

**Evidence of Subclinical Heart Disease in an Asymptomatic Hypertensive Urban ED
Population**

BY

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THESIS

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LIST OF ABBREVIATIONS

DD	diastolic dysfunction
EHR	electronic health record
BMI	body mass index
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
LA	left atrial size
LAP	left atrial pressure
LVH	left ventricular hypertrophy
E-wave	early mitral inflow filling
A-wave	late diastolic mitral inflow filling
HF	Heart Failure
RAAS	Renin-angiotensin-aldosterone system
CCB	Calcium Channel Blockers
BP	Blood pressure
ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin-II receptor blockers
LV	left ventricular

SUMMARY

Approximately 50% of heart failure cases are due to diastolic failure.¹ Generally, it is thought that asymptomatic diastolic dysfunction precedes the development of diastolic heart failure, representing an ideal time for intervention.² At this time, there are no therapies/treatment for diastolic heart failure (also known as heart failure with preserved ejection fraction), thus placing a greater emphasis on prevention. The leading cardiovascular risk factor for heart failure with preserved ejection fraction is uncontrolled hypertension. Not only do minorities have higher rates of uncontrolled/untreated hypertension, but also suffer greater cardiovascular complications such as heart failure. Among all racial/ethnic groups, African American has the highest prevalence of cardiovascular risk burden, uncontrolled hypertension and diastolic heart failure. Previous studies have examined study diastolic dysfunction progression rates in non-minority populations only. The objective of this study was to prospectively determine the point prevalence of subclinical heart disease (diastolic dysfunction and left ventricular hypertrophy) in a minority ED population with a significant cardiovascular risk burden. The study design and setting involved a prospective cross sectional analysis conducted at the University of Illinois Hospital & Health Sciences System Emergency Department. A total of 47 patients were enrolled. The mean age was 44 years (SD 11.5 years), 58 % (n=27) were women, 21% (n=10) were smokers, 81% had hypertension (n=39), and 26% (n=10) required blood pressure treatment in the ED. The average BMI was 30.59 (SD=8.53). Racial/ethnicity included African Americans 70% (n=33), Latinos 22% (n=10), Caucasian 4% (n=2), Asian and Native Americans 2% (n=1 respectively). Subclinical hypertensive disease was found in 45 % (n=21) with 43% (n=12) having left ventricular hypertrophy, 14% (n=6) having evidence of diastolic dysfunction and 7% (n=3) having abnormal ejection

SUMMARY (continued)

fraction. After adjusting for other covariates, systolic BP ($p=0.04$), creatinine ($p=0.02$), and being on the Angiotensin Converting Enzymes Inhibitors (ACEI) ($p=0.06$) were associated with subclinical heart disease in multivariate regression analysis.²

This study found a significant point prevalence of subclinical heart disease in patients with asymptomatic hypertension evaluated in an urban ED setting.² This is particularly important in the prevention of hypertension-related cardiovascular complications such as heart failure. Studies have shown that left ventricular (LV) remodeling and the development of left ventricular hypertrophy (LVH) precedes the development of subclinical LV dysfunction (i.e. diastolic dysfunction) and aggressive treatment of hypertension can greatly attenuate the initial development of LVH.²

I. INTRODUCTION

Hypertension affects more than 76 million individuals in the United States and uncontrolled hypertension is one of the leading contributing factors for cardiovascular-related morbidity and mortality with rates that are 3.5-fold greater among minority groups as compared to non-minority groups.¹⁻⁴

Emergency departments serve a high-risk population with many patients utilizing the emergency department as part of their primary care access.^{3, 4} Uncontrolled/untreated hypertension is a frequent condition among patients presenting to emergency departments (ED) and is a finding in up to 25% of ED patients.^{5,6} Up to half of the patients presenting with elevated BP to the ED are not presently under medical care making the ED visit their only point of contact with health care providers.⁵ Among known hypertensives, approximately 42% report medication non-adherence.⁶ Although emergency departments serve high-risk patients, as a cohort this group represents an understudied population in regards to a role for secondary disease prevention.

Early identification of asymptomatic cardiac disease is an important component of cardiovascular disease prevention.^{7,8} A retrospective review found that hypertension was independently associated with the progression of asymptomatic diastolic dysfunction to the development of symptoms with a two-year cumulative probability of 31.1%.⁷ Studies have estimated the prevalence of asymptomatic diastolic dysfunction can be as high as 48% among high-risk groups with cardiovascular risk factors.⁸ Levy et al. in a cohort of African American patients identified from an urban ED found a 90% point prevalence of subclinical hypertensive heart disease.⁹

Left ventricular hypertrophy (LVH) is one of the strongest predictors of adverse cardiovascular outcomes in a hypertension population.¹⁰⁻¹³ de Simone et al. in a cohort of hypertensive individuals without prevalent cardiovascular disease found that the presence of left ventricular hypertrophy was associated with a higher risk of diastolic dysfunction than individuals with normal left ventricular mass.¹² Early recognition of left ventricular hypertrophy is important because it is reversible and antihypertensive medications can decrease the associated cardiovascular morbidity and mortality.^{13,14}

The study objective was to determine the point prevalence of left ventricular hypertrophy and diastolic dysfunction in a diverse urban emergency department (ED) population with asymptomatic hypertension utilizing real-time bedside ED echocardiograms and to examine the correlation between subclinical disease and patient cardiovascular risk profiles.² Understanding the prevalence of subclinical disease and relationship to risk factors for overt cardiovascular disease might allow targeted prevention strategies.

II. METHODS

A convenience sample of emergency department patients with elevated blood pressures (blood pressure $\geq 140/90$ mm Hg) with or without a history of hypertension were consented and enrolled from the University of Illinois Hospital and Health Sciences System Emergency Department. There were a total of eight emergency department patients with normal blood pressures randomly selected (one per study enrollment session) and consented to serve as controls. Patients were enrolled at various times of the days including early mornings, weekends and nights to obtain a representative sampling of patients. Inclusion criteria: Adult ED patients with blood pressures $\geq 140/90$ (on 2 or more measurements taken at least 30 minutes apart in the emergency department) and/or a past medical history of hypertension. Exclusion criteria: Patients presenting with hemodynamic instability, history of heart failure, renal failure, or an inability to provide consent were excluded from study participation.

I.A. Cohort study variables

Baseline demographic characteristics (age, gender, race/ethnicity, body mass index (BMI), tobacco use), use of antihypertensive medications, primary/chief complaint for the ED visit by organ system, comorbidities (past medical history), clinical data (blood pressure, blood urea nitrogen, creatinine, and hemoglobin levels), and the presence (or absence) of selected echocardiography parameters (diastolic dysfunction grade, ejection fraction, left ventricular hypertrophy (LVH)) were recorded.

I.B. Echocardiograms

Subjects had bedside echocardiograms performed by ultrasound fellowship trained ED

physicians. All echocardiographic measurements were performed using a commercially available ultrasound system equipped with a harmonic 4.0 MHz variable-frequency phased –array transducer. Patients were classified as having subclinical hypertensive heart disease if any of the following were identified using standard echocardiogram criterion: left ventricular hypertrophy, abnormal ejection fraction, or diastolic dysfunction.^{2, 15,16}

Determining diastolic function in patients' with normal ejection fraction: Diastolic function was evaluated by estimating LA pressure using E/e' ratio. Diastolic dysfunction considered to be present if E/e'(septal) was greater than or equal to 15, if E/e'(lateral) was greater than or equal to 12, if septal e' was less than 8cm/sec, if lateral e' was less than 10cm/sec. Diastolic function was considered to be absent if E/e'(septal or lateral) was less than or equal to 8. For patients with E/e' between 9-12, patient was considered to have elevated LAP if LA diameter was greater than 46mm in the short axis.

Determining diastolic dysfunction in patients' with reduced ejection fraction: Diastolic dysfunction considered absent if E/A ratio was less than 1 and E was less than 50cm/s. Diastolic dysfunction was considered present if E/A ratio was greater than 2, if septal e' was less than 8cm/sec, if lateral e' was less than 10cm/sec or if E/e' (average) was greater than 15.

Grading of diastolic dysfunction: Once diastolic dysfunction was determined, the E/A ratio was used to determine the grade of diastolic dysfunction. If E/A ratio was less than 0.8, then the patient was considered to have grade I diastolic dysfunction. If E/A was between 0.8-1.5, then the patient was considered to have grade II diastolic dysfunction. If E/A was greater than 1.5, the patient was considered to have grade III diastolic dysfunction. Diastolic left ventricular function was reported as normal or abnormal.¹⁷ Diastolic

dysfunction was graded on a 3 point ordinal scale; (1) mild diastolic dysfunction (Grade I, impaired relaxation); (2) moderate diastolic dysfunction (Grade II, pseudo-normal); and (3) severe diastolic dysfunction (Grade III, restrictive).

Bedside cardiac ultrasound measurements: Mitral flow velocities were recorded in the apical 4-chamber view, placing the pulsed-wave Doppler sample volume between the tips of the mitral leaflets, and peak E and A waves, as well as the deceleration time of the E wave, were measured.¹⁷ The tissue Doppler imaging of the septal and lateral mitral annulus was performed on all patients. Doppler tissue imaging was evaluated by placing the sample volume at the lateral and septal mitral annulus to assess peak tissue velocities of relaxation. Left atrial diameter was measured in short axis at end systole. Left ventricular free wall thickness was measured in the parasternal long view at end diastole. Left ventricular hypertrophy was reported as present or absent.¹⁸ Ejection fraction, defined as was noted as normal ($\geq 55\%$) or abnormal ($< 55\%$). Emergency department echocardiograms were independently reviewed for classification accuracy by a board certified Cardiologist (Interobserver agreement 82%; Cohen's kappa statistic 0.95)

I.C. Data Analysis

Descriptive characteristics of study participants including demographics, physical measures, medication use, medical history, and echocardiogram parameters were correlated with the presence or absence of subclinical heart disease. For continuous variables, t-tests or Wilcoxon two-sample tests were used to test significance of difference between the those subjects with and without subclinical heart disease as appropriate; for categorical variables, Pearson's chi-square test or Fisher's exact test were used as appropriate. The following covariates were examined: age, gender, body mass index (BMI), presence of diabetes, tobacco use, blood urea nitrogen, creatinine, history of hypertension,

blood pressure treated in the ED, and antihypertensive medication classification (i.e. angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, vasodilators, and central agonists). Covariates were selected based upon the reviewed medical literature. Backward stepwise elimination logistic regression analysis was performed to examine the association of risk factors with subclinical heart disease.

The University of Illinois Institutional Review Board reviewed and approved this study.

III. RESULTS

III.A. Description of Cohort Characteristics

A total of 47 emergency department patients were enrolled. There was no predominance of cardiac symptoms among presenting chief complaints (multiple complaints 28%, musculoskeletal 26%, cardiac 21%, gastrointestinal 15%, ENT 2%, and pulmonary 2%). The mean age was 44 years (SD 11.5 years), 58 % (n=27) were women, 21% (n=10) were smokers, 81% had hypertension (n=39), and 26% (n=10) required blood pressure treatment in the ED. The average BMI was 30.59 (SD=8.53). Race/ethnicity included African Americans 70% (n=33), Latinos 22% (n=10), Caucasian 4% (n=2), Asian and Native Americans 2% (n=1 respectively). ² The demographics of the subject population reflect those of the primary service area for the medical center with 40% African American, 30% Latino, 20% Caucasian and an increasing number of Asians and Native Americans. Subclinical hypertensive disease was found in 45% (n=21) with 43% (n=12) having left ventricular hypertrophy, 14% (n=6) having evidence of diastolic dysfunction and 7% (n=3) having abnormal ejection fraction. ² Of those subjects demonstrating diastolic dysfunction, the majorities were at grade 2 (Grade I- 33% n= 2, Grade 2- 50% n=3, Grade 3- 17% n=1). (Table 2)

III.B. Covariates associated with subclinical heart disease

Bivariate analyses were performed to first identify variables that are significantly associated with either having left ventricular hypertrophy, diastolic dysfunction or low ejection fraction. Based upon analysis, subjects with evidence of Stage II hypertension (SBP > 160, p< 0.0156; DBP >100, p < 0.0066) or elevated blood urea nitrogen levels (p< .0266) were

statistically significantly more like to have evidence of subclinical heart disease.

(Table 1)

Based upon those results, variables were selected in order to narrow down the pool of variables to be included in the final regression model. In a multivariate analysis done via stepwise backward elimination logistic regression, eight covariates (SBP, DBP, BUN, Cr, history of hypertension, Beta Blockers, ACEi, and BP treated in ED) were examined. After adjusting for other covariates, systolic BP ($p=0.04$), blood urea nitrogen ($p=0.02$), and creatinine ($p=0.02$) were associated with subclinical heart disease in multivariate regression analysis.² (Table 2)

IV. DISCUSSION

Our study found a point prevalence of subclinical heart disease of 45% in this diverse urban ED population with asymptomatic hypertension with the majority having evidence of left ventricular hypertrophy (43%).² This represents a higher proportion compared to population studies such as the Multi-Ethnic Study of Atherosclerosis (MESA), which found a 9.8% prevalence of left ventricular hypertrophy among study participants and 13.1 % prevalence among hypertensive participants.^{18,19} The MESA study is a longitudinal cohort study of men and women 45 to 84 years of age without clinical cardiovascular disease.^{18,19} Our findings are not surprising given that hypertensive patients presenting to the ED are a particularly high-risk group for target organ damage (TOD) and its consequences with >50% with stage II or higher hypertension (SBP > 160 or DBP >100).^{20,21} In a separate study among an African American cohort conducted in an urban ED, Levy et al. found a 90% point prevalence of subclinical hypertensive heart disease; however the majority demonstrated evidence of diastolic dysfunction (89.7%) and more than half of the subjects had evidence of both left ventricular hypertrophy and diastolic dysfunction (57.3%) demonstrating more advanced progression of subclinical disease.⁹ Several studies have attempted to define factors that may explain higher hypertension-related risk in the ED.^{20,22} In a previous study in a mostly minority, urban population, patients with hypertensive urgencies and emergencies (hypertension and symptoms of target organ damage) were more likely to report lack of primary care physician, decreased medication adherence, and lack of health insurance than patients with history but controlled hypertension in the ED.²⁰

The ED visit may be a good teachable moment opportunity for some of our most vulnerable

populations to come in contact with health care providers and an ideal setting for HTN and TOD surveillance and to initiate treatment interventions. Early identification of subclinical heart disease (such as diastolic dysfunction and left ventricular hypertrophy) is a critical component of secondary cardiovascular disease prevention. Our study found significant percentages of both uncontrolled /untreated hypertension (73%) in this study cohort, thus reinforcing the need and the pivotal role that emergency departments can play in screening and referral of patients.

One of the primary goals of antihypertensive therapy is to reduce cardiovascular events and data suggest that blood pressure management is the primary determinant of cardiovascular risk reduction.²³ This is particularly important in the prevention of hypertension-related cardiovascular complications such as heart failure because studies have shown that left ventricular (LV) remodeling and the development of left ventricular hypertrophy (LVH) precedes the development of subclinical LV dysfunction (i.e. diastolic dysfunction) and aggressive treatment of hypertension can greatly attenuate the initial development of LVH.^{12,13} Our study found that the majority of participants with abnormal bedside echocardiograms had left ventricular hypertrophy indicating a window of potential opportunity for intervention.

Previous studies have reported that independent predictors of diastolic dysfunction included arterial hypertension, evidence of left ventricular hypertrophy (LVH), obesity, diabetes, and coronary artery disease.²⁴ Our study cohort had significant percentages of LVH and obesity, thus representing another significant opportunity for cardiovascular risk factor modification. In addition, studies have shown that in patients with established LVH, disease regression is possible hence providing an objective target for monitoring the effectiveness of clinical interventions.¹⁵

known.^{25,26} Recently, the significant relationship of LVH and diastolic function with cardiovascular and renal outcomes in African Americans with hypertension chronic kidney disease has been documented.²⁷ African Americans are disproportionately affected by hypertension, LVH, and chronic renal disease with disease progression leading to death, stroke, heart failure and end-stage renal disease.²⁸ Our study cohort included a population at high risk for hypertensive cardiovascular complications (African-American 70%, and Hispanic 22%), and among risk factors examined found systolic BP and creatinine were statistically significant with the presence of subclinical heart disease.

IV.A. Limitations

This study involved a small convenience sample of emergency department patients from a single urban academic emergency department and may not accurately reflect the true extent of subclinical heart disease in an asymptomatic hypertensive population. In addition, although there was an attempt to include all racial/ethnic groups in the study cohort, certain racial groups remained underrepresented; however the demographics of the cohort were representative of the overall ethnic composition of the patient population at this medical center.

IV. B. Conclusion

Our study demonstrates that patients with hypertension in the ED are at high risk for asymptomatic hypertensive heart disease compared to the general population. In the vast majority of hypertensive patients the occurrence of major CV events is preceded by the development of asymptomatic abnormalities at the vascular and cardiac level, such as left

ventricular hypertrophy and dysfunction. The ED visit may be a ideal teachable moment opportunity for some of our most vulnerable populations and a model setting for HTN and TOD surveillance and to initiate treatment interventions. Using ED limited bedside echocardiography we were able to identify patients with asymptomatic hypertensive heart disease. In patients with elevated BP and no symptoms related to their BP, identification of hypertensive heart disease can help risk stratify and identify patients in need for more aggressive therapy and decrease likelihood for progression of hypertensive heart disease and sequel such as heart failure and renal failure.

Table 1: Demographics, Clinical Parameters, and Echocardiogram Data for Study Cohort

Covariates	Overall N=47	Subclinical Heart Disease (N=16)	No Evidence of Subclinical Heart Disease (N=29)	P value,
Mean Age, y (SD)	44.0 (11.5)	46.4 (11.1)	43.3 (11.9)	0.41
Gender, N (%)				0.77
• Male	18 (40.9)	7 (43.8)	11 (39.3)	
Race/Ethnicity, N (%)				0.60
• African Americans	31 (70.5)	13 (81.3)	18 (64.3)	
• Latinos	9 (20.5)	3 (18.7)	6 (21.4)	
• Caucasian	2 (4.6)	0	2 (7.1)	
• Asians	1 (2.3)	0	1 (3.6)	
Body Mass Index, kg/m ²		29.4 (5.9)	30.7 (9.5)	0.61
History of Hypertension, N (%)	36 (80)	15 (93.8)	21 (72.4)	0.1275
BP treated in ED	26 (72.2)	6 (46.2)	20 (87.0)	0.0087
Taking antihypertensive medications, N (%)				
• ACEI or ARB	13 (28.9)	7 (43.8)	6 (20.7)	0.1023
• Beta Blockers	13 (28.9)	7 (43.8)	6 (20.7)	0.1023
• Calcium Channel Blockers (CCB)	6 (13.3)	2 (12.5)	4 (13.8)	0.90
• Diuretics	3(6.4)	1(6.25)	2(6.9)	
• Other	9 (20)	5 (31.3)	4 (13.8)	0.16
Tobacco Use	9 (20.5)	3 (18.8)	6 (21.4)	0.83
History of Diabetes	18 (40)	8 (50)	10 (34.5)	0.31
Vital signs, mean (SD)				
• Systolic Blood Pressure		173.1 (26.1)	151.5 (28.1)	0.0156
• Diastolic Blood Pressure		101.9 (14.2)	88.8 (14.9)	0.0066
Renal Function				
• Serum creatinine, g/dL		3.92 (5.87)	0.92 (0.37)	0.0780
• Blood urea nitrogen, g/dL		21.2 (12.7)	12.8 (6.3)	0.0266
Hemoglobin		11.7 (2.5)	12.5 (2.4)	0.31

Table 2: Multivariate Logistic Regression for covariates and subclinical heart disease in an Urban ED population with Asymptomatic Hypertension

Effect	p-value	Odds Ratio Estimate	Odds Ratio 95% CI
Systolic Blood Pressure	0.0463	1.096	(1.002, 1.200)
Blood Urea Nitrogen	0.0268	0.550	(0.324, 0.934)
Creatinine	0.0244	>999.999	(3.037, >999.999)
Use of ACEi	0.0611	13.876	(0.884, 217.740)

Table 2: Multivariate Logistic Regression involving Clinical parameters, Antihypertensive Medication Classification, Hypertension history/treatment and subclinical heart disease in an urban ED population with elevated blood pressures.

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 2007 Illinois Department of Public Health: Center for Minority Health “Understanding Factors Associated with Emergency Department Use among Minority Elderly” Prendergast HM, PI, 20,000 Funded
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2. Prendergast HM, Schlichting A, Bell K, Mackey E: “Certification Requirements for Coaching Staff of Illinois High School Athletic Teams,” Illinois College of Emergency Physicians (ICEP) Research Forum, 2005, Chicago, IL
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