The New England Journal of Medicine

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VOLUME 347 JULY 18, 2002 NUMBER 3

RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE EMERGENCY DIAGNOSIS OF HEART FAILURE

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ABSTRACT

Background B-type natriuretic peptide is released from the cardiac ventricles in response to increased wall tension.

Methods We conducted a prospective study of 1586 patients who came to the emergency department with acute dyspnea and whose B-type natriuretic peptide was measured with a bedside assay. The clinical diagnosis of congestive heart failure was adjudicated by two independent cardiologists, who were blinded to the results of the B-type natriuretic peptide assay.

Results The final diagnosis was dyspnea due to congestive heart failure in 744 patients (47 percent), dyspnea due to noncardiac causes in 72 patients with a history of left ventricular dysfunction (5 percent), and no finding of congestive heart failure in 770 patients (49 percent). B-type natriuretic peptide levels by themselves were more accurate than any historical or physical findings or laboratory values in identifying congestive heart failure as the cause of dyspnea. The diagnostic accuracy of B-type natriuretic peptide at a cutoff of 100 pg per milliliter was 83.4 percent. The negative predictive value of B-type natriuretic peptide at levels of less than 50 pg per milliliter was 96 percent. In multiple logistic-regression analysis, measurements of B-type natriuretic peptide added significant independent predictive power to other clinical variables in models predicting which patients had congestive heart failure.

Conclusions Used in conjunction with other clinical information, rapid measurement of B-type natriuretic peptide is useful in establishing or excluding the diagnosis of congestive heart failure in patients with acute dyspnea. (N Engl J Med 2002;347:161-7.)

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CURRENTLY, there are 5 million Americans with congestive heart failure, with nearly 500,000 new cases every year.[1] The prevalence of symptomatic heart failure in the general European population ranges from 0.4 percent to 2.0 percent.[2] Because of the high total direct costs of care for heart failure, estimated at $10 billion to $38 billion per year, the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services) targeted heart failure as the disease most worthy of cost-effective management.[3] To provide cost-effective treatment for patients with congestive heart failure, rapid and accurate differentiation of congestive heart failure from other causes of dyspnea must be accomplished. Heart failure is often difficult to diagnose in the emergency department or urgent care setting, however. The symptoms may be nonspecific, and physical findings are not sensitive enough to use as a basis for an accurate diagnosis.[4,5] Although echocardiography is considered the gold standard for the detection of left ventricular dysfunction, it is expensive, is not always easily accessible, and may not always reflect an acute condition.[6] Misdiagnosis of congestive heart failure can be life-threatening, because

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treatments for congestive heart failure are hazardous to patients with other conditions, such as chronic obstructive pulmonary disease, that have the same primary symptoms at presentation.[1,7]

B-type natriuretic peptide is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload.[8,9] Levels of B-type natriuretic peptide have been shown to be elevated in patients with left ventricular dysfunction and correlate with the New York Heart Association class, as well as with prognosis.[10-15] A previous study, using a radioimmunoassay for the detection of B-type natriuretic peptide, suggested that B-type natriuretic peptide may be useful in distinguishing between cardiac and noncardiac causes of acute dyspnea.[16] Recently, a pilot study using a rapid (15-minute) whole-blood assay for B-type natriuretic peptide demonstrated that bedside measurement of B-type natriuretic peptide added to the ability of the physician to diagnose congestive heart failure in the urgent care setting.[17] We performed a seven-center, multinational trial to validate and characterize the use of B-type natriuretic peptide levels in the diagnosis of congestive heart failure in a broad population of patients with dyspnea.

METHODS

Study Population

The study was approved by the institutional review boards of participating study centers. A total of 1586 patients from seven sites (five in the United States, one in France, and one in Norway) were enrolled from April 1999 to December 2000. To be eligible for the study, a patient had to have shortness of breath as the most prominent symptom. Patients under 18 years of age and those whose dyspnea was clearly not secondary to congestive heart failure (for example, those with trauma or cardiac tamponade) were excluded. Patients with acute myocardial infarction or renal failure were also excluded. Patients with unstable angina were excluded unless their predominant symptom at presentation was dyspnea.

Once the patient was identified as having dyspnea, written informed consent was obtained, and a blood sample was collected for measurement of B-type natriuretic peptide. A research assistant collected other data, including information from the medical history, the physical examination, results of other blood tests, interpretations of chest roentgenograms, and interpretations of other diagnostic tests. Echocardiograms were strongly encouraged in the emergency department on an outpatient basis or in the hospital if the patient was admitted.

For each patient enrolled in the study, physicians assigned to the emergency department (emergency department specialists or general-medicine internists), who were blinded to the results of the measurements of B-type natriuretic peptide, assessed the probability that the patient had congestive heart failure (by assigning a value of 0 to 100 percent clinical certainty) as the cause of his or her symptoms. If a patient had a history of congestive heart failure, the physician classified the patient as having either an acute exacerbation of congestive heart failure or dyspnea from another cause, with underlying left ventricular dysfunction (as, for example, in the case of a patient with left ventricular dysfunction who was seen for bronchitis).

Confirmation of the Diagnosis

To determine the actual diagnosis, two cardiologists reviewed all medical records pertaining to the patient and independently classified the diagnosis as dyspnea due to congestive heart failure, acute dyspnea due to noncardiac causes in a patient with a history of left ventricular dysfunction, or dyspnea not due to congestive heart failure. The cardiologists were presented with the components and a summary of the Framingham congestive-heart-failure score (two major or one major and two minor criteria) and the National Health and Nutrition Examination Survey (NHANES) congestive heart failure score (scores of 3 or more) calculated from the case-report form. Both cardiologists were blinded to the B-type natriuretic peptide level as well as to the emergency department physicians' diagnosis. They did have access to the emergency department data sheets and any additional information that became available after the evaluation in the emergency department. This information included the reading of the chest roentgenogram in the emergency department by a radiologist; medical history obtained from a medical chart that was not available to the emergency department physicians at the time of presentation; the results of subsequent tests, such as echocardiography, radionuclide angiography, or left ventriculography, performed at the time of cardiac catheterization; and the hospital course for patients admitted to the hospital. For patients with a diagnosis other than congestive heart failure, confirmation on the basis of the following observations was attempted: normal chest roentgenogram (absence of heart enlargement and pulmonary venous hypertension); roentgenographic signs of chronic obstructive lung disease, pneumonia, or lung cancer; normal heart function according to echocardiography, radionuclide ventriculography, or left ventriculography performed at the time of cardiac catheterization; abnormal pulmonary-function test results or follow-up results in the pulmonary clinic; response to treatment with nebulizers, corticosteroids, or antibiotics in the emergency department or hospital; and the absence of admission to the hospital for congestive heart failure over the next 30 days. In all cases of congestive heart failure, the two cardiologists were asked to agree on the severity according to the New York Heart Association class.

Measurement of Levels of B-Type Natriuretic Peptide

During the initial evaluation, a blood sample was collected into a tube containing potassium EDTA. B-type natriuretic peptide was measured with use of a fluorescence immunoassay kit (Triage, Biosite) for the quantitative determination of B-type natriuretic peptide in whole-blood and plasma specimens. The precision, analytic sensitivity, and stability characteristics of the system have been previously described.[18,19] Values for B-type natriuretic peptide were determined on site by the bedside method with either whole-blood or plasma samples.

Statistical Analysis

Comparisons of B-type natriuretic peptide values among diagnostic groups were performed by the t-test for independent samples and analysis of variance. Log-transformed values for B-type natriuretic peptide were used in these analyses to reduce the effects of skewness in the distribution of B-type natriuretic peptide levels. To evaluate the value of B-type natriuretic peptide measurements in the diagnosis of congestive heart failure, we compared the sensitivity, specificity, and accuracy of B-type natriuretic peptide measurements with those of individual clinical findings. We also used a multiple logistic-regression model combining clinical findings and B-type natriuretic peptide values to predict the final diagnosis. For each of the different clinical and roentgenographic findings identified by emergency department physicians, and for different threshold B-type natriuretic peptide levels, we computed the sensitivity, specificity, and accuracy, defined as the sum of the concordant cells divided by the sum of all cells in the two-by-two table. To determine the most parsimonious combination of indicators to pre-

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dict the presence or absence of congestive heart failure, we applied multiple stepwise logistic regression with the use of a P value of 0.05 or less for entry into the model. The predictors included historical, clinical, and roentgenographic findings, along with information on B-type natriuretic peptide (100 pg per milliliter or above). We also evaluated the unique contribution of B-type natriuretic peptide over and above other predictors by entering B-type natriuretic peptide last in a separate model. Finally, we constructed receiver-operating-characteristic curves to illustrate various cutoff values of B-type natriuretic peptide.

The academic investigators designed the study, analyzed the data, and wrote the manuscript. Biosite supplied the diagnostic kits and managed the technical aspects of data accrual and storage.

RESULTS

The base-line characteristics of the overall study group of 1586 patients are shown in Table 1. The mean age was 64 years. There were 883 men (56 percent) and 703 women (44 percent); 773 patients were white (49 percent), 715 were black (45 percent), and 98 were members of other races (6 percent). On examination, 7 percent of patients had an S_3 gallop, 43 percent had rales in the lower lung fields, 22 percent had jugular venous distention, and 42 percent had edema of the legs or feet.

The final diagnosis was congestive heart failure in 744 patients (47 percent), dyspnea due to noncardiac causes in 72 patients with a history of left ventricular dysfunction (5 percent), and no finding of congestive heart failure in 770 patients (49 percent). In 97 percent of patients with congestive heart failure, the final diagnosis of congestive heart failure was confirmed by other tests (chest roentgenogram in 79 percent of patients, echocardiography in 77 percent, radionuclide ejection fraction in 15 percent, cardiac catheterization in 19 percent, and response to treatment in 86 percent). Figure 1 presents a box plot of B-type natriuretic peptide values for the three groups of patients. The difference among groups was significant ($P<0.001$ for each pairwise comparison). Patients with a diagnosis of acute congestive heart failure had mean (±SD) B-type natriuretic peptide levels of 675±450 pg per milliliter, whereas those without congestive heart failure had B-type natriuretic peptide levels of 110±225 pg per milliliter. The 72 patients who had base-line ventricular dysfunction without an acute exacerbation had a mean B-type natriuretic peptide level of 346±390 pg per milliliter.

Ninety-nine patients met the clinical criteria for cor pulmonale. Cor pulmonale was a derived variable that required a history of obstructive or restrictive lung disease and the presence of hepatic congestion and peripheral edema on physical examination. The final diagnoses, as adjudicated by the reviewing cardiologists, were as follows: 78 patients (79 percent) were considered to have congestive heart failure as the primary cause of dyspnea, 19 (19 percent) to have dyspnea not due to congestive heart failure, and 2 (2 per-

TABLE 1. BASE-LINE CHARACTERISTICS OF 1586 PATIENTS WITH DYSPNEA.

CHARACTERISTIC	VALUE
Age (yr)*	64±17
Sex (%)	
Male	56
Female	44
History (%)	
Congestive heart failure	33
Myocardial infarction	27
Chronic obstructive pulmonary disease	41
Diabetes	25
Symptoms (%)	
Shortness of breath	
Slight hill	92
Level ground	78
Own pace	76
Orthopnea	53
Paroxysmal nocturnal dyspnea	46
Nocturnal cough	44
Signs (%)	
Elevated jugular venous pressure	22
Rales	
Lower lung fields	43
Upper lung fields	12
Wheezing	28
S_3 gallop	7
Murmurs	19
Lower-extremity edema	42

*Plus–minus value is the mean ±SD.

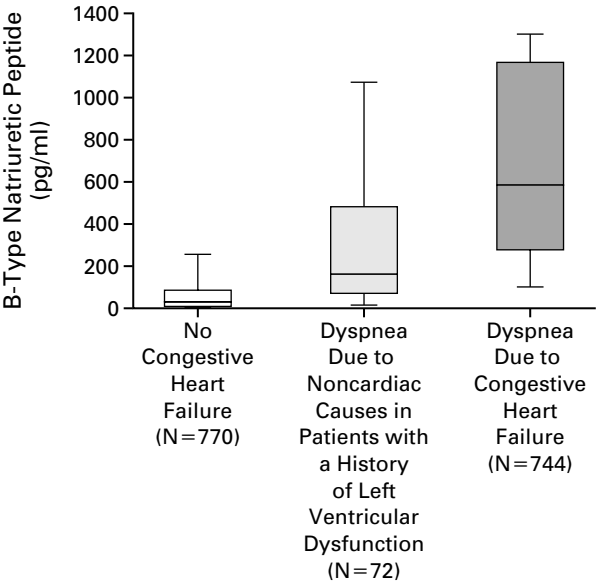

Figure 1. Box Plots Showing Median Levels of B-Type Natriuretic Peptide Measured in the Emergency Department in Three Groups of Patients.

Boxes show interquartile ranges, and I bars represent highest and lowest values.

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cent) to have stable left ventricular dysfunction with dyspnea from a noncardiac cause.

Figure 2 shows B-type natriuretic peptide values in relation to New York Heart Association functional class, as determined by both cardiologists together. B-type natriuretic peptide values differed significantly as a function of the severity of congestive heart failure ($P<0.001$). The mean B-type natriuretic peptide levels were 244±286 pg per milliliter among patients in class I, 389±374 pg per milliliter among those in class II, 640±447 pg per milliliter among those in class III, and 817±435 pg per milliliter among those in class IV.

The best clinical predictor of congestive heart failure was an increased heart size on chest roentgenogram (accuracy, 81 percent), followed by a history of congestive heart failure (75 percent). Rales were the most accurate finding on physical examination (69 percent accuracy), and a history of paroxysmal nocturnal dyspnea had an accuracy of 60 percent.

The B-type natriuretic peptide level was the single most accurate predictor of the presence or absence of congestive heart failure. The capacity of B-type natriuretic peptide to differentiate congestive heart failure from other causes of dyspnea was assessed with a receiver-operating-characteristic curve analysis (Fig. 3). The area under the receiver-operating-characteristic curve when B-type natriuretic peptide was used to differentiate congestive heart failure from other causes of dyspnea was 0.91 (95 percent confidence interval, 0.90 to 0.93; $P<0.001$). A B-type natriuretic peptide cutoff value of 100 pg per milliliter had a sensitivity of 90 percent, a specificity of 76 percent, and an accuracy of 83 percent for differentiating congestive heart failure from other causes of dyspnea. Lower values were associated with more accurate negative predictive values (for a B-type natriuretic peptide value of 50 pg per milliliter, the negative predictive value was 96 percent). For the diagnosis of congestive heart failure in our study population, a B-type natriuretic peptide cutoff of 100 pg per milliliter was more accurate (83 percent) than either the NHANES criteria (67 percent) or the Framingham criteria (73 percent), the two most commonly used sets of criteria for diagnosing congestive heart failure.[20]

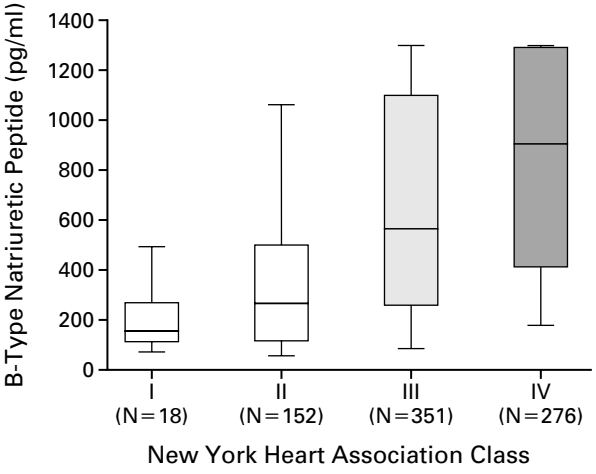

Figure 2. Box Plots Showing Median Levels of B-Type Natriuretic Peptide among Patients in Each of the Four New York Heart Association Classifications.

Boxes show interquartile ranges, and I bars represent highest and lowest values.

In multiple logistic-regression analyses, we determined that the addition of B-type natriuretic peptide increased the combined explanatory power of the history, symptoms, signs, radiologic studies, and laboratory findings (Table 2). The model showed that a history of heart failure and cephalization of vessels on chest roentgenography were strong independent predictors of congestive heart failure. A value of 100 pg per milliliter or more for B-type natriuretic peptide was the strongest independent predictor of congestive heart failure, with an odds ratio of 29.60. B-type natriuretic peptide also added significant additional information when it was entered after other clinical indicators ($P<0.001$).

DISCUSSION

Our findings validate and extend the observations made in a pilot study using a B-type natriuretic peptide test to aid in the diagnosis of congestive heart failure.[17] The B-type natriuretic peptide cutoff point we judged to be optimal for making the diagnosis of congestive heart failure was slightly higher than that found in the pilot study (100 vs. 80 pg per milliliter), but it corresponds to the manufacturer's recommended cutoff level for the diagnosis of congestive heart failure. Furthermore, B-type natriuretic peptide levels by themselves were more accurate than any other finding in the history, physical finding, or laboratory value in delineating the cause of dyspnea. B-type natriuretic peptide performed better than either the NHANES or the Framingham criteria, arguably the most widely accepted criteria for the diagnosis of congestive heart failure. The calculated area under the curve of 0.91 was similar to that of prostate-specific antigen for the detection of prostate cancer (area under the curve, 0.94) and was superior to those of Papanicolaou smears and mammography (area under the curve, 0.70 and 0.85, respectively).[21-23]

The accuracy of the diagnosis of congestive heart failure by clinical means and standard testing is often inadequate.[24-26] Echocardiographic imaging may be difficult to perform in a patient who cannot remain

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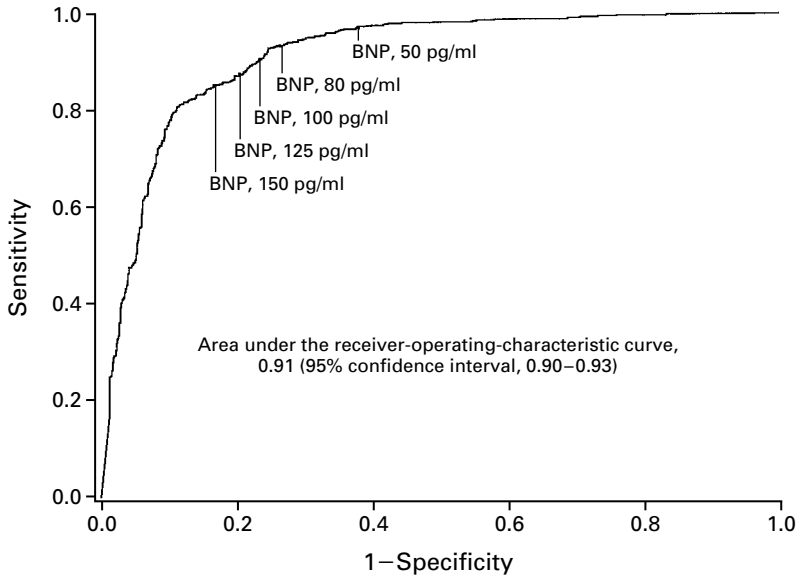

BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

Figure 3. Receiver-Operating-Characteristic Curve for Various Cutoff Levels of B-Type Natriuretic Peptide (BNP) in Differentiating between Dyspnea Due to Congestive Heart Failure and Dyspnea Due to Other Causes.

still because of dyspnea or who has a coexisting condition such as obesity or lung disease. Echocardiography may also not be sensitive enough to delineate cardiac causes of acute dyspnea — for example, when severe hypertension leads to pulmonary edema.

Unlike acute coronary syndromes, in which biomarkers such as cardiac troponins and creatine kinase MB fraction not only establish the diagnosis but also are correlated with both severity and prognosis, congestive heart failure in the urgent care setting has not had a gold standard for either diagnosis or prognosis. This fact is underscored by Rame et al., who found a paucity of indicators of the severity of disease or outcome in patients with congestive heart failure who were examined and discharged in an urban county emergency department, accounting for the subsequent 61 percent rate of failure of outpatient treatment.[27]

Table 2. Multiple Logistic-Regression Analysis of Factors Used for Differentiating between Patients with and Those without Congestive Heart Failure.

Predictor	P Value	Odds Ratio (95% CI)*
Age	0.04	1.02 (1.00–1.03)
History of congestive heart failure	<0.001	11.08 (6.55–18.77)
History of myocardial infarction	<0.001	2.72 (1.63–4.54)
Rales	<0.001	2.24 (1.41–3.58)
Cephalization of vessels	<0.001	10.69 (5.32–21.47)
Edema	<0.001	2.88 (1.81–4.57)
Jugular venous distention	0.04	1.87 (1.04–3.36)
B-type natriuretic peptide ≥100 pg/ml	<0.001	29.60 (17.75–49.37)

*The odds ratio reflects the odds for patients with the characteristic in question, as compared with those without the characteristic. The odds ratio for age represents the exponent for each year of age in the logistic equation. CI denotes confidence interval.

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The source of B-type natriuretic peptide in plasma is mainly the ventricles, which suggests that B-type natriuretic peptide may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides.[7,28] The promoter region of the B-type natriuretic peptide gene contains the rapid-turnover nucleic acid sequence TATTTAT, which suggests that the rate of turnover of B-type natriuretic peptide messenger RNA is high and that B-type natriuretic peptide is synthesized in bursts.[29,30] This release appears to be directly proportional to the degree of ventricular-volume expansion and pressure overload.[31]

Our study, along with others, demonstrates the relation of B-type natriuretic peptide levels with the severity of heart failure,[15,28,32] and it underscores the prognostic importance of this peptide in a number of settings.[11,13,15,33,34] In a population similar to ours, Harrison et al. followed 325 patients for six months after they presented to the emergency department with dyspnea.[15] B-type natriuretic peptide levels (according to the same B-type natriuretic peptide assay we used) determined at the initial emergency department visit were closely correlated with outcomes, with 54 percent of the patients who had B-type natriuretic peptide levels of more than 480 pg per milliliter having a subsequent congestive-heart-failure event at six months. A B-type natriuretic peptide level of more than 230 pg per milliliter was associated with a relative risk of 7.0 for a congestive-heart-failure event in patients whose doctors failed to make the diagnosis of congestive heart failure.

The value of natriuretic peptides has already been recognized by their inclusion in the recent European guidelines for the diagnosis of chronic heart failure.[35] The present study addresses the diagnosis of heart failure in a large, heterogeneous population of patients with dyspnea in the acute care setting. These results supplement the established "rule-out" value of B-type natriuretic peptide stated in the European guidelines by offering valuable information concerning the positive predictive value of B-type natriuretic peptide, as well as the assessment of the severity of disease. The results demonstrate that rapid measurement of the B-type natriuretic peptide level in the blood will improve the ability of clinicians to differentiate patients with dyspnea due to congestive heart failure from those with dyspnea due to other causes in acute care settings. This should be especially true among patients in whom the diagnosis of congestive heart failure is not clinically straightforward. The B-type natriuretic peptide test is now available in a rapid format, thus making diagnostic information immediately available to the acute care physician. Use of this test, in conjunction with other clinical information, should lead to more accurate initial diagnoses of congestive heart failure.

Presented in part at the 51st Scientific Sessions of the American College of Cardiology, Atlanta, March 17–20, 2002.

Triage devices and meters and some financial support were provided by Biosite, San Diego, Calif. Drs. Maisel and McCullough have received honorariums from Biosite for speaking and consulting.

We are indebted to the emergency department staff at the following study centers for their efforts: San Diego Veterans Affairs Medical Center, San Diego, Calif.; Henry Ford Hospital, Detroit; Hospital of the University of Pennsylvania, Philadelphia; Hôpital Bichat, Paris; Ullevål University Hospital, Oslo, Norway; the University of Cincinnati Medical Center, Cincinnati; and Hartford Hospital, Hartford, Conn.; and to Roberta A. Sullivan, B.S.N., M.P.H., for assistance with the preparation of the manuscript.

APPENDIX

Additional investigators include the following: the University of California, San Diego, Veterans Affairs Medical Center, San Diego: P. Hlavin, A. Lenert, and A.Y. Chiu; Henry Ford Hospital, Detroit: M. Whitican and J. Babiarz (study coordinators); the University of Pennsylvania, Philadelphia: E. Loh and F.D. Sites (study coordinator); Hôpital Bichat, Paris: M.C. Aumont, V. Beaumesnil, L. Hafi, A. Desplanques, and J. Benessiano (coinvestigators); Ullevål University Hospital, Oslo, Norway: A. Finsen, J.S. Riis, and T.O. Klemsdal (site coinvestigators); the University of Kentucky College of Medicine, Lexington: S. Lamba (coinvestigator).

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