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Symptom Variability, Not Severity, Predicts Rehospitalization and Mortality in Patients with Heart Failure

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Abstract

Background—Inability of heart failure (HF) patients to recognize worsening symptoms that herald an exacerbation is a common reason for HF readmissions.

Aims—To examine the relationship between patterns of HF symptom variability, and HF event-free survival.

Methods—Patients with HF (N = 71) rated HF symptoms daily for 30 days. Symptoms were rated on a 10 point scale anchored at the extreme ends by “worst symptom could be” and “best symptom could be”. Patients were followed for an average of 1 year to track HF and cardiac rehospitalizations and all-cause mortality.

Results—Cox regression comparing event-free survival between patients who had highly variable symptom ratings across the 30-days and those whose symptoms were less variable revealed worse event-free survival in patients with more variable symptoms of shortness of breath or edema. Symptom variability predicted event-free survival independently of severity of symptoms, ejection fraction, comorbidities, age and gender. Symptom severity did not predict rehospitalization or mortality.

Conclusion—Regardless of symptom severity, patients whose symptoms fluctuated in an improving and worsening pattern were at substantially greater risk for poorer event-free survival. These patients may become accustomed to this pattern such that they expect symptoms to improve and thus do not seek treatment with worsening symptoms.

Most of the high cost of heart failure (HF) care is attributable to hospitalizations for exacerbations of chronic HF.^{1–8} Exacerbations of HF are the most common reason that people older than 65 are hospitalized.^{7, 9–11} Most such hospitalizations are thought to be preventable.¹² Failure of patients to recognize or respond to worsening symptoms before they become extreme is a common cause of preventable rehospitalizations.^{13–17}

Symptom escalation is the most common reason HF patients go to an emergency department, yet very few relate worsening symptoms to their HF.¹⁸ Patients reported delaying seeking care because they adopted a “wait and see” approach to their symptoms or

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because they did not want to use or did not trust the healthcare system.¹⁸ In a in-depth study of the reasons for HF patient delay in seeking treatment for escalating symptoms, 50% of patients did not realize their HF status was deteriorating, and only 4 of 88 patients interviewed realized that their symptoms were related to their HF.¹⁸ These data suggest that some phenomenon inherent to symptom expression or interpretation impedes patient recognition of escalating symptoms.

Few investigators have examined reasons that HF patients have such difficulty determining that their worsening symptoms are related to HF. Riegel and Carlson¹⁹ examined facilitators and barriers to HF patient self-care. They noted that HF patients usually did not recognize escalating symptoms, often confused their HF symptoms for those of other comorbid conditions or attributed them to aging, and rarely linked their worsening symptoms to HF.¹⁹ Patients also reported that they rarely monitored their symptoms. Although these data provide important insights, the fundamental reasons that HF patients do not seek treatment earlier in the course of symptom escalation remains unclear.

The trajectory of any single symptom or group of symptoms in patients with HF is variable in that symptom intensity can change from day to day or week to week.^{20,31} Based on these findings and clinical observations, we hypothesized that differences in symptom patterns experienced by patients with HF might contribute to patients' difficulty recognizing escalating symptoms and result in a higher HF hospitalization rate. Accordingly, the purpose of this study was to examine the relationship between patterns of HF symptom variability and severity, and event-free survival. We hypothesized that patients with greater variability in their symptoms would have more difficulty recognizing worsening symptoms that heralded an exacerbation, and as a consequence, would experience worse event-free survival.

METHOD

This was a longitudinal study in which we used patients' daily symptom ratings to predict time to the composite endpoint of HF rehospitalization or mortality. Patients rated their HF symptoms daily for 30 days and then were followed for an average of one year to determine outcomes.

Sample and setting

A total of 71 patients with a confirmed diagnosis of chronic HF were enrolled in this study. Patients were eligible for participation if they were community dwelling and had no obvious cognitive impairment. They were ineligible if they had had an acute myocardial infarction in the previous 3 months, had a stroke with neurological impairment, or had other major, active co-morbidities with symptomology similar to that seen in HF (e.g., chronic obstructive pulmonary disease). Patients were recruited from the cardiology clinics associated with one of three academic medical centers, two in the United States and one in Australia.

Measurement

Symptoms were measured using the Daily Symptom Scale (DSS), a valid and reliable measure of symptom presence and severity across a number of days.²⁰ The DSS is a self-report symptom diary in which patients rate the severity of symptoms daily. Symptoms are rated on a 10 point visual analog scale, where 10 is the worst the symptom could be, 1 is the best the symptom could be, and 0 is the absence of the symptom. The symptoms rated using this scale were shortness of breath, swelling, fatigue, and difficulty sleeping. Patients rated their symptoms daily for 30 days.

The outcome assessed in this study was the composite endpoint of hospitalization for HF or mortality from HF. In order to collect data on this endpoint, all patients or their families were followed using monthly phone calls to check on their status. In addition, events indicated by patients or family members were verified using review of the hospital administrative database and medical record review. Events were confirmed by a specially trained cardiovascular nurse and ambiguous events adjudicated by a heart failure specialist.

Data on the following covariates were collected: left ventricular ejection fraction (LVEF), comorbidities (assessed using the Charlson Comorbidity Index), use of angiotensin converting enzyme inhibitors or beta-blockers, age, and gender. These data were collected using patient interview and medical record review.

Procedure

Institutional Review Board approval was obtained from all sites. The investigation conformed to the principles outlined in the Declaration of Helsinki. Informed, signed consent was obtained from all participants. At baseline, all patients were carefully instructed about how to use the DSS to rate their symptoms at the same time every day. When completed, the symptom diaries were reviewed with the patient to resolve any questions or ambiguities in ratings. Patients or their families were contacted monthly by phone for follow-up.

Data analysis

In order to insure that symptom patterns were accurately interpreted, patterns across the 30 days of patients reporting were analyzed both qualitatively and quantitatively. Symptom patterns were identified in terms of variability across the reporting period and severity across the reporting period.

In the qualitative analysis, figures of the daily ratings for each patient were generated and 10 trained nurses with expertise in HF care examined the figures for each patient and categorized the patterns into mild, moderate or severe symptoms, and high or low variability. The categorizations were compared among the nurses and there was greater than 98% agreement.

Patterns across the 30 days of patients reporting also were analyzed quantitatively. Symptom patterns were identified in terms of variability across the reporting period and severity across the reporting period. Symptom severity was determined by calculating the mean of symptom ratings across the 30 day reporting period for each patient. Symptom variability was determined by calculating the standard deviation of symptom ratings across the 30 day reporting period for each patient. Based on these standard deviations, patients were categorized into high and low variability patterns (Figure 1) based on the median of the standard deviation in the sample. The concordance between the qualitative and quantitative analyses was greater than 99%, providing support for the validity of the method of describing symptom variability.

Spearman rho correlation coefficients were calculated for the bivariate relationships between the severity and variability of each of the four symptoms. To determine the relationships between symptom variability and outcomes, survival analyses were conducted while controlling for symptom severity. Cox regression techniques were used to construct Cox proportional hazard models in which symptom variability categorized as high or low was used to predict time to the composite endpoint controlling for the covariates of symptom severity, age, gender, LVEF, angiotensin converting enzyme inhibitor use and beta-blocker use. We also compared the number of HF admissions per patient between the high and low variability groups using independent t-tests.

RESULTS

A total of 71 patients completed this study (Table 1). Ratings of the four symptoms revealed that 98.5%, 97.2%, 98.5%, and 97.2% experienced shortness of breath, edema, fatigue and sleeping difficulty, respectively, at some point during the 30 day recording period. Only one (1.4%) patient reported an absence of shortness of breath during the 30 day period, while 3 (4.2%) reported only one day without shortness of breath. The remaining 67 (94.4%) patients had some level of shortness of breath every day of the monitoring period. With regard to edema, 58 (81.7%) patients reported some degree of edema daily during the 30 day period, one (1.4%) patient reported only one day without edema out of the 30 monitored, while 12 (16.9%) reported no edema during the monitoring period. With regard to fatigue, 63 (88.7%) patients reported fatigue every day, one (1.4%) patient reported no fatigue during the monitoring period, and the remaining patients (9.8%) reported a few days free of fatigue. A total of 64 (90.1%) patients reported experiencing difficulty sleeping every day of the monitoring period, while 2 people (2.8%) reported that sleeping difficulty was never a problem during the monitoring period. Another four (5.6%) patients were free of sleep difficulty one to six days of the monitoring period. Average severity and variability ratings are displayed in Table 2, and demonstrate the relatively high severity of symptom ratings.

Symptom severity ratings for each of the symptoms were low to moderate, and positively related as demonstrated by a low correlation coefficient of 0.265 for the relationship of edema severity to shortness of breath severity to a high correlation coefficient of 0.676 for the relationship of severity of sleeping difficulty to severity of fatigue (Table 3). Symptom variability ratings were low to moderate, and positively related to each other for all of the symptoms with the exception of fatigue and edema. For example, as variability in shortness of breath increased, the severity of difficulty sleeping also increased. Symptom variability correlations ranged from a low of 0.214 for fatigue and edema, and a high of 0.45 for edema and shortness of breath (Table 3). Symptom variability ratings were inversely correlated to symptom severity ratings when the correlations were significant (Table 3). Thus, as variability in shortness of breath increased, severity of shortness of breath decreased.

During the follow-up period there were two deaths from HF and eighteen HF hospitalizations. A comparison of the number of HF hospitalizations per patient between groups categorized as low and high symptom variability revealed fewer HF hospitalizations per patient in the group with lower symptom variability compared to the group with higher symptom variability related to shortness of breath (0.11 ± 0.32 hospitalizations per patient versus 0.42 ± 0.81 hospitalizations per patient, $p = 0.04$), and edema (0.06 ± 0.24 hospitalizations per patient versus 0.46 ± 0.81 hospitalizations per patient, $p = 0.006$). There were no differences in HF hospitalization rates between those with low compared to high variability in the symptom of sleeping difficulty (0.24 ± 0.50 hospitalizations per patient versus 0.30 ± 0.81 hospitalizations per patient, $p = 0.68$) or in the symptom of fatigue (0.20 ± 0.53 hospitalizations per patient versus 0.33 ± 0.72 hospitalizations per patient, $p = 0.38$).

Cox proportional hazards modeling demonstrated that symptom variability in shortness of breath and edema (Figures 2 and 3), but not sleeping difficulty or fatigue, predicted event-free survival. Patients with high compared to low variability in daily ratings of the symptoms of shortness of breath and edema had a greater risk of early events independent of age, gender, NYHA functional classification, and symptom severity ratings (Table 4). For example, patients with a highly variable shortness of breath symptom pattern had 4 times higher risk of earlier events than those with a stable symptom pattern.

DISCUSSION

This study demonstrated that regardless of symptom severity, patients whose symptoms of shortness of breath and edema fluctuated widely were at substantially greater risk for worse event-free survival than those whose symptoms did not vary widely on a day to day basis. These findings may provide some insights into the reasons that patients with HF commonly do not seek assistance from a healthcare provider in a timely manner for their escalating symptoms.

Patients with highly variable daily symptom patterns may become accustomed to such fluctuations in symptoms. As a consequence, they expect escalating symptoms to improve as they have in the past and thus they do not seek treatment in a timely manner with worsening symptoms. Patients whose symptoms do not fluctuate widely may be more easily alarmed by escalating symptoms because they are not the norm and as a consequence, patients may be more likely to contact their healthcare provider earlier in the escalation of symptoms and avoid hospitalization.

Why some patients' HF symptoms are highly variable and others are not is unclear. Patients with highly variable symptom patterns may be erratically adherent to medications and the low sodium diet resulting in fluctuating symptoms. Some patients, particularly those with more experience dealing with HF,^{19, 21, 22} make adjustments to medications (e.g., taking an extra dose of diuretic) or diet (e.g., cutting down substantially on sodium intake after a high sodium meal or multiple high sodium meals) that could result in wide symptom variations. Although in the short term, this strategy may seem adaptive, in the long run, if nonadherence is a continued behavior, it results in a greater likelihood of rehospitalization for an exacerbation of HF.²³⁻²⁵ This explanation, however, is unlikely to explain most cases, as it is not common for patients to employ self-management strategies in response to worsening symptoms.¹⁶

Jurgens and colleagues have explored the phenomenon of somatic awareness in the context of HF symptom recognition.^{16, 26} Somatic awareness is an individual's sensitivity to physical sensations that occur as a result of physiologic or pathophysiologic changes.²⁶ Although not well-studied, this phenomenon is related to patient delay in seeking treatment for acute cardiac symptoms (i.e., low somatic awareness is associated with increased delays),²⁷ and low somatic awareness may be related to increased severity of ischemic heart disease.²⁸ Based on this, one would hypothesize that high somatic awareness would be related to improved treatment-seeking behaviors for patients with HF and escalating symptoms; however, Jurgens and colleagues have found that high somatic awareness was related to longer delays in seeking treatment for escalating symptoms in HF patients.²⁶ These data suggest that patients with HF have substantial difficulty appropriately interpreting symptoms even when sensed. Thus, even though patients in our study could track symptoms on a daily basis, it may be that tracking changes alone does not translate into appropriate interpretation.

Emotional factors also play an unexpected role in interpretation of the meaning of symptoms, thus hindering appropriate responses. In one study, anxiety was inversely related to duration of dyspnea such that patients who had dyspnea for a longer time prior to hospitalization experienced less anxiety.¹⁶ There was no relationship between anxiety and duration of other symptoms of HF.¹⁶ These findings provide more evidence that patients with HF have difficulty interpreting the meaning of their symptoms in the context of having HF. Many of these patients reported not feeling fearful or anxious about symptoms because they were used to having symptoms. Similarly, patients in our study with highly variable

symptoms were likely used to having fluctuating symptoms and were, thus, not alarmed when symptoms escalated.

In this sample, symptom severity did not predict outcomes while symptom variability independently predicted outcomes even when controlling for symptom severity. Symptom severity commonly fails to predict delay time in acute myocardial infarction patients and was unrelated to delay in seeking treatment for worsening HF symptoms in prior studies.^{26, 29, 30} Symptoms were present on all days studied in the vast majority of patients. Given the omnipresence of symptoms, patients were likely habituated to their symptoms even when severe; thus, symptom severity did not predict outcomes.

A limitation of the current study is the relatively small sample size. More symptom patterns may have become evident with a larger sample.

The challenge of understanding the complexities of symptom monitoring, recognition, and management in patients with HF depends on specific research targeted to the phenomenon of symptom variability. Questions that need to be answered by researchers include the following. Do patients with high symptom variability delay seeking treatment when symptoms escalate? What factors contribute to differences in symptom patterns across time in patients with HF? What are the reasons for symptom variability? Is there a physiologic reason for different patterns of symptom variability? Why do some patients have highly variable symptom patterns while others do not?

Research focused on patient self-monitoring of HF symptoms also is warranted. Previous investigators have demonstrated that patients commonly have difficulty sensing their own symptoms, do not monitor their own symptoms, and do not link symptoms to their HF.^{16, 18, 19, 26} Although we demonstrated in this study that patients with HF were capable of monitoring and sensing symptoms severity daily for an extended period, our data suggested that symptom monitoring alone may not be sufficient if patients are unable to respond to their symptoms or appropriately interpret their significance. Thus, our current approach to teaching patients to monitor their symptoms may continue to be ineffective until we can determine how to assist HF patients to link their symptoms to worsening of HF and to then choose the appropriate response to this situation.

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Figure 1.
Examples of high and low symptom variability over a 30 day period

Figure 2. Survival curve ($p = 0.04$) derived from the multivariate Cox proportional hazards model based on variability in shortness of breath symptom ratings over a 30 day period, and adjusted for New York Heart Association functional classification, age, and gender.

Figure 3.

Survival curve ($p = 0.009$) derived from the multivariate Cox proportional hazards model based on variability in edema symptom ratings over a 30 day period, and adjusted for New York Heart Association functional classification, age, and gender.

Table 1

Sample characteristics (N=71)

Characteristics	Mean ($\pm$ S.D) or N (%)
Age, years	62 ($\pm$ 14)
Female	29 (41%)
Ethnicity	
Caucasian	62 (87%)
African-American	8 (11%)
Marital Status	
Married/ cohabitate	45 (63%)
Single/divorced/ widowed	26 (37%)
Left ventricular ejection fraction, %	30 ($\pm$ 13)
NYHA class	
I/II	32 (45%)
III/IV	35 (49%)
Comorbidities	
Hypertension	45 (63%)
Prior AMI, CABG, or PCI	41 (58%)
Stroke	9 (13%)
Peripheral vascular disease	10 (14%)
Diabetes mellitus	26 (37%)
Poor kidney function	14 (20%)
ACE I or ARB	55 (77%)
Beta blocker	56 (79%)
Digoxin	32 (45%)
Diuretics	59 (83%)

Notes. NYHA = New York Heart Association, AMI = acute myocardial infarction, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, ACE I: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blocking agents

Table 2

Patient Severity and Variability Symptom Ratings

Symptom	Variability	Severity
	Mean $\pm$ SD	Mean $\pm$ SD
Shortness of breath	.83 $\pm$.57	7.2 $\pm$ 2.3
Edema	.80 $\pm$.68	6.2 $\pm$ 3.4
Fatigue	1.2 $\pm$.69	6.3 $\pm$ 2.0
Difficulty Sleeping	1.0 $\pm$.70	6.8 $\pm$ 2.3

Symptom severity scale of 0 (no symptom) to 10 (the worst the symptom could be) Symptom Variability = standard deviation of symptom ratings across the 30 day reporting period

Table 3

Correlations Among Symptom Severity and Symptom Variability

	1	2	3	4	5	6	7	8
1. Variability in SOB	1							
2. Severity of SOB	-	1						
3. Variability in edema	0.351*		1					
4. Severity of edema	0.453*	0.448*		1				
5. Variability in sleep difficulty	0.197	0.265*	0.002		1			
6. Severity of sleep difficulty	0.238*	-0.168	0.235*	-0.016		1		
7. Variability in fatigue	-0.155	0.522*	-	0.469*	-0.194		1	
8. Severity of fatigue	0.420*	-0.056	0.214	0.080	0.355*	-0.013		1
	0.292*	0.565*	-	0.404*	-0.112	0.676*	-0.078	
			0.399*					1

Note. SOB= shortness of breath; Spearman rho correlation coefficients with 2-tailed significance

* Statistically significant at $P < 0.05$

Table 4

Adjusted Odds Ratios for Event-free Survival Predicted from Symptom Variability in Shortness of Breath and Edema

	Odds Ratio	95 th % Confidence Interval	p value
<i>Shortness of breath</i>			
Age	1.00	.97-1.00	.86
Male	.62	.22-1.79	.38
Left ventricular ejection fraction	.96	.92-1.00	.08
Comorbidity score*	.59	.22-1.58	.29
Angiotensin converting enzyme inhibitor	.72	.28-1.82	.49
Beta-blocking agent	1.72	.67-4.41	.26
Symptom severity	.89	.82-1.04	.14
High symptom variability compared to low	2.89	1.04-7.68	.04
<i>Edema</i>			
Age	.99	.97-1.02	.85
Male	.55	.19-1.53	.25
Left ventricular ejection fraction	.91	.94-1.02	.34
Comorbidity score*	.64	.26-1.60	.35
Angiotensin converting enzyme inhibitor	.68	.27-1.68	.40
Beta-blocking agent	1.53	.57-4.16	.39
Symptom intensity	1.16	.97-1.39	.11
High symptom variability compared to low	4.09	1.16-14.39	.03

Cox regression model omnibus tests of model coefficients: $p = 0.009$ for overall model for edema and $p = 0.03$ for overall model for shortness of breath

* Comorbidity score derived from Charlson Comorbidity Index where higher score indicates greater comorbidity burden