ABSTRACT

Objective: Early recognition of left ventricular hypertrophy is important because anti-hypertensive treatment decreases morbidity and mortality. The ideal screening method for left ventricular hypertrophy in hypertensive emergency department (ED) patients has not been identified. Our objective was to determine the diagnostic accuracies of electrocardiogram (ECG) and N-terminal Pro-B-type natriuretic peptide (Pro-BNP) for left ventricular hypertrophy individually and in combination in hypertensive ED patients.

Methods: Prospective diagnostic study in an academic urban tertiary care hospital ED with annual census of 65,000 visits. Inclusion Criteria: Adult ED patients with systolic blood pressure greater than or equal to 160 mm Hg or diastolic blood pressure greater than or equal to 100 mm Hg on 2 or more measurements taken 60 minutes apart. Exclusion criteria: Patients with heart failure, renal insufficiency/failure, acute myocardial infarction, or without recent or scheduled echocardiograms. All patients received echocardiograms and had Pro-BNP levels measured using a RAMP point-of-care device (Response Biomed). We calculated diagnostic test characteristics with 95% confidence intervals.

Results: A total of 49 patients were enrolled. The average age was 57.9 years, 26.5% were male, 63.3% were African American. Thirty-two
patients (65%) had left ventricular hypertrophy by echocardiogram. Twenty-one (43%) had ECG evidence of left ventricular hypertrophy. Median Pro-BNP level was 268 picograms/mL. The combination of the two tests provided the greatest specificity (94%, 95% CI (69-99.7%) and positive predictive value (94%, 95% CI (68-99.7%).

Conclusions: The combination of ECG and Pro-BNP is a promising screening algorithm for identification of hypertensive ED patients with left ventricular hypertrophy.
INTRODUCTION

At least 50 million Americans have hypertension warranting some form of treatment\(^1\). In addition, suboptimal blood pressure control is the number one attributable risk for death throughout the world\(^2\). Hypertension precedes the development of heart failure in approximately 90% of heart failure patients and increases risk for heart failure by 2- to 3-fold\(^3\).

A recent re-classification of heart failure recognizes that therapeutic interventions performed even before the appearance of left ventricular hypertrophy can reduce the morbidity and mortality of heart failure\(^4\).

Current left ventricular hypertrophy screening tests, such as electrocardiogram (ECG) have been found lacking sensitivity. Therefore, a rapid, inexpensive, screening test for left ventricular hypertrophy in hypertensive emergency department patients could identify patients most in need of urgent follow-up and treatment. N-terminal Pro-B-type natriuretic peptide (Pro-BNP) release is one of the earliest responses to hemodynamic pressure overload and is elevated in patients with left ventricular hypertrophy\(^5\).

In this pilot study, we seek to determine the diagnostic accuracies of Pro-BNP and ECG individually and in combination for predicting left ventricular
hypertrophy in hypertensive emergency department patients. Our primary outcome was echocardiographic evidence of left ventricular hypertrophy.

METHODS

Study Design
Observational study of diagnostic test performance. Our institutional review board approved this study and all subjects gave informed consent.

Study Setting and Population
Patients were enrolled at an academic urban tertiary care hospital ED with annual census of 65,000 visits from October 2007 to August 2008. Patients over the age of 18 years with systolic blood pressure \( \geq 160 \text{ mm Hg} \) or a diastolic blood pressure \( \geq 100 \text{ mm Hg} \) on 2 or more measurements at least 60 minutes apart in the emergency department were eligible. We excluded patients with a history of renal insufficiency or failure (as defined by a glomerular filtration rate \( \leq 60 \text{ ml/min/1.73m}^2 \) calculated by the Modification of Diet in Renal Disease formula\(^6\)), who were determined to have acute coronary syndrome (as defined by abnormal troponin T value on their first cardiac marker or ST segment elevation on ECG), with a known history of heart failure, or who were unable to provide informed consent. We also excluded patients who did
not have echocardiogram data in the previous 3 months or who were not scheduled to have an echocardiogram as part of their clinical care.

**Study Protocol**

Trained research coordinators prospectively screened electronic ED tracking boards and medical records for eligible patients. Each patient was approached for consent. After consent, research coordinators collected a 3 milliliter (mL) blood specimen and determined Pro-BNP levels using a point-of-care platform (RAMP platform, Response Biomedical, Vancouver, BC Canada). All coordinators received formal in-service training on the point-of-care device, and had extensive formal training in venipuncture. One author, a board-certified emergency physician, blinded to Pro-BNP levels, scored all ECGs dichotomously for left ventricular hypertrophy using the Selvester score. In addition, a research coordinator prospectively recorded demographic, laboratory, radiographic, medication, ECG, and echocardiogram data from patients, providers, and electronic medical records on standardized case report forms. Response Biomedical provided supplies for measuring Pro-BNP, staff training, and research coordinator salary support. The authors retained full control over the data and all decisions regarding the writing and publication of the manuscript.
Key Outcome Measures

An echocardiogram reporting left ventricular hypertrophy was the primary outcome. We chose this because it is a marker of hypertensive damage to the heart and a precursor to heart failure. It is also routinely measured in all echocardiograms. We used it as a dichotomous outcome to facilitate diagnostic characteristic analysis. Echocardiograms were performed and read as per usual care by board-certified cardiologists blinded to study hypothesis, ECG, and Pro-BNP values.

Data Analysis

For Pro-BNP, a receiver operator curve was calculated for predicting left ventricular hypertrophy on echocardiogram and area under curve was calculated. Based on this analysis, the ideal cut point was identified, and diagnostic test characteristics calculated with 95% confidence intervals for a dichotomized Pro-BNP. Diagnostic test characteristics for ECG were calculated using similar dichotomized variable analysis with 95% confidence intervals. Likewise, we calculated the diagnostic test characteristics of a combination of the dichotomized Pro-BNP and ECG results, considering the combination positive if either individual test or both were positive. We performed a logistic regression analysis with left
ventricular hypertrophy as outcome and using the continuous Pro-BNP and dichotomous ECG as independent main effect variables plus an interaction variable. To calculate odds ratios with 95% confidence intervals, univariate logistic regression analyses were calculated for each dichotomized variable (ECG, N-terminal proBNP, and combination of both.) All statistics were calculated using SAS 9.2 Enterprise Guide 4.2 (Cary, NC).

RESULTS
A total of 56 patients were enrolled, of whom 7 did not have complete data and were excluded. The average age was 57.9 years. Patients were predominantly female (73.5%) and African American (63.3%). The most common symptoms reported were chest pain (50.7% of subjects), headache or dizziness (18.8%), or shortness of breath (11.6%). The range of initial blood pressure readings extended from 162 to 254 millimeters Hg for systolic pressures (mean 200.1, SD 23.4) and 75 to 135 millimeters Hg (mean 100.7 SD 14.9) for diastolic pressures, with a normal distribution for both. The majority (77.5%) reported taking some form of antihypertensive medication as outpatients. Thirty-two patients (65%) had evidence of left ventricular hypertrophy on echocardiogram. All of these echocardiograms were performed after
patient enrollment as part of usual clinical care. Among these patients, the most commonly reported symptom was chest pain 31.9% (compared to 18.8% of those without left ventricular hypertrophy). Twenty-one (43%) had ECG evidence of left ventricular hypertrophy. Median Pro-BNP level was 268 picograms/mL with a positively skewed distribution of values. A receiver operator curve for Pro-BNP as a continuous variable was calculated with area under the curve of 0.70. Based on these calculations, an ideal cutoff point of 258 picograms/mL was identified. The diagnostic test characteristics N-terminal proBNP and ECG alone and in combination are summarized in Table 1. The combination of the two tests provided the greatest specificity and positive predictive value.

In logistic regression analysis, the overall model was significant. ECG was an independent predictor of outcome but Pro-BNP was not. There was no significant interaction between ECG and Pro-BNP. The odds ratios calculated from univariate logistic regression with dichotomized variables for ECG, Pro-BNP, and the combination of both were 6.0 (95% CI 1.44-25.0), 1.0 (95% CI 1.00-1.01), and 5.5 (95% CI 1.53-19.7), respectively.

**DISCUSSION**
In this proof-of-concept study, we have demonstrated the feasibility of left ventricular hypertrophy screening in hypertensive ED patients using Pro-BNP and ECG. While individually these tests demonstrated only modest sensitivity and specificity for identifying left ventricular hypertrophy, in combination they demonstrated high specificity and positive predictive value.

The role of the ED in screening for hypertensive end-organ damage has been widely debated. It is known that many undertreated hypertensive patients are seen in the ED, and the long-term consequences of undertreated hypertension are well established. However, hypertension screening in the ED may increase cost and impede patient flow. Therefore, a rapid, inexpensive, ED screening paradigm is desirable.

Researchers have long observed that BNP levels are higher in patients with left ventricular hypertrophy. While its use for screening hypertensive patients in outpatient settings has been described, the use of BNP for hypertensive screening in the ED has not been extensively studied.

This pilot study suggests that due to its high specificity and positive predictive value, a combination of Pro-BNP and ECG could be used to prioritize patients for more intensive anti-hypertensive therapies. These two tests are very rapid, inexpensive, and non-invasive. They would thus make an ideal tool for the busy emergency physician who wishes to
identify high-risk hypertensive patients without slowing down departmental flow. While its modest sensitivity would indicate that many patients with left ventricular hypertrophy would be missed by this screening method, currently, screening and referral from the ED occurs so infrequently that even identifying only the highest-risk patients would be an improvement. This may particularly be the case when outpatient referral resources are scarce or overburdened. This finding may have significant public health implications.

Limitations

It is known that plasma BNP levels are affected by factors other than ventricular wall stretch\textsuperscript{10}. While we were able to control for some confounders of BNP level such as renal dysfunction, we were unable to control the timing of medications taken due to the emergency department setting. Our study is limited by convenience sampling and small sample size. We are thus unable to control for age or weight. In addition, due to small sample size we are unable to assess the role for BNP screening in subpopulations of left ventricular hypertrophy such as concentric remodeling or eccentric hypertrophy. It should also be noted that almost 74% of our patients were female, possible due to this small sample size.

Conclusion
A combination of ECG and Pro-BNP demonstrates high specificity and positive predictive value for left ventricular hypertrophy on echocardiogram. Future study with more rigorous control and increased sample size is warranted.
Table 1. Diagnostic Test Characteristics of N-terminal pro-BNP (NT-proBNP) and Electrocardiogram (ECG) Alone and In Combination for Left Ventricular Hypertrophy (LVH). Diagnostic test characteristics listed with 95% confidence intervals. NT-proBNP was considered positive if level was greater than 258 picograms/milliliter. ECG was considered positive if Sylvester score was positive. PPV = Positive Predictive Value, NPV = Negative Predictive Value, LR + = Likelihood Ratio Positive, LR - = Likelihood Ratio Negative.
References


