

Background. The neurohormone B-type natriuretic peptide (BNP) is released from ventricular myocytes in response to wall tension caused by ventricular volume expansion and pressure overload. Measurement of BNP has been approved as an aid to the diagnosis of congestive heart failure (CHF). In the prospective BNP Multinational Study, we sought to determine the diagnostic utility of BNP in the emergency department (ED) evaluation of dyspnea in a broad spectrum of patients. **Methods.** A total of 1,586 patients who presented to the ED with acute dyspnea as their primary complaint upon arrival underwent measurement of BNP with a point-of-care device. Patients with acute myocardial infarction or renal failure as the cause of dyspnea were excluded. Emergency physicians were asked to give a blinded, pre-test probability of the diagnosis being CHF. The gold standard for CHF was adjudicated by two independent cardiologists, blinded to BNP results, who reviewed all clinical data and standardized CHF scores. The primary end point was diagnostic accuracy. The analysis used a Bayesian approach that took into account: 1) the a priori pre-test probability from the ED clinician; 2) the BNP test converted to a likelihood ratio through the range of diagnostic values; and 3) a post-test probability generated from these two values. The final diagnosis was CHF in 744 (46.9%), a history of CHF and left ventricular (LV) dysfunction but dyspnea due to noncardiac causes in 72 (4.5%), and not CHF in 770 (48.5%). Median levels of BNP in the patients with CHF as a final diagnosis were 600 pg/ml, in those with LV dysfunction but a noncardiac cause of dyspnea, 150 pg/ml, and in patients without CHF, 50 pg/ml ($p < 0.0001$). Among the patients with a final diagnosis of CHF, BNP levels varied significantly as a function of New York Heart Association (NYHA) class; the median BNP values for NYHA class I ($n = 18$), II ($n = 152$), III ($n = 351$), and IV ($n = 276$) were 150, 250, 550, and 900 pg/ml, respectively. At a cutoff of 100 pg/ml, BNP had a diagnostic sensitivity of 90%, a specificity of 76%, a positive predictive value of 79%, and a negative predictive value of 89%. For the primary end point of diagnostic accuracy, clinical judgment (with ED physicians required to be at least 80% certain of a CHF diagnosis) achieved an accuracy of 74.0%, the BNP test achieved an accuracy of 81.1%, and clinical judgment combined with the BNP test achieved an accuracy of 81.6% ($p < 0.0001$). In 43% of cases, the ED physician was uncertain of the final diagnosis (ED probabilities between 20% and 80%). In these cases, if BNP at a cutoff of 100 pg/ml, clarified 75% of those cases, leaving an absolute 11% of patients in whom there was uncertainty, implying additional testing would be warranted. **Conclusions.** The BNP test adds independent diagnostic information to the traditional components of the CHF evaluation (history, physical exam and chest X-ray). Mean BNP values reflect functional class in patients with heart failure (HF). In patients for whom the conventional ED diagnosis of HF is equivocal, the use of BNP at a cutoff of 100 pg/ml, will correctly classify 74% of cases. The

implications of this study are that BNP should be included as a component in the initial diagnostic evaluation of dyspnea, where it can play a role in confirming the clinical diagnosis and, importantly, in improving diagnostic accuracy in the large proportion of cases where there is uncertainty.

COMMENTARY

B-type natriuretic peptide is now accepted as an adjunctive diagnostic test to confirm the presence of HF. This trial represents an important step by investigators in assessing the value of plasma BNP as an aid in the diagnosis HF in the setting of the hospital ED. The value of the test lies mainly in its negative predictive value, although, increased plasma BNP levels may help to identify patients with more advanced HF. Plasma BNP was more accurate than the clinical judgment of the ED physician. The Breathing Not Properly study confirms the utility of plasma BNP as an aid in the diagnosis of HF. However, the design of the study did not allow for a direct testing of whether BNP adds value to clinical judgment, which is perhaps a more important question in the "real world." Patients with HF may have intermediate plasma BNP levels when clinically stable or only mildly symptomatic. Age, gender, and diastolic function can also alter plasma BNP levels. Normal levels and very high levels are seemingly of greatest value. However, the intermediate BNP values may possibly be used to guide therapeutic decisions. There is already a suggestion that BNP-guided therapy may be more beneficial to patients than non-BNP-guided conventional therapy. However, this hypothesis needs to be tested in a randomized controlled trial.

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Heart Allograft Rejection: Detection With Breath Alkanes in Low Levels (the HARDBALL Study)

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Background. Endomyocardial biopsy remains the gold standard for the detection of tissue rejection in patients with transplanted hearts. However, the procedure is costly, highly invasive, of limited accuracy, and can cause infection, arrhythmias, or other complications. A sensitive and non-invasive screening test for heart transplant rejection would represent an advance. The rejection process is accompanied by oxidative stress caused by increased mitochondrial production of reactive oxygen species. Oxidative stress degrades polyunsaturated fatty acids in membranes by lipid peroxidation, which releases alkanes and methylalkanes, volatile organic compounds (VOCs) that are excreted in the breath.

Methods. We evaluated a breath test for oxidative stress—the breath methylated alkane contour (BMAC)—using a proprietary breath VOC collection device as a screening tool in heart transplant recipients at seven institutions prior to their scheduled endomyocardial biopsy. We also collected breath samples from healthy, age-matched normals. Collection of the 1,061 breath samples required approximately 2 min of each patient's time. A site pathologist and two reviewers independently scored biopsies for International Society for Heart and Lung Transplantation (ISHLT) rejection grade. Breath VOCs were analyzed by gas chromatography and mass spectroscopy, and the BMAC was derived from alveolar gradients (relative abundance in breath minus relative abundance in air) of C4-C20 alkanes and monomethylalkanes. The BMAC results were compared with the jointly agreed ISHLT scores, and VOC markers of rejection were identified by discriminant analysis.

Results. The independent-reviewer biopsy results disclosed 645 patients (60.8%) with ISHLT rejection grade 0 (no rejection) and 281 (26.5%) with grade 1 (mild) rejection, 93 (8.8%) with grade 2 (moderate) rejection, and 42 (4.0%) with grade 3 (severe) rejection. Compared with the independent reviewers, a biopsy reading by a site pathologist had a sensitivity of 42.4% and specificity of 97.0% for grade 3 rejection. Breath test results revealed nine VOCs whose levels represented markers of grade 3 rejection. In a predictive model, the breath markers had a sensitivity of 78.6% and specificity of

62.4%; the cross-validated model had a sensitivity of 59.5% and specificity of 58.8%. Thus, the breath test for markers of oxidative stress was more sensitive but less specific for grade 3 heart transplant rejection than were biopsy readings by site pathologists. The negative predictive value of the breath test for grade 3 rejection was 97.3%, which was similar to that of a biopsy reading by a site pathologist (97.5%) (i.e., in a patient with a negative breath test, a biopsy contributes no additional clinical information). **Conclusions.** Based on these findings, a screening breath test could potentially reduce the number of endomyocardial biopsies for heart transplant rejection by at least one-half with no loss of diagnostic accuracy.

COMMENTARY

The "holy grail" in the surveillance for cardiac rejection in heart transplant patients has always been the discovery of a noninvasive, inexpensive, readily available, "low-tech" alternative to the use of the endomyocardial biopsy, a technique that possesses none of these characteristics but is currently considered the gold standard. The assay described in the *HARDBALL* study is another in a long series of technologies that are candidates for replacing surveillance heart biopsies, and it is certainly one of the most unusual, basically being a breathalyzer test.

The study shows a surprising lack of consistency between biopsy interpretation by the pathologist at the transplant program site and the independent pathologist working with the authors. It also shows that, although only 9 of 42 (independent pathologist-interpreted) biopsies with grade 3 rejection were predicted by the threshold level of volatile organic compounds that the authors set for the breath sample, the negative predictive value for grade 3 rejection was 97.3%. These results are difficult to evaluate given the disparity of pathology interpretation, and adoption of the technology also awaits further investigation and correlation with the presence or absence of concurrent patient illnesses, such as hemodynamic compromise and infection, which theoretically could decrease sensitivity and specificity of anything that is a marker of oxidative stress.

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LATE-BREAKING CLINICAL TRIALS III

Results of the InSync ICD Clinical Trial

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Background. More than one-third of patients with moderate-to-severe heart failure (HF) have ventricular dyssynchrony, which leads to poor left ventricular (LV) function, limited exercise tolerance, and impaired quality of life (QOL). The InSync ICD trial is a multicenter, double-blind controlled study evaluating the safety and effectiveness of cardiac resynchronization therapy (CRT) in patients with advanced (New York Heart Association [NYHA] class III to IV) systolic HF, LV ejection fraction $\leq 35\%$, ventricular