Episodes of Acute Heart Failure Syndrome are Associated with Increased Levels of Troponin and Extracellular Matrix Markers

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Short title: Troponin and ECM markers in AHFS

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Abstract

**Background:** Increased myocyte loss and extracellular matrix (ECM) turnover are central mechanisms that contribute to pathologic myocardial remodeling in chronic heart failure (HF). We tested the hypothesis that episodes of acute heart failure syndrome (AHFS) are associated with transient increases in markers of myocyte injury and ECM turnover beyond those observed in chronic stable HF.

**Methods and Results:** Markers of myocyte injury and ECM turnover were assessed in 80 patients prospectively divided into 3 groups: AHFS (n = 39); chronic stable systolic HF (n = 21); and control subjects without HF (n = 20). Myocyte injury was assessed by measuring plasma troponin I. ECM turnover was assessed by measuring plasma matrix metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs), and pro-collagen N-terminal types I (PINP) and III (PIIINP). In the AHFS group, biomarkers were obtained a) at the time of hospital admission for an episode of HF decompensation, b) at the time of hospital discharge, and c) several weeks after discharge in patients who had returned to a chronic stable compensated state. In patients with stable HF (vs. non-HF controls), there was a small increase in troponin I, and little or no difference in any marker of ECM turnover. In patients with AHFS, troponin I and three markers of ECM turnover (MMP-2, TIMP-1 and PIIINP) were elevated (vs. chronic stable HF), and all fell toward chronic HF levels in patients who returned to a compensated state.

**Conclusion:** Episodes of AHFS are associated with transient increases in markers of myocyte injury and ECM turnover that may reflect an acceleration of pathologic myocardial remodeling during AHFS.

**Key Words:** Troponin, matrix metalloproteinase, tissue inhibitor of metalloproteinase
Introduction

Pathological remodeling of the heart involves structural and functional abnormalities of cardiac myocytes and the extracellular matrix (ECM) that are mediated by several stimuli including mechanical strain, neurohormones and inflammatory cytokines \(^1\). The importance of myocardial remodeling in the progression of chronic systolic HF is appreciated, and highlighted by the demonstration that therapies that inhibit myocardial remodeling, such as ACE inhibitors and beta blockers, ameliorate clinical outcomes including HF hospitalization and death \(^2\).

Patients with chronic HF frequently experience episodes of AHFS that are characterized by interstitial fluid overload, elevated cardiac filling pressures, depressed cardiac output, and the attendant symptoms \(^3\). It is not known whether processes central to pathological myocardial remodeling, such as myocyte injury / loss and ECM turnover, are activated by episodes of decompensation. However, AHFS is associated with increased mechanical strain on the heart, activation of neurohormonal systems, and increased inflammation and oxidative stress \(^4;5\), stimuli that are known to mediate myocardial injury and ECM turnover. Therefore, it is possible that myocyte loss and ECM turnover are accelerated during episodes of AHFS.

To test this thesis, we prospectively measured circulating markers of myocyte injury and ECM turnover in patients with a history of chronic systolic HF at the time of admission to the hospital for an episode of AHFS. We then used two strategies to establish a relationship between the episodes of AHFS and the biomarkers. First, we compared patients with AHFS to patients with chronic stable HF who had a similar level of myocardial dysfunction. Second, in a subgroup of the patients with AHFS, we measured the biomarkers sequentially as patients returned to a chronic compensated state early (days) and late (months) after the episode of AHFS.
Methods

Subjects. Three groups of subjects were prospectively recruited into this study: a) patients admitted to the hospital for treatment of AHFS, b) patients with chronic stable HF, and c) control subjects without HF.

Patients with AHFS were identified from patients admitted to Boston University Medical Center for an episode of systolic HF complicated by volume overload. Systolic HF was defined as a previous diagnosis of HF and echocardiographic demonstration of systolic left ventricular (LV) dysfunction with an ejection fraction (LVEF) < 45%. The diagnosis of AHFS with volume overload was defined clinically by the presence of worsening symptoms of dyspnea, paroxysmal nocturnal dyspnea and/or orthopnea in conjunction with clinical signs of circulatory congestion (elevated jugular venous pressure, hepatojugular reflux, hepatomegaly and/or peripheral edema). Patients with concomitant acute coronary syndromes within the prior 3 months, primary infectious or inflammatory processes, or severe hemodynamic instability requiring intravenous vasoactive drugs were excluded. Also excluded were patients with aortic stenosis, malignancy, significant renal (creatinine > 3 mg/dL) or hepatic (cirrhosis or active hepatitis) dysfunction, and rheumatologic diseases.

Patients with chronic stable HF were recruited from the Cardiomyopathy Clinic at Boston University Medical Center. They had chronic stable symptoms, had not been hospitalized during the previous two months, were not volume-overloaded by clinical examination, and did not require a change in diuretic therapy on that visit. Non-HF control subjects were recruited from the ambulatory clinic or inpatient services at Boston University Medical Center. They had no history, symptoms or findings of HF. The research protocol was approved by the Institutional
Review Board at the Boston University Medical Center. Written, informed consent was obtained from all participants.

**Data and sample collection.** For control subjects and stable HF patients, clinical data and blood samples were collected at a single time-point. Patients with AHFS had clinical data and blood samples obtained at least twice: a) during the first 24 hours of admission, b) and again just prior to hospital discharge. In a subset of the AHFS patients, blood samples were obtained a third time, late after discharge, if they met the criteria for chronic stable compensation which were; a) no evidence of volume overload by clinical examination, b) no current need for diuretic adjustment, and c) no hospital admission for AHFS within the prior 2 months. A subjective dyspnea score was used to access symptom severity. Using an analog visual scale (0 = the most severe dyspnea ever experiences, and 100 = no dyspnea), the patients were asked to score their symptoms at the time of admission and again at the time of discharge.

**Biomarkers.** Blood samples were centrifuged and the plasma and serum were frozen at −70°C until the assays were performed. N-terminal proB-type natriuretic peptide (NT-proBNP) was analyzed in plasma using a commercially available ELISA kit (Alpco Diagnostics). Troponin I was measured in serum using a high sensitivity commercial chemiluminometric assay (ADVIA Centaur Ultra Troponin I; Siemens Medical Solutions Diagnostics). The detection threshold for this assay is 0.006 ng/mL, and abnormal levels are defined as values exceeding the 99th percentile of a reference control population (≥ 0.05ng/mL). Pro-collagen type I N-terminal peptide (PINP) and pro-collagen type III N-terminal peptides (PIIINP) levels were assessed in serum samples using a radioimmunoassay (Orion Diagnostica, Finland). Gelatinases (MMP-2 and -9) and tissue inhibitors of MMPs (TIMP-1, -2 and -4) were measured with commercially available ELISA kits (Amersham Pharmacia Biotech, Buckinghamshire, UK for MMPs and
TIMP-1 and -2; R&D Systems Minneapolis, USA for TIMP-4). All specimens were processed in duplicate, and the mean intra-assay coefficient of variation was less than 7% for all assays.

**Statistical analysis.** Continuous variables are expressed as mean ± standard deviation or median and interquartile (IQ) range, and categorical variables are expressed as the number of patients or percentage. Comparisons among all groups for clinical variables were performed using ANOVA or chi-square tests as appropriate. Comparisons among groups for all biomarkers were performed using ANOVA and Tukey multiple-comparison post-hoc tests, or Kruskal-Wallis test for non-normally distributed variables. Admission values were used as the reference for AHFS group for all between-group comparisons. Troponin I values were also categorized according to the detectable and abnormal thresholds of the assay and analyzed using $\chi^2$ statistics. Within AHFS group, admission values were compared to values at discharge and with stable compensation by using a paired $t$ test or a Wilcoxon rank test. We further compared both compensated groups (chronic compensation values for AHFS and Stable group) by using a Student $t$ test. The effects of medications, renal function and hepatic function on biomarkers were assessed by univariate, followed by multivariate, regression analysis. Medications and markers of renal or hepatic function with significant relationships were added to models with the respective biomarker as the dependent variable. A value of $p < 0.05$ was considered significant.

**Results**

**Patient demographics and clinical characteristics (Table 1).** A total of 80 subjects were included in this study as follows: AHFS = 39, chronic stable HF = 21, and non-HF control = 20. The groups were not different with regard to age or gender distribution; and had similar frequencies of diabetes, hypertension and ischemic heart disease. The use of HF medications was
lower in non-HF controls, as expected, but similar in the AHFS and stable HF groups. Patients in the chronic stable HF group were predominantly in NYHA class I and II, whereas patients with AHFS were all in NYHA class III or IV. NT-pro-BNP levels in patients with AHFS were markedly elevated, and higher than in chronic stable HF patients (Figure 1A).

**Hemodynamic and echocardiographic characteristics (Table 2).** LV size and function, although markedly abnormal, were similar in the chronic HF and AHFS groups. In both HF groups, the mean LV end-diastolic dimension was 59 - 60 mm, and the ejection fraction was 24%.

**Troponin I.** The mean troponin I level was elevated in both HF groups (vs. non-HF controls), and was highest in the AHFS group (Figure 1B). Compared to non-HF controls, a higher proportion of patients in both HF groups had detectable troponin levels >0.006 ng/mL): 91% of stable HF and 98% of AHFS group (vs. 53% of non-HF patients; p <0.001 for both). Likewise, troponin I levels ≥ 0.05 ng/mL, the institutional criteria for an abnormal elevation, were present in 27% of stable HF patients and 49% of AHFS patients, but none of the non-HF controls (p<0.001 vs. controls for both).

**ECM markers.** PINP and PIIINP reflect collagen synthesis. PIIINP was markedly increased in patients with AHFS, as compared to both stable HF patients and non-HF controls (Figure 2A), whereas PINP levels were similar in the 3 groups (Fig 3A). Neither PIIINP nor PINP was elevated in patients with stable HF, as compared to control subjects without HF.

ECM degradation is regulated by MMPs and TIMPs. None of the MMPs or TIMPs was elevated in stable HF patients, as compared to non-HF controls. In patients with AHFS, MMP-2 and TIMP-1 levels were increased, as compared to patients with stable HF or non-HF controls (Figures 2B and 2C). In contrast, MMP-9 and TIMP-2 were not different in patients with AHFS
vs. stable HF (Figures 3B and 3C). TIMP-4 levels were increased in patients with AHFS compared to non-HF controls, but were not different from patients with stable HF (Figure 3D).

**HF etiology.** We evaluated whether the observed differences in biomarkers were related to the etiology of HF. Patients with ischemic HF represented 37% of HF patients (45% of stable HF and 34% of AHFS, p = 0.34). Troponin I levels tended (p = 0.19) to be higher in the patients with non-ischemic HF (0.046 ng/mL; IQ range, 0.025 - 0.087 ng/mL) as compared to patients with an ischemic etiology (0.028 ng/mL; IQ range, 0.022 – 0.068 ng/mL). Likewise, all ECM markers were similar (p > 0.4 for all) in patients with ischemic vs. non-ischemic HF. Among AHFS patients, the presence or absence of CAD was not associated with troponin levels (patients with CAD = 0.063 ng/mL; IQ range, 0.028 - 0.10 ng/mL; patients without CAD = 0.044 ng/mL; IQ range, 0.027 - 0.07 ng/mL; p=0.49) or any of the ECM markers (p >0.3 for all markers).

**Medications, renal and liver function.** When patients were grouped by medications, there were no significant differences for troponin or any of the ECM markers with regard to use of ACEi/ARB, beta-blockers or spironolactone. Likewise, controlling for ACEi/ARB or beta-blocker use had no effect on the inter-group differences observed for troponin and ECM markers (data not shown).

Serum creatinine concentration was similar in the chronic stable HF group and the AHFS group at the time of admission (Table 1), and within the AHFS group creatinine was unchanged upon recompensation (1.32 ± 0.5 mg/dL; p = 0.93 vs. admission). Within the AHFS group, creatinine correlated with TIMP-1 (r = 0.36; p = 0.04), but not with troponin (r = -0.041; p = 0.812) or any other ECM marker (p > 0.50 for all). When the analysis was performed across all HF patients, there was no correlation with troponin (r = 0.044, p = 0.748) or any ECM marker (p > 0.50 for all). Controlling for creatinine in the TIMP-1 regression model had no effect on the
observed inter-group differences in TIMP-1. Alkaline phosphatase was similar in all three groups (Table 1), and was unchanged upon recompensation (117 ± 55; p = 0.47 vs. admission).

**Effect of acute therapy.** For the patients with AHFS, the duration of hospital admission averaged 5 ± 6 days. The predominant treatment during the admission was the use of intravenous diuretics leading to an average weight loss of 3.6 ± 0.7 kg. This diuresis was associated with a marked improvement in HF symptoms as reflected by an increase in the dyspnea subjective score from 33 to 85 (p<0.0001). Likewise, NT-proBNP decreased from 1869 ± 1345 fmol/mL to 1415 ± 1160 fmol/mL over the course of the admission (p< 0.05) (Figure 1C).

Troponin I values were unchanged at the time of discharge (0.055 ng/mL; IQ range, 0.027 - 0.1 ng/mL) as compared admission (0.046 ng/mL; IQ range, 0.028 – 0.08 ng/mL, p = 0.77) (Figure 1D). Among the ECM markers, MMP-2 was decreased at discharge, whereas PIIINP and TIMP-1 remained elevated (Figure 2D-F).

**Chronic compensation.** In a subgroup of 16 AHFS patients who subsequently met the criteria for chronic stable HF (see Methods), biomarkers were measured again an average of 8 ± 3 months after discharge. NT-proBNP levels returned to values similar to the stable HF group (p = 0.43) (Figure 1C). Compared to levels observed during decompensation, both troponin I (Figure 1D) and all 3 of the ECM markers that were elevated with AHFS (PIIINP, MMP-2 and TIMP-1) were decreased (the p-values for admission vs. chronic compensation were 0.04, 0.04, 0.005 and 0.008 for troponin I, PIIINP, MMP-2 and TIMP-1, respectively) (Figure 2D-F). In contrast, the markers that were not increased with AHFS (PINP, MMP-9 and TIMP-2), remained unchanged from admission values (the p-values for admission vs. chronic compensation were 0.95, 0.40 and 0.34 for PINP, MMP-9 and TIMP-2, respectively) (Figure 3E-H). Creatinine levels did not change at the follow-up visit (admission = 1.36 ± 0.6 mg/dL; discharge = 1.31 ±
0.5 mg/dL; late = 1.32 ± 0.5 mg/dL; p = 0.93). Likewise, hepatic enzymes did not change at the follow-up visit (data not shown).

Discussion

The major finding of this study is that episodes of AHFS are associated with transient increases in the blood levels of troponin I, a marker for cardiac myocyte injury, and three markers for ECM turnover (MMP-2, TIMP-1 and PIIINP). Compared to patients with chronic stable HF, troponin I and these ECM markers were elevated in patients with AHFS. Of note, when AHFS patients returned to chronic stable HF, all of the elevated markers returned to or towards the levels observed in the chronic stable HF group. In contrast, patients with stable HF had only a modest increase of troponin I levels above that in non-HF controls, and little or no alteration in any of the ECM markers.

Troponin, a marker of myocyte injury, is known to be elevated in patients with HF in the absence of epicardial coronary artery disease. In patients with HF, elevated troponin levels are associated with a worse prognosis. While troponin I is highly specific for cardiac myocytes, circulating levels may also be elevated due to renal insufficiency. However, this does not appear to underlie our observations, since serum creatinine levels were similar in the chronic stable HF and AHFS groups (see Table 1). Furthermore, there was no relationship between troponin and creatinine levels within the AHFS group and across all HF patients. Thus, we believe that the transient elevation in circulating troponin I in our AHFS patients primarily reflects increased release from the myocardium, and thus, may indicate myocyte injury and/or death. A common cause of cardiac myocyte death is ischemia due to coronary artery disease. However, troponin levels in our study were similar in patients with non-ischemic and ischemic HF, suggesting that
other factors might be responsible. Of note, episodes of AHFS are associated with non-ischemic processes that are known to cause myocyte death including mechanical strain, oxidative stress and neurohormonal activation 14-17.

Quantitative and qualitative alterations in the composition of the cardiac ECM are another important component of pathologic myocardial remodeling 18. ECM composition is determined by the balance of degradative and synthetic processes, and accordingly, circulating levels of MMPs, TIMPs and collagen fragments have proved useful in providing evidence of increased ECM turnover in patients with HF 19-26. In cross-sectional studies of patients with systolic HF, alterations in circulating MMP and TIMP levels are related to the extent of LV remodeling and predict clinical outcomes 27-29, thus supporting the clinical relevance of these biomarkers.

No prior study has assessed the relationship of ECM turnover to episodes of AHFS, nor is it known whether ECM turnover is increased during an episode of AHFS. In this regard, our study provides two new observations about ECM turnover in HF. First, markers of ECM turnover were not increased in our patients with chronic stable HF. Second, during episodes of AHFS there were marked increases in three markers of ECM turnover (MMP-2, TIMP-1 and PIIINP). The relationship of these biomarkers to AHFS was supported by the sequential demonstration in a subgroup of AHFS patients that these markers returned to or toward the levels observed in compensated patients with chronic stable HF. The levels of matrix markers can be influenced by alterations in renal and/or hepatic clearance that may occur in AHFS. An effect on ECM levels related to renal function seems unlikely because serum creatinine and hepatic enzymes were similar in the chronic stable and AHFS groups.
We believe that our ability to identify differences in troponin and ECM biomarkers in the patients with AHFS, as compared to those with chronic stable HF, reflects two relatively unique aspects of our study design. First, we prospectively grouped patients as compensated (i.e., chronic stable) or decompensated (i.e., AHFS requiring admission to the hospital). In this regard it is noteworthy that, while the chronic stable and decompensated HF groups had identical degrees of LV dilation and systolic dysfunction, they differed markedly with regard to symptom severity, NYHA functional class and BNP levels. Prior studies have generally examined patients with heterogeneous or ill-defined levels of clinical stability and compensation. A second important feature of our design is the use of a non-HF control group that had a similar incidence of concomitant cardiovascular risk factors and conditions that are associated with ECM turnover, including hypertension 30, diabetes 31 and coronary artery disease 32.

Several limitations of this study need to be appreciated. First, while troponin is highly specific for the myocardium, circulating matrix markers may reflect events in other organs. A second limitation is the relatively small number of patients, which may have decreased our ability to detect small changes in ECM markers in the stable HF group, and to correct completely for factors that affect these biomarkers. However, the number of patients was adequate to detect increased troponin levels in the stable group, and thus it is unlikely that an important difference in ECM biomarkers was missed in that group. A third limitation is that we can not completely exclude the possibility that small changes in renal or hepatic function contributed to altered levels via effects on clearance. However, in this regard it is helpful to note that the observed changes in three ECM markers were not associated with changes in four other, structurally-similar ECM markers (i.e., PINP, MMP-9, TIMP-2 and TIMP-4) which should have been subject to similar effects related to clearance pathways.
When the symptoms of AHFS are sufficient to preclude ambulatory management, patients are admitted to the hospital for intensive therapy that focuses on fluid removal, and in some cases, the bolstering of hemodynamic function with vasodilators and positive inotropic agents. The primary goal of therapy is to alleviate symptoms and to restore the compensated state. Ongoing cardiac myocyte injury and/or death, and qualitative and quantitative changes in ECM composition are central mechanisms in myocardial remodeling. Accordingly, an important implication of our observations is that episodes of decompensation may be associated with an acceleration of pathological myocardial remodeling.

Gheorghiade et al. 33 recently concluded that "should further research establish the presence and magnitude of myocardial injury in AHFS, preventing or limiting it with acute interventions may result in improvement in long-term outcome." We believe that our prospective study provides some of the first direct support for this notion by demonstrating that episodes of AHFS are associated with transient increases in markers of both myocyte injury and ECM turnover. These observations should stimulate further studies of the pathobiology of AHFS, and ultimately, may have implications regarding the importance of preventing episodes of AHDF and the identification of therapeutic targets related to cell death and ECM turnover in this setting.
Sources of Funding

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Disclosures

None.
References


Figure Legends

Figure 1. NT-proBNP and troponin I levels. **Panel A.** Mean NT-proBNP values in non-HF controls, and patients with chronic stable HF or an episode of acute heart failure syndrome (AHFS). **Panel B.** Troponin I levels in patients with chronic stable HF or an episode of AHFS. **Panel C.** NT-proBNP levels in AHFS patients at the time of admission, discharge and after chronic recompensation. **Panel D.** Troponin I levels in AHFS patients at admission, discharge and with chronic recompensation. * p < 0.05 vs Control, † p < 0.05 vs Stable, ‡ p < 0.05 vs Admission.

Figure 2. Extracellular matrix (ECM) markers that were increased with AHFS. Panels A, B and C show mean PIIINP, MMP-2 and TIMP-1 values, respectively, for non-HF controls, stable HF and AHFS patients. Panels D, E and F show PIIINP, MMP-2 and TIMP-1 values, respectively, in AHFS patients at admission, discharge and with chronic recompensation. * p < 0.05 vs Control, † p < 0.05 vs Stable, ‡ p < 0.05 vs Admission.

Figure 3. ECM markers that were not increased with AHFS. Panels A, B, C and D show mean PINP, MMP-9, TIMP-2 and TIMP-4 values, respectively, for non-HF controls, stable HF and AHFS patients. Panels E, F, G and H show PINP, MMP-9, TIMP-2 and TIMP-4 values, respectively, in AHFS patients at admission, discharge and with chronic recompensation.
Figure 1

A

NT-proBNP (fmol/mL)

Control Stable HF ADHF

0 500 1000 1500 2000 2500

* †

B

Troponin (ng/mL)

Control Stable HF ADHF

0.00 0.02 0.04 0.06 0.08 0.10 0.12

* †

C

NT-proBNP (fmol/mL)

Admission Discharge Recompensation

0 500 1000 1500 2000 2500

‡

D

Troponin (ng/mL)

Admission Discharge Recompensation

0.00 0.02 0.04 0.06 0.08 0.10 0.12

‡
Figure 2

A

Control Stable HF ADHF

PIINP (μg/L)

B

Control Stable HF ADHF

MMP-2 (ng/mL)

C

Control Stable HF ADHF

TIMP-1 (ng/mL)

D

Admission Discharge Recompensation

PIINP (μg/L)

E

Admission Discharge Recompensation

MMP-2 (ng/mL)

F

Admission Discharge Recompensation

TIMP-1 (ng/mL)
Figure 3

A

Control  Stable HF  Decomp HF

PINP (µg/L)

B

Control  Stable HF  ADHF

MMP-9 (ng/mL)

C

Control  Stable HF  ADHF

TIMP-2 (ng/mL)

D

Control  Stable HF  ADHF

TIMP-4 (ng/mL)

E

Admission  Discharge  Recompensation

PINP (µg/L)

F

Admission  Discharge  Recompensation

MMP-9 (ng/mL)

G

Admission  Discharge  Recompensation

TIMP-2 (ng/mL)

H

Admission  Discharge  Recompensation

TIMP-4 (ng/mL)
Table 1. Demographics and clinical characteristics.

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<th>Stable HF (n=21)</th>
<th>AHFS (n=39)</th>
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<td>Age, years</td>
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<td>Body mass index, kg/m²</td>
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<td>Creatinine, mg/dL</td>
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<td>82 ± 21</td>
<td>113 ± 69</td>
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<td>6/12/3/-</td>
<td>-/-/15/24†</td>
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<td>NT-proBNP, fmol/mL</td>
<td>318 ± 116</td>
<td>664 ± 448</td>
<td>1869 ± 1345*†</td>
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<td>35</td>
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<td>Beta-blockers, %</td>
<td>50</td>
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<td>Spironolactone, %</td>
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Values are means ± SD, number of patients or percentages. * p < 0.05 vs. Controls; † p < 0.05 vs. Stable Heart Failure. ACEi, Angiotensin Converting Enzyme inhibitors; ARB, Angiotensin II Receptor Blockers.
Table 2. Hemodynamic and echocardiographic characteristics.

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<th>AHFS (n=39)</th>
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<td>128 ± 14</td>
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<td>Diastolic Blood Pressure, mmHg</td>
<td>74 ± 8</td>
<td>71 ± 9</td>
<td>75 ± 13</td>
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<td>Heart rate, bpm</td>
<td>69 ± 15</td>
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<td>LV End-Diastolic Diameter, mm</td>
<td>47 ± 5</td>
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<td>31 ± 3</td>
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<td>LV Ejection Fraction, %</td>
<td>63 ± 3</td>
<td>24 ± 10*</td>
<td>24 ± 10*</td>
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Values are means ± SD, number of patients or percentages. * p < 0.05 vs. Control group; † p < 0.05 vs. Sable Heart Failure group. NYHA, New York Heart Association; LV, left ventricle.
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