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Physical and Psychological Symptom Biomechanics in Moderate to Advanced Heart Failure

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Abstract

Background: There is a common dissociation between objective measures and patient symptomatology in heart failure (HF).

Objective: To explore the relationship between cardiac biomechanics and physical and psychological symptoms in adults with moderate to advanced HF.

Methods: We performed a secondary analysis of data from two studies of symptoms among adults with HF. Stepwise regression modeling was performed to examine the influence of cardiac biomechanics (left ventricular internal diastolic diameter (LVIDd), right atrial pressure (RAP), and cardiac index) on symptoms.

Results: Average age of the sample ($n=273$) was 57 ± 16 years, 61% were male, and 61% had class III or IV HF. LVIDd ($\beta=4.22\pm1.63$, $p=0.011$), RAP ($\beta=0.71\pm0.28$, $p=0.013$), and cardiac index ($\beta=7.11\pm3.19$, $p=0.028$) were significantly associated with physical symptoms. LVIDd ($\beta=0.10\pm0.05$, $p=0.038$) and RAP ($\beta=0.03\pm0.01$, $p=0.039$) were significantly associated with anxiety. There were no significant biomechanical determinants of depression.

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Declaration of Conflicting Interests
None Declared

Conclusion: Cardiac biomechanics were related to physical symptoms and anxiety providing preliminary evidence of the biological underpinnings of symptomatology among adults with HF.

Keywords

Heart Failure; Symptoms; Biomechanics; Hemodynamics

Background

It is widely recognized that heart failure (HF) is a complex and heterogeneous disorder.^{1, 2} Beyond the hallmark physical symptoms like shortness of breath and fatigue,³ a majority of adults with HF also experience significant psychological symptoms, such as depression and anxiety.⁴ Pointedly, symptoms are the main progenitor for healthcare utilization^{5, 6} and the principal driver of quality-of-life among adults with HF.⁷ But, objective measures of HF severity often correlate poorly with HF symptoms.^{8–12} As such, we are largely bereft of insight into the biological underpinnings of symptoms in HF.

However, there are differences in how symptoms were assessed across these few studies on the biological underpinnings of HF symptoms. For example, Guglin, et al.¹² used data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial in which symptoms were derived from a history and physical examination performed by a provider (details in Drazner et al.¹³). Other studies rated only the presence or absence of symptoms^{8, 9} or used measures that primarily assess quality of life,^{8–10} and only one study inquired about psychological symptoms.¹¹ The primary aim of this study was to quantify relationships between objective biomechanical indices of heart function (dimensions, contractility, pressures, and flow) and physical and psychological symptoms (depression and anxiety) among adults with moderate to advanced HF. We hypothesized that there would be significant associations between cardiac biomechanics and physical and psychological symptoms.

Methods

We performed a secondary analysis of unique patient data collected during two prospective cohort studies of symptoms among adults with HF (study 1 focused on gender differences in symptoms,¹⁴ and study 2 focused on symptom response behaviors¹⁵). Participants were recruited through a single outpatient HF clinic in the Pacific Northwest between 2010 and 2012. Key inclusion criteria (identical between studies) were age 21 years or greater with New York Heart Association (NYHA) functional class of II–IV HF (i.e. current HF symptoms). Transplantation and mechanical circulatory support were exclusion criteria, as was a diagnosis of major cognitive impairment. Both studies were approved by our institutional review board, and written consent was obtained from all participants.

Measurement

Data on age, gender, marital status, race, and education were obtained using an identical socio-demographic questionnaire in both studies. Functional status (i.e. NYHA) was assessed by an attending HF cardiologist during the same visit as enrollment. History,

etiology, and treatment of HF were collected through a review of the electronic medical record. Comorbid conditions were summarized using the Charlson Comorbidity Index.¹⁶ Cardiac biomechanical indices were obtained via a review of the medical record including echocardiographic and right heart catheterization reports. Specifically, we collected data on left ventricular internal diastolic diameter (LVIDd) in centimeters, left ventricular ejection fraction (LVEF), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and cardiac index by Fick equation. The median times since right heart catheterization and echocardiography to symptom assessment were 11 and 42 days, respectively.

Physical Symptoms

The Heart Failure Somatic Perception Scale (HFSPS) was designed to measure perceived severity of both nonspecific symptoms (e.g. fatigue and weight gain) and acute symptoms (e.g. orthopnea and dyspnea) in HF.¹⁷ Scores on the HFSPS range from 0 to 90, with higher scores indicating worse perceived symptom severity. The HFSPS was chosen over other instruments because it is a physical symptom measure tailored specifically for HF, and not a measure of quality-of-life¹⁸ or health status¹⁹ that other groups have used as a proxy for physical symptoms. Theta reliability of the original HFSPS was 0.71–0.78.¹⁷

Psychological Symptoms

Depression was measured using the 9-Item Patient Health Questionnaire (PHQ9).²⁰ The PHQ9 scores each of the 9 related DSM-IV criteria for depression. Scores on the PHQ9 range from 0 to 27 with higher scores indicating worse depression. The PHQ9 is a valid and reliable measure of depression in HF.²¹ Anxiety was measured using the 6-item Brief Symptom Inventory anxiety scale (BSIANX).²² Scores on the BSIANX (calculated by adding the ratings and dividing the total by the number of items in the subscale) range from 0 to 4 with higher scores indicating higher anxiety. The BSIANX is a valid and reliable measure of anxiety in HF.²³

Statistical Analysis

All analyses were performed using Stata/MP version 11MP (StataCorp, College Station, TX). Standard descriptive statistics were used to describe the sample. Internal consistency of each measure was quantified using Cronbach's alpha. We used backward stepwise regression modeling ($p < 0.20$ retention) to examine the influence of cardiac biomechanical indices on symptom measures and to identify parsimonious multivariate models that were not saturated with non-significant factors. Factors entered into each model were LVIDd, LVEF, PCWP, RAP, cardiac index, ischemic vs. non-ischemic etiology, Charlson Comorbidity Index, months living with HF, treatment with an angiotensin converting enzyme inhibitor/angiotensin receptor blocker and a beta adrenergic blocker, serum sodium, serum hemoglobin, ratio of serum blood urea nitrogen to creatinine, stage 3 or higher chronic kidney disease, atrial fibrillation, gender, age, body mass index, education, and marital status.

Results

The average age of the sample ($n=273$) was 57 years, 61.2% of participants were male, and 61.2% had NYHA Class III or IV HF (Table 1). The sample had enlarged ventricles (average LVIDd = 6.1cm), reduced contractility (mean LVEF = 28.3%), low cardiac output (mean cardiac index = 2.1 L/min/m²), and high left-and right-sided filling pressures (average PCWP and RAP were 19.0mmHg and 9.6mmHg, respectively). Cronbach's alpha of the HFSPS, PHQ9, and BSIANX were 0.91, 0.88, and 0.85, respectively.

Cardiac biomechanics and clinical characteristics explained 17.1% of variance in HFSPS scores ($F=3.4$, $p<0.01$), 16.1% of variance in PHQ9 scores ($F=6.2$, $p<0.0001$), and 24.1% of variance in BSIANX scores ($F=3.5$, $p<0.001$) (Table 2). In addition to other clinical characteristics, LVIDd ($\beta=4.22\pm1.63$, $p=0.011$), RAP ($\beta=0.71\pm0.28$, $p=0.013$), and cardiac index ($\beta=7.11\pm3.19$, $p=0.028$) were significant determinants of physical symptoms, and LVIDd ($\beta=0.10\pm0.05$, $p=0.038$) and RAP ($\beta=0.03\pm0.01$, $p=0.039$) were significant determinants of anxiety. In other words, greater ventricular dilation and higher right-sided filling pressures were associated with worse physical symptoms and worse anxiety, and higher cardiac output was associated with worse physical symptoms. The ratio of serum blood urea nitrogen to creatinine was the only factor significantly associated with physical symptoms, depression, and anxiety.

Discussion

In this sample of 273 patients with moderate to advanced HF, objective cardiac biomechanical indices were significantly related to perceived physical symptoms and anxiety, but not to depression. In several instances, intuitive relationships between biomechanics and symptoms were observed in multivariate models. Larger left ventricular diameter and higher right-sided filling pressures were associated with both worse physical symptoms and anxiety. There were also examples of significant relationships between cardiac biomechanics and symptom perceptions that did not appear intuitive. For example, higher cardiac index was associated with worse physical symptoms. Moreover, and similar to other findings,¹² a higher blood urea nitrogen-to-creatinine ratio, which is typically associated with poor prognosis in HF, was associated with lower levels of physical symptoms and lower levels of both depression and anxiety in this sample. Notably, very few other objective clinical characteristics in our model were significantly associated with symptom measures. Thus, although our findings provide insight into symptom biomechanics in HF, there is more to be learned about the intersection between the complex and multidimensional symptoms experienced by persons with HF and underlying pathogenic mechanisms.

Many other groups have reported weak or no relationships between objective measures of HF severity and HF symptoms. One reason why we may have observed significant relationships centers on our choice of symptom measures, including the HFSPS and BSIANX, instead of the investigator-developed scales or quality-of-life/health status measures used by others as proxies for symptoms.^{8–10, 12} Because of our choice of symptom

measures, however, we cannot comment on the direct relationship between HF biomechanics and quality-of-life or health status like prior reports.^{9–10}

Clinically, our findings indicate that while there were significant relationships between cardiac biomechanics and HF symptoms, one shouldn't be considered surrogate for the other as there is still much to be learned about the complexity of HF symptom pathophysiology. In particular, future studies should examine non-intuitive findings such as the relationship between cardiac index and symptoms as well as the relationship between blood urea nitrogen-to-creatinine ratio and symptoms. Inconsistencies in both objective parameters and symptom measures across related studies hamper our ability to make strong and summative conclusions about the pathogenic underpinnings of symptoms in HF. Methodological approaches chosen to examine symptom biology have also been rather simple (i.e. correlations and linear regression) in contrast to the complexity of symptom pathophysiology. Thus, more advanced statistical methods of integrating multiple objective cardiac parameters and multiple symptoms should be employed in future research. Finally, although findings from this and other cross-sectional studies have contributed to a foundational understanding of HF symptom biology, longitudinal studies are needed to understand the convergence/divergence of changes in HF pathogenesis and physical and psychological symptoms over time.

Limitations

Our sample was relatively young and racially homogenous, and a high proportion had HF of non-ischemic etiology compared with many other HF cohorts. Thus, our findings may not be generalizable to all patients with HF. Furthermore, because of limitations inherent in cross-sectional research, we cannot comment on the temporality of HF symptoms and cardiac biomechanics, which further supports the need for longitudinal studies. Finally, as our understanding of symptom biology improves we can evolve to testing theoretical models as opposed to simply generating data-driven models as in the results of this study.

Conclusion

Larger left ventricular diameter and higher right-sided filling pressures are associated with worse physical symptoms and anxiety in adults with HF. Longitudinal studies are needed to gain further insight into HF symptom biomechanics in general and the convergence/divergence between objective parameters and symptoms in particular.

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What's New?

There is a paucity of knowledge regarding the biological underpinnings of symptoms in heart failure. Objective cardiac biomechanics were compared with corresponding physical and psychological symptoms of heart failure among a sample of 273 patients with moderate to advanced heart failure. They found the following:

- Larger left ventricular diameter is associated with worse physical symptoms and anxiety in heart failure.
- Higher right-sided filling pressures are associated with worse physical symptoms and anxiety in heart failure.
- Relationship between heart failure symptoms and pathophysiology warrants further study.

Table 1:

Characteristics of the sample (n=273)

	Mean±SD, or n (%)
Patient Characteristics:	
Age (years)	57.3±13.2
Male	167 (61.2%)
Non-Hispanic Caucasian	231 (84.6%)
Education level	
Less than high school	89 (32.6%)
>High school but < college	122 (44.7%)
College degree	62 (22.7%)
Body Mass Index (kg/m ²)	31.0±7.4
Charlson Comorbidity Index (weighted)	2.3±1.4
Atrial Fibrillation	109 (39.9%)
Stage 3 Chronic Kidney Disease	40 (14.7%)
General Heart Failure Characteristics:	
Time with Heart Failure in years: median [IQR]	4.2 [0.8–7.5]
NYHA Functional Class	
Class II	106 (38.8%)
Class III	157 (57.5%)
Class IV	10 (3.7%)
Heart Failure Etiology	
Non-ischemic	174 (63.6%)
Ischemic	99 (36.3%)
Prescribed a β -blocker	246 (90.8%)
Prescribed an ACE-I or ARB	223 (81.6%)
Serum sodium (mEq/L)	137.8±3.3
Serum hematocrit (%)	39.0±5.8
Serum BUN-to-creatinine ratio (mg/dL:1)	20.2±9.5
Cardiac Biomechanics:	
Left ventricular internal end-diastolic diameter (cm)	6.1±1.1
Left ventricular ejection fraction (%)	28.3±12.4%
Pulmonary capillary wedge pressure (mm/Hg)	19.0±8.5
Right atrial pressure (mm/Hg)	9.6±5.5
Cardiac index (L/min/m ² by Fick equation)	2.1±0.5
Symptomatology:	
Physical symptoms (HFSPS Score; 0–90)	24.6±16.7
Depression (PHQ9; 0–27)	7.2±6.1
Anxiety (BSI; 0–4)	0.53±0.63

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BSI, Brief Symptom Inventory; HFSPS, Heart Failure Somatic Perception Scale; IQR, interquartile range; NYHA, New York Heart Association; PHQ9, Patient Health Questionnaire; SD, Standard Deviation

Table 2:
Influence of Cardiac Biomechanics and Clinical Characteristics on HF Physical and Psychological Symptoms

	HFSPS			PHQ9			BSIANX		
	$\beta \pm SE$	t	p-value	$\beta \pm SE$	t	p-value	$\beta \pm SE$	t	p-value
Age (years)				-0.12 $\pm$ 0.03	-3.80	<0.001	-0.01 $\pm$ 0.01	-3.06	0.003
Male	-8.04 $\pm$ 3.58	-2.24	0.027						
> High school but < college							-0.31 $\pm$ 0.13	-2.42	0.017
College degree				-2.35 $\pm$ 1.09	-2.15	0.033			
Charlson Comorbidity Index				0.92 $\pm$ 0.29	3.16	0.002			
Atrial Fibrillation	-6.61 $\pm$ 3.15	-2.10	0.038						
LVIDd (cm)	4.22 $\pm$ 1.63	2.59	0.011				0.10 $\pm$ 0.05	2.10	0.038
RAP (mm/Hg)	0.71 $\pm$ 0.28	2.53	0.013				0.03 $\pm$ 0.01	2.09	0.039
Cardiac Index (L/min/m ²)	7.11 $\pm$ 3.19	2.23	0.028						
BUN/Cr ratio	-0.44 $\pm$ 0.17	-2.64	0.009	-0.11 $\pm$ 0.04	-2.78	0.006	-0.02 $\pm$ 0.01	-2.98	0.004
Beta Adrenergic Blocker							-0.50 $\pm$ 0.19	-2.61	0.010
Model R^2 /Adjusted R^2		0.171/0.120			0.161/0.135			0.241/0.172	

Abbreviations: BUN/Cr, blood urea nitrogen to creatinine ratio; BSIANX, Brief Symptom Inventory Anxiety Score; HFSPS, Heart Failure Somatic Perception Scale; LVIDd, left ventricular internal diastolic diameter; PHQ9, Patient Health Questionnaire; RAP, right atrial pressure (mm/Hg); SE, standard error.

Note: Results reported were factors retained in backward stepwise models that included left ventricular internal diastolic diameter, left ventricular ejection fraction, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, ischemic vs. non-ischemic etiology, Charlson Comorbidity Index, months living with heart failure, treatment with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, treatment with a beta adrenergic blocker, serum sodium, serum hemoglobin, ratio of serum blood urea nitrogen to creatinine, stage 3 or higher chronic kidney disease, atrial fibrillation, gender, age, body mass index, education and marital status. Only significant factors displayed for economy of presentation.