCM was based on the presence of myocardial hypertrophy in the absence of local or systemic etiologies (9,10). All patients had a plasma BNP level obtained for clinical purposes at the time of evaluation. Plasma BNP was measured by fluorescence immunoassay (Biosite Diagnostics [now Alere, Inc.], San Diego, California) using a Beckman Coulter DXI 800 instrument. When possible, BNP levels were processed immediately after phlebotomy. Otherwise, samples were spun down and plasma frozen until the sample was analyzed (no more than 3 days). The precision, sensitivity, and stability of this particular BNP assay were previously described (11). Comprehensive resting 2-dimensional transthoracic echocardiography was performed in all patients, as previously described (12).

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Symptom-limited graded exercise testing was performed using a motor-driven treadmill (Quinton, Seattle, Washington) with an accelerated Naughton protocol. Continuous electrocardiographic monitoring (Marquette Electronics, Milwaukee, Wisconsin) and breath-to-breath metabolic measurement (Medical Graphics, St. Paul, Minnesota) were used, as previously described (13). All patients provided consent for use of their medical records for research purposes in accordance with Minnesota law and an institutional review board–approved study.

Statistical analysis. Continuous variables are expressed as mean ± SD; BNP and left ventricular (LV) outflow tract were not normally distributed and are reported as median with interquartile range. Correlations of continuous variables were examined using Spearman rank correlation coefficients. Comparison of continuous variables was performed using the Wilcoxon rank sum test. Wilcoxon signed rank tests were used for comparison of repeated measures of BNP. For comparisons of contingency variables, the Fisher exact test was used. For multivariate modeling, BNP was transformed using log(BNP). Multivariable linear regression modeling with mixed-direction stepwise selection method (p value threshold to enter = 0.15; to leave, 0.05) was used to determine clinical predictors of log(BNP). Survival free of the study endpoints (all-cause mortality and combined endpoint of mortality and occurrence of septal reduction therapy [SRT]) were assessed using Kaplan-Meier survival curves, with log-rank test p values reported. Cox proportional hazard analysis was performed to determine the relationship of BNP with study endpoints.

Table 1 Baseline Characteristics

Age, yrs	52 ± 16
Male	477 (62)
NYHA functional class	
I	238 (31)
II	230 (30)
III–IV	304 (39)
Presyncope	391 (51)
Syncope	151 (20)
Implantable cardioverter-defibrillator	174 (23)
Family history of HCM	253 (33)
Family history of SCD	178 (23)
Previous myectomy	97 (13)
Previous septal ablation	40 (5)
Medications	
Beta-receptor antagonist	641 (83)
Calcium channel blocker	339 (44)
ACE inhibitor/ARB	226 (29)
Amiodarone	80 (10)
Disopyramide	79 (10)
Systolic blood pressure, mm Hg	119 ± 17
Diastolic blood pressure, mm Hg	71 ± 11
Heart rate, beats/min	64 ± 11
Body mass index, kg/m^2	30.0 ± 6.2

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association; SCD = sudden cardiac death.

Results

Study population. Baseline characteristics of the study population are listed in Tables 1 and 2. Mean age was 52 ± 16 years (62% male). The vast majority had mild or no symptoms (61% were New York Heart Association [NYHA] functional class I or II). Median BNP for the entire study population was 177.5 (interquartile range [IQR]: 71 to 395) pg/ml. BNP was associated with multiple clinical and echocardiographic parameters, although the correlations with these clinical variables were modest (Spearman ρ range, −0.02 to 0.45) (Table 3). Multivariate linear regression modeling of log(BNP) (2.2 ± 0.5 log [pg/ml]) using variables from Table 3 revealed multiple significant covariates (model R = 0.69): septal thickness ($p < 0.0001$), medial E/e′ ($p = 0.0001$), resting LV outflow tract gradient ($p < 0.0001$), right ventricular systolic pressure ($p = 0.0006$), ejection fraction ($p = 0.0008$), moderate or greater mitral regurgitation ($p = 0.005$), body mass index ($p = 0.006$), age ($p = 0.004$), E/A (peak early diastolic velocity/peak late diastolic velocity) ratio ($p = 0.003$), and left atrial volume index ($p = 0.02$).

Cardiopulmonary exercise was performed in 429 patients (Table 4). BNP was related to both peak oxygen consumption (Vo_2) (Spearman $\rho = -0.44$, $p < 0.0001$) and percent predicted Vo_2 achieved during cardiopulmonary exercise testing (Spearman $\rho = -0.33$, $p < 0.0001$). Of 264 patients with mild or no symptoms (NYHA functional class I or II) who underwent exercise testing, the BNP level was

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CI = confidence interval
HCM = hypertrophic cardiomyopathy
IQR = interquartile range
LV = left ventricular
SRT = septal reduction therapy
Vo_2 = oxygen consumption

Table 2 Echocardiography Data

LV outflow tract gradient, mm Hg	13 (0–49)
Resting obstruction, >30 mm Hg	275 (36)
LV ejection fraction, %	68 ± 8
LV ejection fraction <50%	19 (2)
LV end-diastolic dimension, mm	46 ± 6
Anteroseptal wall thickness, mm	18 ± 6
Posterior wall thickness, mm	13 ± 3
Moderate or severe mitral regurgitation	101 (13)
Estimated right ventricular systolic pressure, mm Hg	35 ± 11
Mitral E velocity, cm/s	0.8 ± 0.3
Mitral A velocity, cm/s	0.7 ± 0.3
E/A ratio	1.4 ± 0.7
Medial e′, cm/s	0.06 ± 0.02
Lateral e′, cm/s	0.08 ± 0.03
Medial E/e′ ratio	17.3 ± 8.3
Lateral E/e′ ratio	12.5 ± 6.7
Left atrial volume index, cm^3/m^3	47 ± 19
Index >40 cm^3/m^3	424 (55)

Values are median (interquartile range), n (%), or mean ± SD.
A = peak late diastolic velocity; E = peak early diastolic velocity; LV = left ventricular; Medial e′ and lateral e′ = annular tissue Doppler signals.

JACC Vol. 61, No. 24, 2013
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Table 3 Relationship of B-Type Natriuretic Peptide to Clinical and Echocardiographic Variables

Variable	Spearman ρ	p Value
Age, yrs	0.12	0.07
Body mass index, kg/m^2	−0.13	0.003
NYHA functional classes III–IV	—	<0.0001
Systolic blood pressure, mm Hg	−0.14	0.003
LV outflow tract gradient, mm Hg	0.26	<0.0001
Resting obstruction	—	<0.0001
Moderate or severe mitral regurgitation	—	<0.0001
LV ejection fraction, %	−0.02	0.0002
Ejection fraction <50%	—	<0.0001
LV end-diastolic dimension, mm	−0.14	0.002
Anteroseptal wall thickness, mm	0.33	<0.0001
Posterior wall thickness, mm	0.17	<0.0001
Estimated right ventricular systolic pressure, mm Hg	0.44	<0.0001
E/A ratio	0.18	<0.0001
Medial E/e′ ratio	0.44	<0.0001
Lateral E/e′ ratio	0.34	<0.0001
Left atrial volume index, cm^3/m^3	0.45	<0.0001

Correlations of continuous variables performed with simple linear regression analysis; Wilcoxon signed-rank tests were used for comparison of B-type natriuretic peptide and nominal variables. Abbreviations as in Tables 1 and 2.

significantly higher in minimally symptomatic patients with a low percent predicted Vo_2 (<80%; n = 185) compared with those with a percent predicted Vo_2 ≥80% (n = 89) (154 [IQR: 57.5 to 365.5] pg/ml vs. 97 [IQR: 43 to 239] pg/ml; Wilcoxon p = 0.04).

Survival. Overall, 30 patients died in follow-up (mean follow-up, 1.7 ± 1.9 years). Patients who died had a higher BNP level than survivors (288.5 [IQR: 214 to 573.8] pg/ml vs. 168.5 [IQR: 68.8 to 387.3] pg/ml; Wilcoxon p = 0.002). Survival free of all-cause mortality was lower with increasing tertiles of BNP (log-rank p = 0.002) (Fig. 1A). Three-year survival by tertile was 99.2% (95% confidence interval [CI]: 94.3% to 99.9%), 94.8% (95% CI: 88.2% to 97.8%), and 89.9% (95% CI: 82.0% to 94.5%). Compared with patients in the first tertile, the hazard ratios for death in the second and third tertiles were 4.88 (p = 0.006) and 6.98 (p = 0.0003), respectively. BNP also was a significant predictor of death in patients without obstructive physiology at rest (n = 497, p = 0.01).

Of the 30 deaths, the cause of death was available for 14 (47%). Five of 14 patients died of noncardiac causes, 4 (29%) had sudden cardiac death, 4 (29%) had a cerebrovascular accident, and 1 (7%) died secondary to a heart failure exacerbation. The incidence per 100 person-year follow-up of all-cause mortality was 2.29 (95% CI: 1.47 to 3.52). For the combined endpoint of sudden cardiac death and unknown cause of death, the incidence per 100 person-year follow-up was 1.45 (95% CI: 0.80 to 2.43).

Table 4 Cardiopulmonary Exercise Data

Exercise capacity, METs	7.3 ± 2.7
Functional aerobic capacity, %	70.2 ± 20.8
Peak double product, beats/min × mm Hg	20,218 ± 7,107
Peak Vo_2, ml/kg/min	20.7 ± 7.2
Vo_2 predicted, %	65.5 ± 19.3

Values are mean ± SD. Cardiopulmonary exercise performed in 429 patients (56%). METs = metabolic equivalents; Vo_2 = oxygen consumption.

Septal reduction therapy. Overall, 471 patients had no history of SRT and no planned surgical procedures within 30 days of biomarker assessment. Of these 471 patients, there were 16 deaths and 69 patients who later underwent SRT in follow-up (66 myectomy, 3 alcohol septal ablation). Patients who later required SRT had a significantly higher BNP at the time of initial assessment (273 [IQR: 129 to 418.5] pg/ml vs. 138.5 [IQR: 50.8 to 343] pg/ml, Wilcoxon p = 0.0002). Increasing tertiles of BNP were associated with lower survival free of need for SRT (3-year Kaplan-Meier estimates by tertile: 88.6% [95% CI: 81.2% to 93.3%], 74.2% [95% CI: 63.9% to 82.3%], and 67.8% [95% CI: 57.5% to 76.7%]; log-rank p = 0.001) (Fig. 1B), and lower survival free of the combined endpoint of death or need for SRT (3-year Kaplan-Meier estimates by tertile: 87.6% [95% CI: 80.0% to 92.6%], 71.6% [95% CI: 61.1% to 80.2%], and 60.9% [95% CI: 50.4% to 70.6%]; log-rank p < 0.0001) (Fig. 1C). Compared with patients in the first tertile, the hazard ratios for death or need for SRT in the second and third tertiles were 2.56 (p = 0.002) and 3.89 (p < 0.0001), respectively. Of note, biomarker ascertainment before and after SRT was performed in 76 patients, with post-procedural BNP assessed 378 days (IQR: 226 to 522 days) after SRT. BNP significantly decreased from 234 pg/ml (IQR: 123 to 507.8 pg/ml) to 151 pg/ml (IQR: 92.3 to 313 pg/ml) in these patients (Wilcoxon p = 0.009).

Discussion

The present investigation is the largest longitudinal study of BNP in patients with HCM. We demonstrate that increases in BNP are associated with adverse survival and a greater need for subsequent SRT. These data demonstrate the potential clinical utility of BNP in HCM and suggest that these biomarkers may be used to help with prognostication of these patients.

Studies of BNP in HCM to date have largely focused on correlation of BNP with echocardiographic parameters or functional class (14–20). Our findings (Table 3) corroborate these smaller studies. However, the prognostic impact of BNP on survival in HCM remains poorly studied, likely given mortality rates similar to those of the general U.S. adult population for all causes (1). Our large cohort of patients with HCM shows that BNP is an independent predictor of survival, even in patients without severe obstruction, and allows further prognostication during assessment of patients with HCM.

Studies assessing BNP and cardiopulmonary exercise in HCM have presented mixed results (15,16,21,22). We present the largest analysis to date of cardiopulmonary exercise data and BNP with HCM and demonstrate significant correlation of both peak Vo_2 and the percent

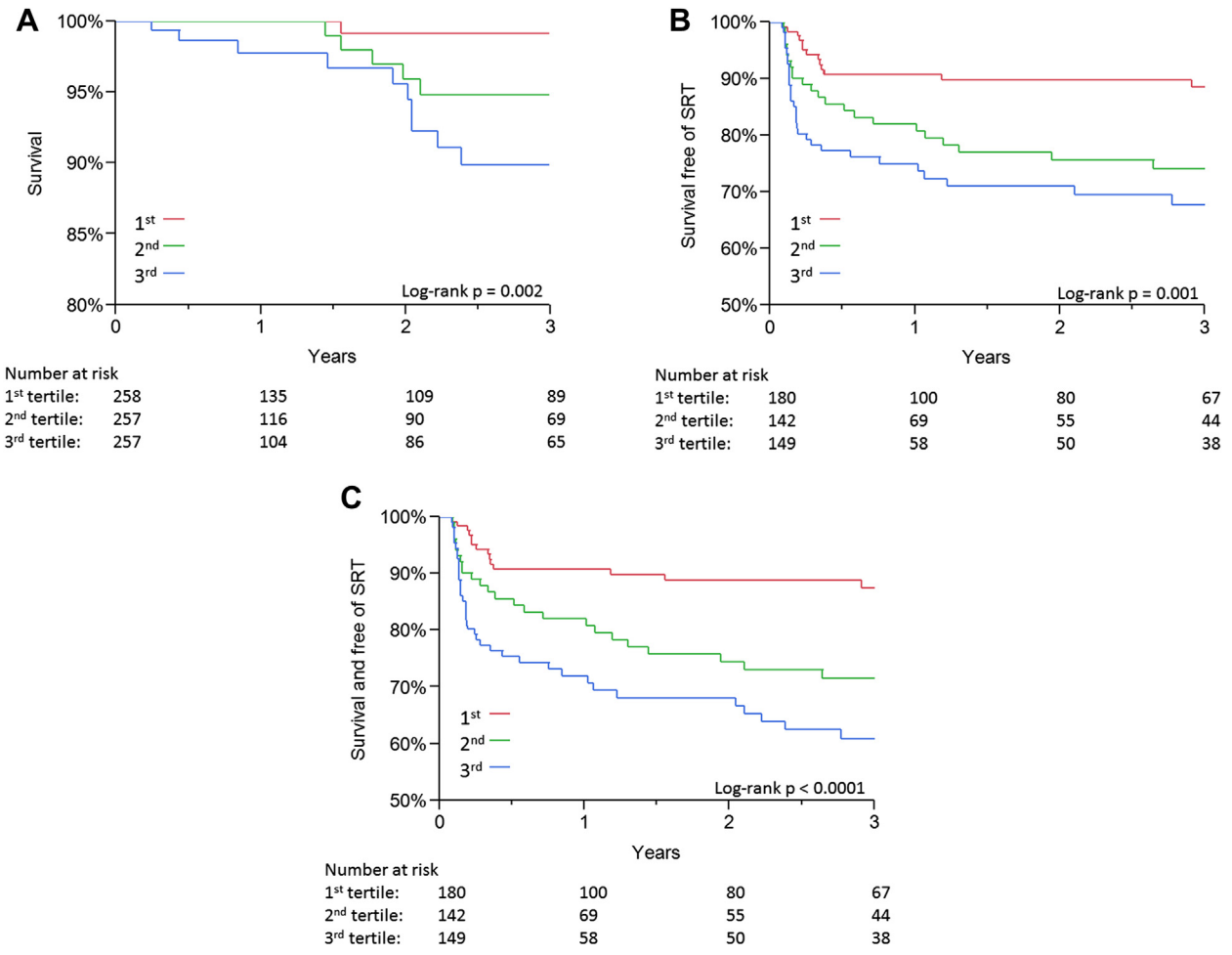

Figure 1 **B-Type Natriuretic Peptide and Survival**

Increasing tertiles of B-type natriuretic peptide were associated with higher mortality (log-rank p = 0.002) **(A)**, greater risk of future septal reduction therapy (SRT) (log-rank p = 0.001) **(B)**, and the combined endpoint of death or need for subsequent SRT (log-rank p < 0.0001) **(C)**.

predicted Vo_2. Furthermore, BNP was significantly increased in patients with poor performance on cardiopulmonary exercise tolerance despite minimal symptoms. Assessment of BNP may provide insight into significant hemodynamic perturbations requiring further scrutiny, regardless of symptom status.

Hemodynamics in HCM are characteristically labile, particularly LV outflow tract obstruction (23,24). Increases in BNP reflect a common end pathway to fluctuating hemodynamic strain. As such, BNP provides insight into the hemodynamic burden on cardiac chambers and the associated adverse ventricular remodeling. Our data reveal a significant decrease in BNP after surgical relief of obstruction. The impact of this change on long-term prognosis remains unclear and requires further study.

Study limitations. The present study is a retrospective analysis, with known inherent limitations, including selection bias. Of note, the majority of the patients were minimally symptomatic or asymptomatic (61% NYHA functional class I or II). Although our study represents the largest longitudinal study of BNP in HCM, the overall mortality rate was only 2.3% per year, and the cause of death could not be determined in a number of patients. Thus, our ability of BNP to predict HCM-related death was limited. Nevertheless, there was a clear relationship between BNP and survival free of all-cause mortality, a hard endpoint in previous HCM publications (25,26).

Conclusions

The present investigation provides insight into the clinical applicability of BNP in a large population with HCM. Increases in BNP have the potential to identify poor cardiopulmonary exercise tolerance in minimally symptomatic patients and help to identify nonobstructive patients with higher mortality. Routine assessment of natriuretic

peptides may be useful in minimally symptomatic patients for prognostic stratification. Given the diverse range of clinical phenotypes associated with HCM, our findings suggest that BNP may have incremental benefit for the clinical evaluation and prognostication of these patients.

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REFERENCES

1. Ommen SR, Nishimura RA. Hypertrophic cardiomyopathy. Curr Probl Cardiol 2004;29:239–91.
2. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004;6:257–60.
3. Gerber IL, Stewart RA, Legget ME, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation 2003;107:1884–90.
4. Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. J Am Coll Cardiol 2003;41:1264–72.
5. Rossi A, Enriquez-Sarano M, Burnett JC Jr., Lerman A, Abel MD, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. J Am Coll Cardiol 2000;35:1256–62.
6. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
7. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126–30.
8. Mutlu B, Bayrak F, Kahveci G, Degertekin M, Eroglu E, Basaran Y. Usefulness of N-terminal pro-B-type natriuretic peptide to predict clinical course in patients with hypertrophic cardiomyopathy. Am J Cardiol 2006;98:1504–6.
9. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. Circulation 1996;93:841–2.
10. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: a discussion of nomenclature. Am J Cardiol 1979;43:1242–4.
11. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002;39:202–9.
12. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation 2007;116:2702–8.
13. Daida H, Allison TG, Squires RW, Miller TD, Gau GT. Peak exercise blood pressure stratified by age and gender in apparently healthy subjects. Mayo Clin Proc 1996;71:445–52.
14. Arteaga E, Araujo AQ, Buck P, Ianni BM, Rabello R, Mady C. Plasma amino-terminal pro-B-type natriuretic peptide quantification in hypertrophic cardiomyopathy. Am Heart J 2005;150:1228–32.
15. Binder J, Ommen SR, Chen HH, Ackerman MJ, Tajik AJ, Jaffe AS. Usefulness of brain natriuretic peptide levels in the clinical evaluation of patients with hypertrophic cardiomyopathy. Am J Cardiol 2007;100:712–4.
16. Kaski JP, Tome-Esteban MT, Mead-Regan S, et al. B-type natriuretic peptide predicts disease severity in children with hypertrophic cardiomyopathy. Heart 2008;94:1307–11.
17. Kim SW, Park SW, Lim SH, et al. Amount of left ventricular hypertrophy determines the plasma N-terminal pro-brain natriuretic peptide level in patients with hypertrophic cardiomyopathy and normal left ventricular ejection fraction. Clin Cardiol 2006;29:155–60.
18. Ogino K, Ogura K, Kinugawa T, et al. Neurohumoral profiles in patients with hypertrophic cardiomyopathy: differences to hypertensive left ventricular hypertrophy. Circ J 2004;68:444–50.
19. Panou FK, Kotseroglou VK, Lakoumentas JA, et al. Significance of brain natriuretic peptide in the evaluation of symptoms and the degree of left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy. Hellenic J Cardiol 2006;47:344–51.
20. Maron BJ, Tholakanahalli VN, Zenovich AG, et al. Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. Circulation 2004;109:984–9.
21. Briguori C, Betocchi S, Manganelli F, et al. Determinants and clinical significance of natriuretic peptides and hypertrophic cardiomyopathy. Eur Heart J 2001;22:1328–36.
22. Kitaoka H, Kubo T, Okawa M, et al. Utility of tissue Doppler imaging to predict exercise capacity in hypertrophic cardiomyopathy: comparison with B-type natriuretic peptide. J Cardiol 2009;53:361–7.
23. Geske JB, Sorajja P, Ommen SR, Nishimura RA. Variability of left ventricular outflow tract gradient during cardiac catheterization in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol Intv 2011;4:704–9.
24. Geske JB, Sorajja P, Ommen SR, Nishimura RA. Left ventricular outflow tract gradient variability in hypertrophic cardiomyopathy. Clin Cardiol 2009;32:397–402.
25. Sorajja P, Nishimura RA, Gersh BJ, et al. Outcome of mildly symptomatic or asymptomatic obstructive hypertrophic cardiomyopathy: a long-term follow-up study. J Am Coll Cardiol 2009;54:234–41.
26. Sorajja P, Ommen SR, Holmes DR Jr., et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2012;126:2374–80.

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