Prevalence, Determinants, and Clinical Significance of Cardiac Troponin-I Elevation in Individuals Admitted for a Hypertensive Emergency

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Hypertensive emergencies (HEs) are frequently accompanied with the release of cardiac troponin I (cTnI); however, determinants and clinical significance of cTnI elevation are largely unknown. A retrospective analysis was performed on patients (n=567) with a diagnosis of HE admitted to two tertiary care centers that primarily serve an inner-city population. Data on demographics, clinical variables, and cTnI were collected through chart review. Using regression analyses, predictors of cTnI elevation were studied and the impact of cTnI on all-cause mortality (data obtained through the Social Security Death Index) was determined. cTnI elevation was observed in 186 (32.3%) admissions with a mean peak cTnI level of 4.06±14.6 ng/mL. Predictors of cTnI were age, history of hypercholesterolemia, blood urea nitrogen level, pulmonary edema, and requirement for mechanical ventilation. During a mean follow-up period of 3.1 years, there were 211 deaths (37%). Neither the presence nor the extent of cTnI elevation was associated with mortality, while age, history of coronary artery disease, and blood urea nitrogen level were predictive of mortality. cTnI elevation commonly occurs in the setting of HEs. Despite a high incidence of adverse clinical outcomes, cTnI elevation was not an independent predictor of mortality in this population. *J Clin Hypertens (Greenwich).* 2011;13:551–556. ©2011 Wiley Periodicals, Inc.

Approximately 72 million people in the United States are affected by hypertension (HTN).[1] Hypertensive emergencies (HEs) are characterized by severe elevations in blood pressure (BP) (>180/120 mm Hg), complicated by new or worsening target organ dysfunction, and require immediate reduction in BP to limit end-organ damage. HEs account for 6% of all patients with clinical emergencies presenting to the emergency department.[2,3]

Patients with HEs frequently have elevations in cardiac biomarkers such as cardiac troponin I (cTnI), despite the absence of symptoms or electrocardiographic (ECG) changes suggesting myocardial infarction.[4,5] However, the importance of cardiac troponin release in HE is currently uncertain.

cTnI is a sensitive and specific marker of myocardial cell injury and is of prognostic value in patients with acute coronary syndromes[6] and a variety of other critical care problems.[5,7–12] The frequency, predictors, and clinical relevance of cTnI elevation in the setting of HEs are currently lacking.

This study sought to specifically explore the prevalence, clinical determinants, and prognostic significance of cTnI release in patients presenting with HEs.

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METHODS

We conducted a retrospective analysis of admissions to two major medical centers that service a predominantly inner-city population for the diagnosis of HE. Together these two hospital systems provide the majority of the emergency department care within the city limits of Detroit, Michigan, and utilize electronic medical record systems. The study was approved by the institutional review boards at both institutions.

Patient Selection

All patients admitted to the inpatient ward or intensive care units with HE as the primary diagnosis (between January 2000 and July 2006) and who had cTnI measured within 12 hours of admission were screened for inclusion into the study. Further, all screened patients had to fulfill the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Report (JNC 7)[3] criteria for HE on review of the medical record. As stated in the JNC 7 guidelines, an HE is characterized by extreme elevations in BP (>180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction.

Exclusion Criteria

All patients with acute coronary syndrome (ACS) or ST-elevation myocardial infarction (STEMI) or those determined to have obstructive coronary artery disease requiring intervention during the index admission were

excluded. Patients with confounding clinical conditions associated with the nonthrombotic release of cardiac biomarkers such as cocaine abuse (historical or documented by positive urine drug screening), electrocardiographically documented ventricular or supraventricular tachycardia (excluding sinus tachycardia), severe aortic stenosis, pulmonary embolism, sepsis, myocarditis, or pericarditis were excluded. Similarly, patients who left the hospital against medical advice, those transferred to another facility, and those missing key clinical variables were also excluded from the analysis.

Of the 595 patients with the diagnosis of HE, 22 (4.0%) were eliminated because no troponin data were available. After careful chart review for the above-listed exclusions, final data sets comprising 567 patients met inclusion criteria and were considered in the final analysis.

Data Collection

A detailed cross-sectional survey of paper and electronic medical records was undertaken for demographic and clinical data. Peak systolic BP (SBP) and diastolic BPs (DBP), as well as heart rate, were noted from emergency medical system field records or the emergency room assessment sheet. Mean arterial pressure (MAP) was calculated as DBP+1/3 (SBP-DBP). Pulse pressure was calculated as the difference between SBP and DBP. Similarly, rate-pressure product or double product was computed by multiplying the peak SBP and heart rate (beats per minute). Data on hypercholesterolemia per National Cholesterol Education Program screening criteria[13] or diabetes as per American Diabetes Association criteria[14] were ascertained from the medical record or from the use of glucose or lipid-lowering agents. Peak levels of blood urea nitrogen (BUN) and creatinine were recorded. The Modification of Diet in Renal Disease (MDRD) formula was used to estimate the glomerular filtration rate (GFR) during the index presentation. Patients were subsequently categorized into chronic kidney disease stages based on their GFR, as defined by the National Kidney Foundation.[15]

The presence of pulmonary edema on admission was defined as acute onset of dyspnea within the preceding 6 hours, with chest radiographic findings of pulmonary interstitial or alveolar edema and increased bronchovascular markings (as interpreted by the radiologist in the medical record).[16–18] Requirement for mechanical respiratory ventilation and left ventricular ejection fraction (LVEF) as assessed by transthoracic echocardiography were also abstracted from the medical records. However, not all individuals included in the analysis had echocardiography performed during their hospitalization. Left ventricular systolic dysfunction was defined as an LVEF $<50\%$. A systolic dysfunction score (SDS) was assigned based on the reported ejection fraction (EF). A normal EF ($\geq 50\%$) was assigned a score of zero, systolic dysfunction was further stratified as mild (40%–49%, SDS=1), moderate (30%–39%, SDS=2), or severe dysfunction ($<30\%$, SDS=3). Left ventricular hypertrophy (LVH) was defined both from the ECG (voltage criteria) and echocardiography if the left ventricular posterior wall or septal wall thickness was reported to be >12.0 mm. All-cause mortality data was assessed from the Social Security Death Index.

cTnI Measurements

The peak troponin value during the index admission was used for the final analysis. cTnI was considered elevated if it was above the normal reference for the particular institution at the time of hospitalization. Due to the extended study period (2000–2006) and the evolution of more sensitive cTnI biomarker assays during this time, cutoff values and reference ranges for cTnI varied within and between institutions. One institution used an Abbott AxSYM microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL) for quantitative determination of serum cTnI, with the normal reference being <2 ng/mL until February 2, 2003, and <0.4 ng/mL afterwards. The second institution used the Abbott AxSYM method until July 1, 2003, with a normal cTnI being <1 ng/mL and the Bayer ADVIA Centaur chemiluminometric-immunoassay (Bayer Diagnostics, Tarrytown, NY), effective July 2, 2003 with a cTnI cutoff of <0.2 ng/mL.

Subgroups With Preserved and Reduced EF

All admissions and patients were stratified into preserved EF (LVEF $\geq 50\%$) and reduced EF (LVEF $<50\%$) groups.

Statistical Analysis

Analyses were conducted on the total number of index admissions for HE (n=567). The admissions were stratified into two groups: elevated cTnI vs normal cTnI levels. Nonbinary variables that were normally distributed were compared using the two-sample *t* tests, otherwise a Wilcoxon rank-sum test was employed. Categoric variables were studied using the Chi-square test.

Clinical variables were selected based on hypothesis and previous research, with respect to cTnI elevation. These variables were entered into a univariate regression analysis and variables with *P* values $<.20$ were subsequently entered into a stepwise logistic regression analysis to determine which predict cTnI elevation. In secondary analysis, a similar evaluation was conducted in the subgroups of patients with preserved EF and reduced EF as defined above. Subsequently, Cox regression analysis was performed to determine the hazard ratio for all-cause mortality. In an attempt to ascertain whether magnitude of troponin release in patients with HE has prognostic significance, patients and admissions with elevated cTnI were stratified into tertiles (based on peak troponin levels, after appropriately adjudicating for institution and cTnI assay cutoffs) and clinical outcomes compared with the

reference group (negative cTnI). We also analyzed the data after converting the cTn1 values into a logarithmic scale as the cTnI values were not normally distributed. All analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NJ), and a P value $<.05$ was considered statistically significant.

RESULTS

The mean age of patients in the study was 58.0±16.0 years; 516 (91%) were African Americans, and 265 (46.7%) were men. cTnI elevation was observed in 186 (32.3%) patients, with a mean peak cTnI level of 4.06±14.68 ng/mL.

Baseline and clinical characteristics of the cohort stratified by cTnI elevation (yes/no) are presented in Table I. No sex differences were noted between cTnI groups. cTnI elevation was associated with more advanced age (63 vs 55 years), lower DBP (122.9 mm Hg vs 128.9 mm Hg), lower MAP (155.3 mm Hg vs 160.8 mm Hg), higher heart rate (102.4 beats per minute [bpm] vs 94.7 bpm), higher double product (22,664 mm Hg*bpm vs 21,261 mm Hg*bpm), and lower LVEF (44.4% vs 50.9%). cTnI elevation was also associated with a higher prevalence of diabetes (37% vs 24%), hypercholesterolemia (34% vs 23%), pulmonary edema (50% vs 21%) on presentation, and need for mechanical ventilation (25% vs 4%). No significant differences in coronary artery disease (17% vs 13%) or evidence of LVH were observed at baseline. Moreover, higher peak BUN levels (43.5 vs 32.9 mg %) and creatinine (3.9 vs 3.0 mg %) were found in the cTnI elevation group.

Next, from stepwise regression analysis (for the above variables), we identified age, history of hypercholesterolemia, peak BUN, pulmonary edema, and requirement for mechanical ventilation as independent predictors of cTnI elevation (Table II). The highest odds ratio (OR) for cTnI elevation was observed for variables associated with respiratory failure: evidence of pulmonary edema (odds ratio [OR], 2.40; 95% confidence interval [CI], 1.559–3.696) and need for mechanical intubation (OR, 3.98; 95% CI, 2.058–7.697).

TABLE I. Baseline Demographic and Clinical Characteristics of Admissions Stratified by Cardiac Troponin-I Positivity (n=735)

Variables	Cardiac Troponin I Elevation		
	No (n=381)	Yes (n=186)	*P* Value
Age, y	55±15	63±16	<.001
African American, %	346 (91)	170 (91)	.81
Male sex, %	190 (50)	75 (40)	.032
Systolic blood pressure on admission, mm Hg	224.5±30.1	220.1±23.8	.085
Diastolic blood pressure on admission, mm Hg	128.9±22.4	122.9±26.1	.006
Mean arterial pressure, mm Hg	160.8±21.5	155.3±21.5	.004
Heart rate, beats per min	94.7±22.4	102.4±23.8	<.0001
Double product, mm Hg × beats per min	21,261±5956	22,664±6215	.013
Blood urea nitrogen, mg %	32.9±25.2	43.5±31.5	<.0001
Creatinine, mg %	3.0±3.6	3.9±4.00	.013
eGFR, mL/min	64.8±32.8	54.1±33.6	<.001
Left ventricular ejection fraction,[a] %	50.9±13.2	44.4±14.4	<.001
Systolic dysfunction score[a]	0.54±0.97	0.91±1.10	.0002
Left ventricular hypertrophy on ECG, %	163 (47)	67 (37)	.025
Left ventricular hypertrophy on echocardiography,[a] %	257 (87)	151 (86)	.615
History of coronary artery disease, %	50 (13)	32 (17)	.19
History of cerebrovascular accident, %	40 (11)	29 (16)	.08
History of coronary artery bypass surgery, %	8 (2)	11 (6)	.017
Evidence of pulmonary edema on presentation, %	75 (21)	93 (50)	<.0001
Need for mechanical intubation, %	17 (4)	47 (25)	<.0001
History of diabetes, %	91 (24)	68 (37)	.0001
History of hypercholesterolemia, %	89 (23)	63 (34)	.008

Abbreviations: ECG, electrocardiography; eGFR, estimated glomerular filtration rate. Data presented as mean (standard deviation) unless otherwise indicated ([a]n=469).

Subgroup Analyses

We identified 172 patients with reduced LVEF. There were 297 patients with preserved LVEF. Mean LVEF of patients with reduced EF was 32.8%±10.1% compared with 57.6%±5.8% for the preserved EF group. At baseline, the reduced EF group had a higher prevalence of pulmonary edema (48% vs 25%; $P<.01$) and elevated troponin (50% vs 30%; $P<.01$). When LVEF was included in the stepwise model, LVEF emerged as one of the independent predictors of cTnI elevation (OR, 0.97; 95% CI, 0.96–0.99) along with age, BUN, pulmonary edema, and need for mechanical intubation (Table II). From stepwise regression analysis, independent predictors for cTnI elevation (Table II) for the subgroup with preserved EF were age, pulmonary edema at presentation, and need for mechanical intubation, whereas age, pulmonary edema, need for mechanical intubation, and BUN predicted cTnI elevation in patients with reduced EF.

Mortality

During a mean follow-up of 3.1 years, there were 211 (37%) deaths. There were 130 (34%) deaths in the normal cTnI level group and 27 (43%) deaths in each of the tertile-based groups. On univariate analysis, cTnI elevation release during the index admission was associated with increased risk for all-cause mortality (hazard ratio [HR], 1.56; 95% CI, 1.19–2.07;

TABLE II. Odds Ratios and 95% Confidence Intervals for Cardiac Troponin-I Elevation for Hypertensive Emergency (n=567): Results From Stepwise Logistic Regression Analyses

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Model without LVEF (n=567)			
Age, y	1.028	1.015–1.041	<.0001
Blood urea nitrogen, mg %	1.009	1.002–1.017	.0129
Pulmonary edema on presentation (yes/no)	2.40	1.559–3.696	<.0001
Need for mechanical Intubation (yes/no)	3.980	2.058–7.697	<.0001
History of hyperlipidemia (yes/no)	1.692	1.091–2.623	.0188
Model with LVEF (n=469)			
Age, y	1.031	1.017–1.045	<.0001
Blood urea nitrogen, mg %	1.008	1.000–1.016	.0430
Pulmonary edema on presentation (yes/no)	1.911	1.201–3.040	.0063
Need for mechanical intubation (yes/no)	4.023	1.913–8.461	.0002
Increasing LVEF, %	0.97	0.96–0.99	.0009
Subgroup analysis restricted to patients with preserved EF (n=297)			
Age, y	1.029	1.013–1.046	.0005
Pulmonary edema on presentation (yes/no)	2.077	1.120–3.849	.0203
Need for mechanical intubation (yes/no)	3.163	1.187–8.430	.0213
Subgroup analysis restricted to patients with reduced EF (n=172)			
Age, y	1.033	1.009–1.059	.0071
Pulmonary edema on presentation (yes/no)	2.326	1.146–4.724	.0195
Need for mechanical intubation (yes/no)	5.222	1.574–17.327	.0069
Blood urea nitrogen, mg %	1.016	1.002–1.030	.0215

Abbreviations: EF, ejection fraction; LVEF, left ventricular ejection fraction.

P=.01); however, after multivariate adjustment, it lost significance (HR, 1.13; 95% CI, 0.84–1.52; *P*=.41). The independent predictors of mortality included age (HR, 1.025; 95% CI, 1.016–1.034; *P*<.0001), history of coronary artery disease (HR, 1.463; 95% CI, 1.028–2.083; *P*=.03), and BUN level (HR, 1.012; 95% CI, 1.008–1.016; *P*<.0001). None of the tertile-based groups were found to be associated with all-cause mortality on both univariate and multivariate analysis (HR for each group, 1.03; 95% CI, 0.91–1.17; *P*=.64). Re-analyzing the data after logarithmic transformation of cTnI values revealed similar results.

DISCUSSION

We sought to determine factors associated with cTnI elevation in the setting of HE and the significance of elevation on subsequent outcome. Our findings are novel and suggest that (1) cTnI elevation in the absence of apparent myocardial infarction is a common event, occurring in roughly a third of admissions for HE; (2) individuals presenting with HE appear to experience an alarming mortality rate of 36% during a relatively short follow-up period of 3.1 years; and (3) cTnI elevation does not appear to be predictive of subsequent mortality. Finally, our study also characterizes previously undocumented predictors of troponin release in the setting of HE.

Determinants of cTnI Release in HE

The predictors of cTnI elevation included age, history of hypercholesterolemia or diabetes, elevated heart rate, higher BUN levels, and evidence of pulmonary edema, with the strongest association of all being the need for mechanical ventilation. Notably, prior known coronary artery disease and left ventricular dysfunction were not correlated with elevation of cTnI. Low levels of troponin release have been shown to have diagnostic and prognostic utility in a wide variety of cardiac and noncardiac scenarios.[19] The pathophysiologic mechanisms responsible for cTNI release in HE are likely multifactorial. Our analysis uncovered several clinical predictors of cTnI release in HE, including tachycardia, a known mediator of demand ischemia. However, neither the double product (an indirect measure of myocardial oxygen demand) nor the extent of SBP elevation at admission was predictive of cTnI elevation. In the subgroup analyses that included measures of left ventricular systolic function, EF emerged as a predictor of troponin release.

Pulmonary edema may accompany severe hypertensive states[16,20] and has been attributed to diastolic dysfunction.[16,17] Our analysis suggests that a precipitous increase in left ventricular filling pressure, attendant myocyte stretch, subendocardial ischemia, and hypoxia may have accounted for the high prevalence of cTnI elevation in individuals with an HE and pulmonary edema or need for mechanical ventilation.[21,22] Frequently, such patients may develop hypoxemia, transient left ventricular dysfunction, and dilation—any or all of which may explain our observation. This has been observed by others.[6,23] Troponinemia in this setting may be a reflection of nonthrombotic release ensuing from demand ischemia.

Another finding that emerged from our analysis is the relation between cTnI elevation and BUN level. Elevation of BUN levels in the setting of an HE is likely the result of vasomotor alterations in renal blood flow and activation of the renin-angiotensin-aldosterone system.[23–25] Thus, worsening BUN may be a more robust surrogate of the cumulative hemodynamic and neurohormonal alterations or "cardiorenal status derangement," while serum creatinine may only reflect "renal status." Analogous to our findings, it is noteworthy that BUN but not creatinine has been shown to be a predictor of mortality in patients with heart failure, and that BUN but not creatinine was

associated with cTnI elevation in this population.[26,27] In contradistinction to cTnT, it should also be noted that impaired renal function in itself does not contribute to raised cTnI levels in the absence of acute coronary syndromes.[10]

Prognostic Significance

Contemporary mortality data on individuals with HE in the United States are sparse. Early data suggest that the outcome of untreated malignant hypertension is extremely poor, with a 1-year survival rate of only 65% in patients presenting with advanced retinopathy.[28] More recent data from the United Kingdom for individuals with malignant hypertension suggest a 5-year survival rate of 74%, with a significantly worse survival for black patients.[29] Our observations suggest that the mortality associated with HE in a predominantly African American inner-city population in the current era remains alarmingly high, estimated at 12% (annual mortality) in our study population. Surprisingly, cTnI release in patients presenting with HE was not associated with all-cause mortality. However, advancing age, history of coronary artery disease, and serum BUN levels emerged as the only significant predictors of mortality on follow-up. Although it is unclear why cTnI was not useful in the risk stratification of our patients with HE, it is conceivable that the disproportionately high overall mortality intrinsic to this population may have mitigated the prognostic utility of cTnI positivity in these patients with HE.

Study Strengths and Limitations

This is the first study to our knowledge to examine the pathophysiology, predictors, and clinical significance of cTnI release encountered in patients with HEs. It is evident from our findings that cTnI is routinely drawn in the large majority of patients presenting with HE even though data on the clinical utility of this biomarker in this setting are nonexistent. In this study, the vast majority (96% of HE patients screened) had troponin drawn. Although we did not analyze emergency department physician bias, we noted a similar trend for ordering this test among emergency department physicians from both institutions; thus, a selection bias if present is likely to be minimal at best.

No comments on racial disparities and HE can be made, as >90% of our cohort consisted of urban-dwelling African Americans, who share a disproportionately higher prevalence of hypertension and are overall understudied. Moreover, we combined data from the two major medical centers in the Detroit area and we feel our cohort is an accurate reflection of HE observed in this community. Our study has the inherent limitations of a retrospective analysis, including a lack of data on medication compliance, socioeconomic, and insurance status. Several variables were abstracted from self-reported data harvested at the time of hospitalization and standardization was not possible. Although patient records were assiduously reviewed for entry criteria, determining new or worsening target-organ injury definitively poses challenges and it is conceivable that some patients with hypertensive urgencies, such as severe BP elevations without new or worsening target-organ injury, were likely included. We did not have estimates of left ventricular mass. Neither cytokines nor neurohormones were measured in our study and brain natriuretic peptide levels were only available in a minority of patients. Despite rigid inclusion criteria and exclusion criteria, it was not possible to definitively exclude underlying occult obstructive coronary artery as a confounding influence because patients did not systematically undergo stress testing or cardiac catheterization. Nevertheless, this would likely be a limitation even in a prospective analysis, stemming from ethical challenges in performing invasive angiography in this population with a particularly high prevalence of chronic kidney disease.

CONCLUSIONS

cTnI elevation release during HE is a frequent epiphenomenon that may confound or complicate management of individuals being treated for HE. It appears that cTnI elevation in individuals presenting with an HE is influenced by a variety of clinical factors disparate from those intuitively believed to be responsible for its release. We observed a disturbingly high incidence of mortality in individuals presenting with an HE, although neither the presence nor the extent of cTnI release was associated with greater odds of death.

Disclosures: None.

Conflict of Interest: None of the authors report any conflict of interests.

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