Cardiac Biomarker Responses to Dobutamine Stress Echocardiography in Healthy Volunteers and Patients with Coronary Artery Disease

To the Editor:

Cardiac stress testing provides important diagnostic and prognostic information in ischemic heart disease (1). The sensitivity and specificity of stress testing are limited, however (2). If a circulating biomarker could reliably reflect the short-lived ischemia that occurs with stress testing and if differences in marker-release patterns could be associated with grades of risk for negative outcomes, one would expect the sensitivity, specificity, and overall utility of stress testing to improve substantially. High-sensitivity cardiac troponin assays have potential to be earlier markers of myocardial ischemia (3, 4). B-type natriuretic peptide signal peptide (BNPsp)3 is a recently discovered circulating biomarker (5). In the setting of ST-segment elevation myocardial infarction, BNPsp concentrations increase early, preceding myoglobin peaks. BNPsp has not been reported to date in less extreme forms of cardiac ischemia.

We document the release of BNPsp, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and troponin T as measured with a high-sensitivity assay (hsTnT) during dobutamine stress echocardiography (DSE) in patients with coronary artery disease (CAD) and in healthy volunteers. Blood samples were collected from 16 CAD patients and 10 healthy volunteers just before DSE and serially for 4 h. Plasma BNPsp was measured with a locally developed RIA (5). hsTnT and NT-proBNP concentrations were measured with commercially available Elecsys assays (Roche Diagnostics). The respective analytical interval, limit of detection, reference interval, and CV data for each marker are as follows: BNPsp: 8–320 pmol/L, 4 pmol/L, 7–25 pmol/L, and <8%; hsTnT: 3–2100 pg/mL, 3 pg/mL, <14 pg/mL, and <5%; NT-proBNP: 5–35 000 pg/mL, 5 pg/mL, <200 pg/mL, and <5%.

Of the 16 CAD patients, 15 (94%) were on β-blockers. The CAD patients and healthy volunteers did not differ with respect to the mean cumulative dose of dobutamine administered [32.0 mg (range, 20.5–41.0 mg) vs 27.2 mg (range, 25.4–32.3 mg), P = 0.332]. The groups and the markers exhibited very different temporal profiles of biomarker increases. Mean hsTnT concentrations in healthy volunteers increased above the 99th percentile of the upper reference limit at 150 min and peaked at 180 min. In contrast, BNPsp concentrations peaked at 30 min and then normalized, falling back below the 99th percentile by 60 min (Fig. 1).

hsTnT concentrations in CAD patients without evidence of inducible ischemia started from a higher baseline and increased above the 99th percentile at 120 min. Concentrations were still increasing at the end of the sampling period. Peak plasma BNPsp concentrations tended to be higher than those for healthy volunteers and did not fall below the 99th percentile until 90 min. hsTnT and BNPsp concentrations varied significantly over time (P < 0.001 for each), but the differences between the 2 groups were not significant (P = 0.343 and 0.554, respectively, by repeated-measures ANOVA). In contrast, NT-proBNP concentrations showed no significant variation over time (P = 0.194).

Three of the 16 patients in the CAD group had echo–positive DSE results and had received higher dobutamine doses (46.7 mg; range, 35–54.3 mg) than the CAD group as a whole (28.7 mg; range, 18–50.6 mg; P = 0.034). These 3 individuals exhibited an exaggerated hsTnT release compared with the other individuals. In contrast, the mean peak BNPsp concentration was lower in this group. Again, the differences did not reach statistical significance by ANOVA (hsTnT, P = 0.104; BNPsp, P = 0.290; NT-proBNP, P = 0.324).

There was a statistically significant relationship between the absolute change (Δ) in the hsTnT concentration and the cumulative dobutamine dose (r² = 0.26; P = 0.015) in the CAD patients. There was no corresponding correlation with Δ BNPsp or Δ hsTnT in the CAD group (r² = −0.028; P = 0.562), and there was no significant correlation between Δ NT-proBNP and Δ BNPsp (r² = 0.083; P = 0.317).

To our knowledge, this study is the first to demonstrate the patterns of release of TnT with a high-sensitivity assay during DSE testing. Our data suggest stepwise increments in DSE-induced increases in plasma hsTnT and BNPsp in healthy volunteers and CAD patients. CAD patients with inducible ischemia also received the highest dobutamine doses, a finding that must be considered. In contrast with hsTnT and NT-proBNP, the release kinetics for BNPsp indicate that it is a much more dynamic marker. The reasons for the attenuated release of BNPsp in individuals with echocardiographically positive test results are unclear. In view of the small sample size, this observation requires verification. If genuine, it is possible that BNPsp release mechanisms are more susceptible

3 Nonstandard abbreviations: BNPsp, B-type natriuretic peptide signal peptide; NT-proBNP, N-terminal pro–B-type natriuretic peptide; hsTnT, troponin T as measured with a high-sensitivity assay; DSE, dobutamine stress echocardiography; CAD, coronary artery disease.
than troponin to ischemic preconditioning, or there may be a depletable pool of this peptide.

Given the results of this pilot study, we propose that both exaggerated cardiac troponin release and attenuated BNPsp release in patients with inducible ischemia during DSE warrant further investigation with a larger sample size—and with longer follow-up—to establish whether specific threshold biomarker responses correspond to worse ischemia and/or a worse prognosis.

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References


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