Clin. Cardiol. 30, 245–250 (2007)

Troponin, B-Type Natriuretic Peptides and Outcomes in Severe Heart Failure: Differences Between Ischemic and Dilated Cardiomyopathies

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Summary

Background: Ischemic (ISCM) and idiopathic dilated (IDCM) cardiomyopathies have different responses to therapy and outcomes. Both may demonstrate elevations in troponin and B-type natriuretic peptides, but biomarker levels have not been reported to differ as a function of the etiology of heart failure (HF). Accordingly, we compared these biomarkers in patients with chronic HF.

Hypothesis: Biomarker levels of troponin T, troponin I, B-type natriuretic peptide (BNP), and N-terminal prohormone brain natriuretic peptide (NT-proBNP) are quantitatively different between ischemic and idiopathic dilated etiologies of chronic HF.

Methods: Forty patients (27 male, 68 ± 2 years; LVEF $25 \pm 1\%$; NYHA Class III–IV) admitted to hospital for acute HF were studied. Biomarkers were drawn at admission prior to treatment intervention.

Results: Of the 40 patients, 27 had ISCM and 13 IDCM. Baseline clinical characteristics were similar with the exception of GFR. cTnT, cTnI, and BNP levels were higher in ISCM patients (cTnT: 0.373 ± 0.145 vs. 0.064 ± 0.016 ng/mL, $p < 0.05$; cTnI: 2.02 ± 0.76 vs. 0.21 ± 0.11 ng/mL, $p < 0.05$; BNP: 776 ± 91 vs. 532 ± 85 pg/mL, $p < 0.05$). Cardiovascular mortality during follow up (10 ± 1 months) was 48% in patients with ISCM and 23% with IDCM ($p < 0.05$).

Conclusions: Patients with acutely decompensated chronic HF have elevations in troponin and BNP. These elevations, as well as mortality are significantly higher in patients with ISCM compared to IDCM. The differential levels in biomarkers may be due to differences in disease pathogenesis, and fit with the adverse prognosis in these patients.

Key words: cardiomyopathy, troponin, NT-proBNP, BNP, heart failure, outcomes

Clin. Cardiol. 2007; 30: 245–250.
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Introduction

Although ischemic (ISCM) and non-ischemic idiopathic dilated cardiomyopathies (IDCM), have similar clinical features despite different pathogenic etiologies, responses to therapy and outcomes differ.[1–6] Thus, one might also expect differences in the frequency and/or magnitude of elevations in biomarkers such as cardiac troponin T (cTnT), cardiac troponin I (cTnI), and the B-type natriuretic peptides (BNP and N-terminal prohormone brain natriuretic peptide (NT-proBNP)), which occur in both forms of heart failure (HF) and predict prognosis.[7–9] However, in most reports, analyses usually done as subset analyses, suggest that values are similar. If these data are correct, there may be different interactions between biomarker elevations and outcomes. However, given this issue has only been addressed as subset analyses, and heretofore not focused upon, we compared baseline (admission) levels of cTnT, cTnI, NT-proBNP, BNP, and cyclic-GMP (cyclic guanosine

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Received: October 9, 2006
Accepted with revision: November 30, 2006

Published online in Wiley InterScience
(www.interscience.wiley.com).
DOI:10.1002/clc.20075
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monophosphate), the intracellular second-messenger signaling pathway for BNP) in hospitalized patients with decompensated chronic HF of ischemic and dilated cardiomyopathy etiologies and related the biomarker values to outcomes over time.

Methods

NT-proBNP, BNP, cardiac cTnT and cTnI, and c-GMP were measured prospectively in a cohort of 40 patients with chronic HF admitted to our hospital (Saint Mary's Hospital, Mayo Clinic, Rochester, MN) for management of decompensated HF during the period of June 2002 to January 2004. Patients with acute coronary syndromes or myocarditis were excluded from enrollment. The designation of ISCM compared to IDCM was predicated upon review of prior angiography in all patients. Patients with ISCM had angiographic findings of severe coronary artery disease (>70% stenoses), history of myocardial infarction, and/or revascularization. Patients diagnosed with IDCM had angiographically normal coronary arteries. Informed written consent was obtained to permit blood draws for the study. The primary medical service determined the course of therapy. This investigation was approved by the Mayo Foundation Institutional Review Board and included only those patients who gave consent for research analysis as required by Minnesota Statute 144.335/CFR 21 (Part 50).

Blood samples were drawn in EDTA and immediately placed on ice, processed, and subsequently stored at $-70\,^{\circ}C$ until batch analysis was performed. All patients were receiving standard oral therapy for HF at the time of admission, which included beta-blockers (70%), ACE-I (45%), ARB (25%), digoxin (53%), diuretics (85%), and aspirin (70%).

NT-proBNP was measured by a sandwich electrochemiluminescence immunoassay on the Roche Elecsys™ 2010 Analyzer (Roche Diagnostics; lower limit of detection, 5 μg/L with inter- and intra-assay CVs of 3.1% and 2.5%, respectively). BNP was measured by the Shionoria assay method (mean ± SE inter- and intra-assay variability of 7.2 ± 1.7 μg/L and 8.0 ± 1.4 μg/mL, respectively) in the laboratory of John C. Burnett, Jr. (Mayo Clinic). Cyclic-GMP was measured by RIA in the laboratory of Dr. Burnett (upper cutoff of the reference interval ⩽1.7 nmol/L; inter- and intra-assay CVs of 4.2% and 2.5%, respectively). Cardiac troponin T (cutoff value for limit of detection <0.01 μg/mL with CV of 10% at 0.035 μg/L) was measured on the Roche Elecsys 2010 Analyzer. Cardiac troponin I was measured using the Dade Status CS Analyzer (Dade, Newark, DE). The troponin I assay has a CV of 6.5% at the upper limit of normal range of 0.06 ng/mL with a limit of detection of 0.01 ng/mL. Renal function was determined at baseline by estimation of glomerular filtration rate (GFR; mL/min/1.73 m^2) by the Modification of Diet in Renal Disease (MDRD) equation.[10]

Post-hospital survival was evaluated at follow-up (mean of 10 ± 1 months, range of 1–22 months). The study was not powered for outcomes assessment, but in-hospital and post-hospital all-cause and cardiovascular mortality were evaluated. Continuous variable data were reported as mean ± SEM and categorical variables as percent of baseline value. Primary comparisons were analyzed by Student's *t*-test with statistical difference accepted for $p \leqslant 0.05$.

Results

Forty patients (27 male; mean age 68 ± 2 years) with decompensated (NYHA Class III–IV) chronic HF were enrolled in the study. Of these, 27 patients had ISCM and 13 IDCM as the etiology of their HF. Patient demographics and clinical characteristics at study entry are shown in Table 1. Baseline clinical features including left ventricular ejection fraction (LVEF) were similar for the two groups with the exception of GFR (ISCM 37 ± 3 vs. IDCM 48 ± 5 mL/min/1.73 m^2, $p < 0.05$). Thirteen patients were in atrial fibrillation (8 ISCM; 5 IDCM) with rate controlled and receiving chronic anticoagulation.

As illustrated in Fig. 1, baseline cTnT and cTnI levels were significantly higher in ISCM compared to IDCM patients. BNP was also higher in ISCM patients whereas NT-proBNP tended to be higher in ISCM patients but the difference was not statistically significant ($p = 0.10$).

No in-hospital mortality occurred. During post-hospital follow-up, however, overall morality was 40% with patients dying in a mean hospital dismissal to time of death of 5.4 ± 1 months (range 1–15 months). Mortality was 48% (13/27) in patients with ISCM and 23% (3/13) in patients with IDCM ($p < 0.05$). All post-hospital mortality was due to cardiovascular-related events (acute MI, sudden death event, or refractory pump failure). We have previously reported that in this cohort of patients, post-hospital nonsurvivors demonstrated lower baseline levels of NT-proBNP and BNP than survivors.[11] This relationship was also demonstrated for survivors and nonsurvivors within the ISCM and IDCM patient groups (Table 2). Nonsurviving patients with IDCM had the lowest levels of NT-proBNP and BNP. Troponin T and I levels were lower in patients with IDCM but levels did not differ statistically between survivors and nonsurvivors within the two groups at baseline (Fig. 2).

Discussion

Our data suggest that there are substantial differences between the biomarker values of patients who present with acute decompensated chronic HF as related to the underlying etiology of the HF syndrome. These observations may explain some of the heterogeneity seen in the biomarker results of clinical studies of HF where etiologies of HF are often mixed. These differences most likely

TABLE 1 Baseline demographic and clinical characteristics in patients with chronic heart failure

	Ischemic cardiomyopathy (N = 27)	Dilated cardiomyopathy (N = 13)
Age (years)	69 ± 2	68 ± 4
Gender (male/female)	20/7	7/6
Duration of HF (months)	58.3 ± 10.9	49.7 ± 12.1
Diabetes mellitus	12 (44%)	7 (54%)
Hypertension	19 (70%)	8 (62%)
Prior MI	25 (93%)	0
Left ventricular ejection fraction, %	24 ± 2	27 ± 3
Serum creatinine (mg/dL)	2.0 ± 0.14	1.9 ± 0.3
GFR (mL/min/1.73 m^2)	37 ± 3	48 ± 5*
Serum sodium (meq/L)	138 ± 0.8	138 ± 1.3
Hemoglobin (g/dL)	11.7 ± 0.22	11.2 ± 0.30
Blood pressure S/D (mmHg)	118 ± 3/60 ± 2	122 ± 7/64 ± 5
Heart rate (bpm)	81 ± 3	87 ± 5
cTnT (ng/mL)	0.373 ± 0.145	0.064 ± 0.016*
cTnI (ng/mL)	2.02 ± 0.755	0.208 ± 0.109*
BNP (pg/mL)	776 ± 91	532 ± 85*
NT-proBNP (pg/mL)	15696 ± 3652	11615 ± 3420
c-GMP (pmole/mL)	11.4 ± 1.25	13.7 ± 2.84

* $p < 0.05$ ISCM vs. IDCM.

reflect differences in the pathophysiology between the groups. Patients with an ischemic etiology, despite similar clinical profiles, had higher levels of cardiac cTnT and cTnI and higher levels of B-type natriuretic peptides than those with IDCM. These differences were associated with a higher rate of mortality which has been previously reported.[4–6] This could be due to the more marked degree of myocardial damage that occurs in patients with decompensated ISCM as indicated by the higher cardiac cTnT values. It may be of value to speculate that the increased injury reflects the conjoint effects of increased wall stress and epicardial coronary artery disease. If so, therapeutic interventions in ISCM patients need to address the myocardial injury in addition to treating the HF syndrome. Such speculation fits with the recent advocacy for the evaluation of HF patients for possible remedial coronary abnormalities. Alternatively, or perhaps in addition, the differential levels of

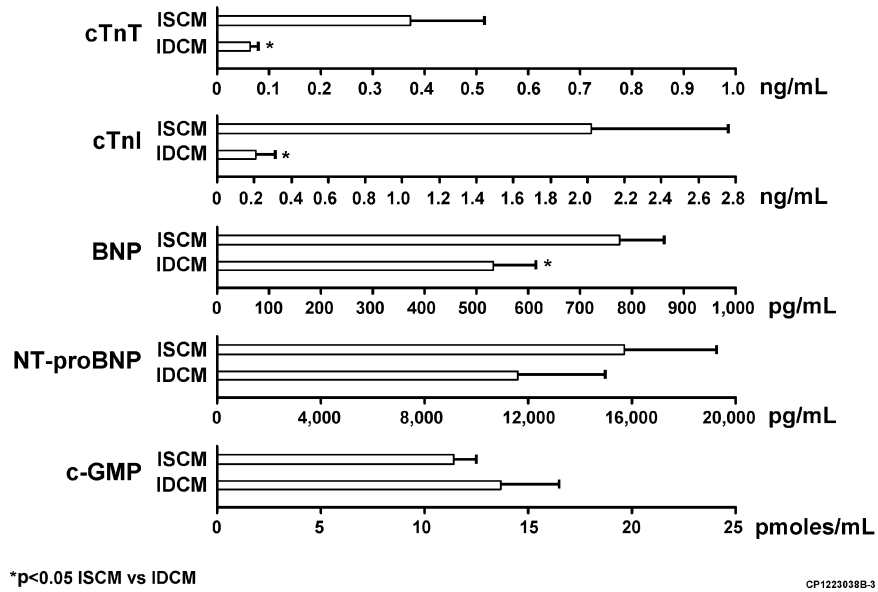

FIG. 1 Comparison of biomarkers at baseline in patients with ISCM and IDCM.

TABLE 2 Biomarker levels in post-hospital survivor and nonsurvivor cohorts

	Survivors, N = 24 baseline				Nonsurvivors, N = 16 baseline			
	CTnT ng/mL	cTnI ng/mL	BNP pg/mL	NT-proBNP pg/mL	cTnT ng/mL	cTnI ng/mL	BNP pg/mL	NT-proBNP pg/mL
Ischemic CM N = 27	0.378 ± 0.243 N = 14	2.62 ± 1.29 N = 14	917 ±153 N = 14	21357 ±6702 N = 14	0.314 ±0.129 N = 13	1.42 ±0.80 N = 13	532** ±64 N = 13	9599** ±1280 N = 13
Dilated CM N = 13	0.072* ±0.019 N = 10	0.15 ±0.09 N = 10	603* ±95 N = 10	12367 ±4410 N = 10	0.039* ±0.027 N = 3	0.05* ±0.04 N = 3	293* ±120** N = 3	9108 ±3102 N = 3

Mean ± SEM.
* = $p < 0.05$, Ischemic CM vs. IDCM.
** = $p < 0.05$ Survivors vs. Nonsurvivors.

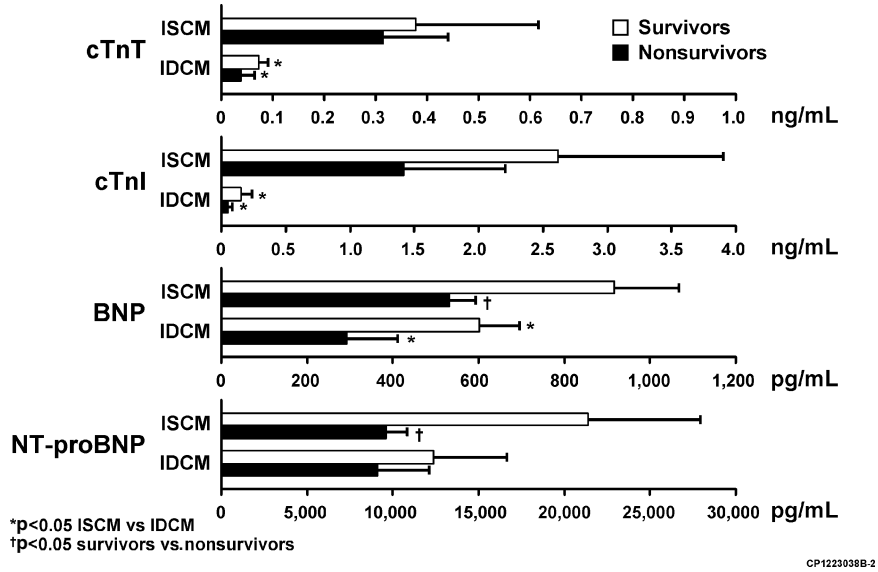

FIG. 2 Comparison of biomarkers in post-hospital survivors and nonsurvivors in patients with ISCM and IDCM.

cTnT, cTnI, and BNP in patients with ISCM and IDCM could be due to differences in disease pathogenesis and progression, which may result from the stimulation of different signaling pathways.[12]

Elevated cardiac cTnT and cTnI levels are well established markers of myocardial injury which are released under conditions of myocardial ischemia and necrosis.[13–16] Progressive ventricular remodeling due to increases in wall stress is also proposed as a mechanism for the development of HF. Increased wall stress also promotes troponin and BNP release.[17–20] It may, therefore, be that in patients with ISCM the conjoint burdens of ischemia induced by abnormalities in coronary flow and structural remodeling are associated with a greater release of these biomarkers than in the myocardium of patients with IDCM, particularly under conditions of acute decompensation. Sub-endomyocardial ischemia is most likely present in IDCM but this may contribute to a much lesser troponin release than the more diffuse ischemia (and necrosis) of advanced stenotic or occlusive epicardial coronary artery disease. Nonetheless, abnormalities in coronary flow clearly can influence the progression of HF. Patients with IDCM associated with endothelial dysfunction and abnormalities in coronary flow have a markedly adverse prognosis.[21–23]

cTnT levels increased significantly over the treatment interval whereas cTnI levels tended to decline, although the differences were not significant. This finding has not been previously reported and could simply be due to the modest numbers of patients studied. Alternatively, it could be indicative of differences between these two analytes in their release and/or response to therapy over time. There are data suggesting that cTnT may be more apt to be elevated when ventricular hypertrophy is present[24,25] and cTnI to be elevated in response to increases in ventricular volume.[26]

B-type natriuretic peptides are released from the myocardium under conditions of increased volume loading and ischemia[27,28] and, as with troponin, BNP release may be more widely stimulated in patients with ISCM compared with IDCM. A role for BNP and NT-proBNP has been proposed in risk stratification[29,30] and also potentially in the monitoring of HF therapy[31] but it has not been established or evaluated if such a role is valid in both ISCM and IDCM patients. Relative BNP levels have also been shown to be associated with age, gender, and obesity.[32,33] As our data suggest, an IDCM etiology of HF is associated with lower levels of B-type natriuretic peptides.

We cannot exclude the possibility that these results reflect the small numbers of patients studied. However, these findings may also reflect the state of acute decompensation which contrasts to the many other reports in stable chronic HF patients. These findings, nevertheless, should be viewed as hypothesis generating.

Although those with ISCM had higher biomarker levels and were at greater risk for mortality, we saw in both those with ISCM and IDCM, in keeping with our previous report, that lower levels of BNP were an adverse prognostic sign. This observation might easily have been obscured by the lumping of patients with ISCM and IDCM together in other data sets. We have previously suggested that end stage HF patients may lose the ability to increase BNP and that in and of itself may be an adverse prognostic finding.[11] Our findings suggest differences between patients with ISCM and IDCM extend to plasma levels of biomarkers cTnT, cTnI, and BNP.

Conclusions

Recognizing these differences as related to the etiology of HF may account in part for the heterogeneity in published biomarker data and contribute to a better understanding of the underlying mechanisms of disease process, progression, and response to therapy. Ultimately, these factors may contribute to a basis for the differences in outcomes and strategies to improve prognosis.

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