Heart & Lung 48 (2019) 208–214

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Device-detected congestion is associated with worse patient-reported outcomes in heart failure☆

Jonathan P. Auld [a,*,1], James O. Mudd [b], Jill M. Gelow [b,2], Karen S. Lyons [a,3], Shirin O. Hiatt [a], Christopher S. Lee [c]

[a] Oregon Health & Science University School of Nursing, 3455 SW US Veterans Hospital Rd., SN-ADM, Portland, OR 97239-2941, USA
[b] Oregon Health & Science University, Knight Cardiovascular Institute, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97239-3098, USA
[c] William F. Connell School of Nursing, Boston College, Maloney Hall, 231140 Commonwealth Avenue, Chestnut Hill, MA 02467, USA

ARTICLE INFO

Article history:
Received 12 August 2018
Received in revised form 7 November 2018
Accepted 4 December 2018
Available online 2 January 2019

Keywords:
Heart failure
Symptom
Quality of life
Intrathoracic impedance
Pulmonary congestion

ABSTRACT

Background: Congestion is a common cause of symptoms in heart failure (HF). Yet, intrathoracic impedance, an objective marker of cardiopulmonary congestion, has not been examined in relation to HF symptoms.
Objective: To determine whether device-detected cardiopulmonary congestion is a predictor of physical and psychological symptoms and health-related quality of life (HRQOL) in adults with HF over 3 months.
Methods: Multivariate generalized linear modeling was used to quantify the association of cardiopulmonary congestion (Optivol® Index exceeding 60 Ω threshold) with HRQOL (12-item Kansas City Cardiomyopathy Questionnaire) and both physical symptoms (Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HF Somatic Perception Scale Dyspnea and Early & Subtle Symptoms subscales) and affective symptoms (9-item Patient Health Questionnaire; 6-item Patient-Reported Outcomes Measurement Information System Anxiety Scale).
Results: The mean age of the sample ($n = 49$) was 62 years old, 39% were women, and 63% had NYHA class III/IV HF. Participants who experienced threshold crossings in the previous 90 days reported on average, 130% higher dyspnea ($p = 0.017$; confidence interval (CI) 10.2%, 437%), 40% higher early & subtle symptoms ($p = 0.029$; CI 3.4%, 89.7%), 106% higher depressive symptoms ($p = 0.003$; CI 19.1%, 257%) and 40% higher anxiety ($p = 0.028$; CI 3.7%, 89.1%). Threshold crossings in the previous 90 days were also significantly associated with a clinically meaningful decrease in HRQOL ($\beta = -16.16 \pm 6.32$; $p = 0.01$).
Conclusions: Intrathoracic impedance measured with the Optivol Index can provide additional information regarding the patient experience of hallmark physical and psychological HF symptoms and HRQOL over 3 months.

Introduction

Heart failure (HF) is a distressing cardiovascular syndrome that is continuing to increase in prevalence in the US. Currently, 6.5 million Americans are diagnosed with HF and that number is projected to increase by 46% by 2030.[1] In spite of recent improvements in medical management and technological advances in the treatment of HF, patients with HF continue to experience poor quality of life due to distressing symptoms such as dyspnea, fatigue, depression and anxiety,[2–4] and HF remains the leading cause of hospital admission for older adults.

Cardiopulmonary congestion resulting from fluid overload and elevated pressures in the heart is a common cause of symptoms and it is a primary reason for HF hospitalization.[5–7] Remote monitoring of pulmonary congestion has been introduced into implantable defibrillator/pacemakers that many patients with HF receive. This device-detected congestion has been associated with increased HF events and worse mortality.[8,9] One area of study that has received little attention with this technology is the association between device-detected cardiopulmonary congestion and patients' experience of physical and psychological symptoms. Patient-reported physical and psychological symptoms in HF are key drivers for healthcare utilization and quality of life.[6,10,11] However, patients are often limited in

☆ **Funding**: This work was supported by the National Institute of Nursing Research (F31NR016660). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

* Corresponding author.
E-mail addresses: auldjpa@msn.com, auldja@uw.edu (J.P. Auld).
[1] Present address: University of Washington School of Nursing, Health Sciences Building, Box 357266, 1959 NE Pacific Street, T613, Seattle, WA 98195–7266, USA.
[2] Present address: Providence St. Joseph Health, 1111 Northeast 99th Avenue Suite 102, Portland, OR 97220, USA.
[3] Present address:William F. Connell School of Nursing, Boston College, Maloney Hall, 231140 Commonwealth Avenue, Chestnut Hill, MA 02467, USA.

https://doi.org/10.1016/j.hrtlng.2018.12.003
0147-9563/$ - see front matter © 2018 Elsevier Inc. All rights reserved.

their ability to recognize and respond to symptoms (i.e. self-care management).[12,13] These limitations include 1) difficulty in identifying the symptoms as related to HF especially in the presence of multiple co-morbidities,[14] 2) symptoms that are subtle and difficult to detect[15] and 3) late recognition of symptoms.[12]

Further complicating the identification of symptoms for patients and clinicians is a dearth of objective markers of heart function related to patient HF symptoms.[16–20] For patients, daily weights are poorly associated with clinical deterioration[21] and for clinicians few hemodynamic indicators of HF are related to symptoms.[16] In a recent study, Lee et al.[22] describes multiple groups with differing profiles of hemodynamic-symptoms mismatch. One group of HF patients experienced very poor hemodynamics with only moderate levels of physical and psychological symptom burden and exhibited an increased clinical event risk compared to patients whose hemodynamics and symptoms were congruent. This study, along with evidence of patient difficulty identifying and managing symptoms, highlights the need to find better methods to monitor physical and psychological symptoms both as an indicator of progressing HF and as a means to improve patient-reported outcomes such as symptoms and HRQOL. The purpose of this study is to determine whether device-detected cardiopulmonary congestion over 3 months is a predictor of physical and psychological symptoms and health-related quality of life (HRQOL) in adults with HF. A better understanding of how an objective measure of worsening HF is associated with symptoms and HRQOL may enhance more patient-specific interventions; reducing costly readmission and improving quality of life.

Materials and methods

This was a National-Institutes of Health-sponsored observational study examining 3 months of device-detected cardiopulmonary congestion data in 49 adult patients with symptomatic HF. Patients from a HF clinic associated with an academic medical center in the Pacific Northwest were identified by their cardiologist as having symptomatic HF (NYHA Class II-IV) and an Optivol® (Medtronic, Minneapolis) enabled device. Between January 2017 and December 2017, identified patients were approached at a pacemaker/ICD clinic visit by a member of the research team not directly involved with HF care for participation in the study. Additional inclusion criteria were the ability to read 5th grade English or Spanish and be reachable by telephone. Exclusion criteria included major surgical procedures or hospitalization within 6 weeks which may interfere with impedance, a heart transplant or implantation of ventricular assist device, documentation of a major psychiatric illness or major and uncorrected hearing impairment. The study was approved by the medical center institutional review board and all participants were provided written and informed consent. At enrollment, the prior 3 months of device data were downloaded and a questionnaire was completed either during the visit or by mail per the participants' preference. The questionnaire collected data on demographic, socioeconomics and information asking patients to evaluate their HF symptoms and HRQOL over the past 3 months. In addition, an assessment of cognitive function was administered at the time of enrollment. Clinical information regarding the patient's HF treatment and co-morbidities were obtained from an in-depth review of the participants' medical record at the time of enrollment.

Measurement

Device-detected cardiopulmonary congestion

Cardiopulmonary congestion was quantified using data that is already generated and stored in patients' implanted Optivol® therapeutic devices. Devices send a high frequency, low amperage, alternating current from the device generator to the right ventricular coil, tip, or ring electrode to measure changes in electronic resistance. Increasing congestion within the lungs results in a reduction in the resistance/impedance to the electronic current.[23,24] Average raw daily impedance is quantified and stored in the device computer; raw average daily impedance is calculated in an identical fashion among all commercially-available Optivol® devices. Post-hoc, several metrics of congestion are calculated including the Optivol® fluid index, which represents day-to-day differences between impedance and a reference impedance threshold of 60 Ω days (Fig. 1). In our study as well as others,[25,26] an Optivol® Index exceeding the 60 Ω threshold constitutes a "threshold crossing", an indicator of a cardiopulmonary congestion event. The data extracted from the devices included the frequency and duration of all threshold crossings in the previous 3 months. Device data is collected beginning 34 days after implantation as pocket healing interferes with impedance.

Physical symptoms

Fatigue was measured using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F v. 4).[27] The FACIT-F assesses patients' tiredness, weakness, and difficulty conducting usual activities due to fatigue.[27,28] Scores of the 13 items range from 0–52 with

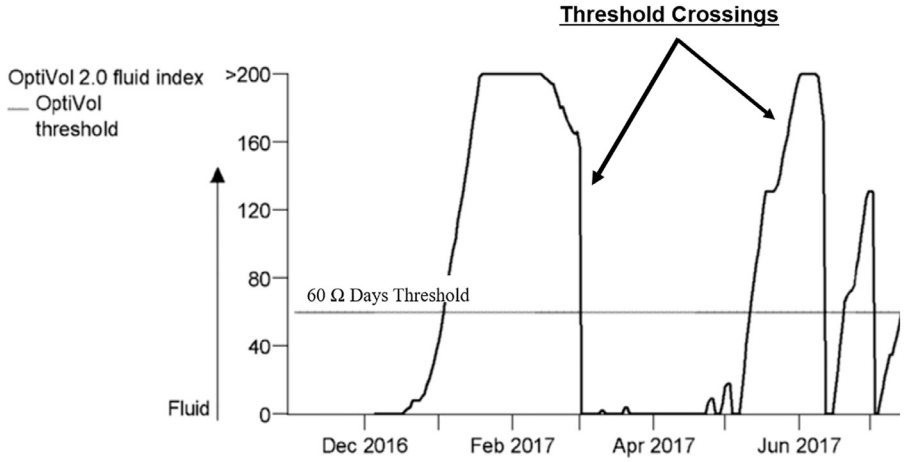

Fig. 1. Optivol® fluid index threshold crossings occur when Optivol® fluid index exceeds 60 Ω days. Threshold crossings are indications of a cardiopulmonary congestion event. The precise number and duration of the threshold crossings were determined.

higher scores indicating more fatigue. The FACIT-F has excellent concordant validity with the Piper fatigue scale ($r = 0.83$) and Profile of Mood States fatigue scale ($r = 0.77$).[29] The scale has also good reliability and validity in adults.[30]

Dyspnea was measured with the 6-item dyspnea subscale of the Heart Failure Somatic Perception Scale (HFSPS Dyspnea).[31] The HFSPS is rooted in the Theory of Unpleasant Symptoms which posits that the patient's physiology and multiple symptoms are important factors in the symptom experience.[32] The HFSPS asks about how much the participant was bothered by HF symptoms related to shortness of breath or other breathing difficulties and provides six response options ranging from 0 (not at all) to 5 (extremely bothersome). The HFSPS dyspnea has excellent internal consistency (alpha = 0.89) concordant validity with the KCCQ functional limitations scale ($r = 0.53$) and independently predicts HF-related clinical events (per point HR = 1.031, $p = 0.031$).[32]

Early and Subtle symptoms were measured with the 7-item early and subtle subscale of the HFSPS (HFSPS E&S).[32] The HFSPS asks about how much the participant was bothered by HF symptoms that can occur prior to more noticeable symptoms such as dyspnea and fatigue. For example, the HFSPS E&S asks patients to rate how much they were bothered by tight clothing, stomach ache, waking to urinate and needing more rest during the day. The HFSPS E&S provides six response options ranging from 0 (not at all) to 5 (extremely bothersome). The HFSPS E&S has good internal consistency (alpha = 0.75) moderate concordant validity with the KCCQ functional limitations scale ($r = 0.39$) and independently predicts HF-related clinical events (per point HR = 1.030, $p = 0.028$).[32]

Psychological symptoms

Depressive symptoms were measured using the 9-item Patient Health Questionnaire (PHQ9). The PHQ9 has 4 response options ranging from 0 (not at all) to 3 (nearly every day).[33] Higher scores (range 0–27) indicate more depression. The PHQ9 has been validated in the HF population. The PHQ9 is 87% sensitive and 76% specific in detecting depressive disorder in the general population.[34]

Symptoms of anxiety were measured with the 6-item patient reported outcomes measurement information system (PROMIS) short form anxiety scale. The PROMIS anxiety SF-6 asks respondents to rate level of fear, anxiousness and worry with 5 response options of never, rarely, sometimes, often, always (scale of 1–5). A raw score is calculated by summing the 6-items with a range of 6–30. Raw scores correspond to T-scores based on large nationally representative samples.[35]

Cognitive dysfunction

Cognitive dysfunction was measured with the Montreal Cognitive Assessment (MoCA). The MoCA assesses a number of cognitive functions including short-term verbal memory recall, visuospatial ability, executive function, attention, concentration, working memory, language, and orientation. The MoCA has been shown to be sensitive and specific to mild cognitive function with a cut-off score of <26 and has been used in patients with HF.[36,37] The MoCA was assessed in person following the detailed instructions and no patients were excluded from the study based on the MoCA score.

Health-related quality-of-life

Heart failure-specific health-related quality of life was measured with the Kansas City Cardiomyopathy Questionnaire Short Version (KCCQ-12). The KCCQ-12 is a 12-item Likert scale comprised of 4 subscales; symptom frequency, physical and social function and quality-of-life. Scores range from 0–100 with higher scores reflecting better function. A KCCQ-12 summary score is created by calculating the mean of the 4 sub-scores. The KCCQ-12 has excellent concordant validity (0.93–0.99) with the original well-validated and reliable item measure and good test-re-test reliability (0.76–0.92).[38] The use of the KCCQ-12 assess multiple aspects of HF-specific HRQOL (quality of life, symptom frequency, physical and social function) that are not measured with the physical symptom instruments.

Statistical procedure

Means, standard deviations, frequency, and percentages were used to describe the sample using Stata/IC v14.2 (Texas). The Student's t test, Mann-Whitney U, analysis of variance (ANOVA), Kruskal-Wallis test, Chi-square or Fischer's exact tests were used to examine differences between participants with no threshold crossings and those with varying frequency and duration of threshold crossings over the previous 3 months. Two different variables were created to describe the Optivol® threshold crossings in this study. One described the presence (or not) of a threshold crossing in the previous 90 days and to paint a broader picture of the variability in congestion the second was a categorical variable with one group having no days above threshold and the following two groups split by the median days above the Optivol® Index threshold. Given some of the symptom and HRQOL variables were modestly skewed, both parametric and non-parametric tests were used to evaluate the differences between the frequency and duration of threshold crossings. Since the levels of significance between the parametric and non-parametric tests were similar, the parametric tests (t tests and ANOVA) were used to describe the differences in symptoms and HRQOL as a function of threshold crossings. Hedge's g was calculated to determine effect sizes between the presence or duration of threshold crossing and symptoms and HRQOL. Generalized linear modeling using either a gamma or normal distribution, depending on the shape of these data, was used to quantify the association of cardiopulmonary congestion (Optivol® Index exceeding 60 Ω threshold) with HRQOL and physical and psychological symptoms. The log likelihood and AIC were used to compare models with lower values indicative of better fit. A p-value < 0.05 was considered significant. For HRQOL models, estimates are in units of the KCCQ summary score. In order to facilitate comparisons across symptoms, the relative difference in symptoms are reported for differing levels of the presence and duration of threshold crossings. The relative differences are reported as a percentage increase or decrease in the symptom score compared to the referent (0 threshold crossings and 0 days above threshold). Post-hoc calculations of observed statistical power exceeded 80% for HRQOL and depressive symptom models. Observed statistical power was 32%, 48% and 67% respectively for fatigue, dyspnea and anxiety models.

In order to avoid oversaturation of multivariate models due to small sample sizes, a limited number of covariates were identified using an empirical/theoretical approach. Covariates significantly different between those with threshold crossing and none (empirical) as well as variables shown by others to be significantly associated with HRQOL or symptoms from the literature were included to adjust the analyses. Specifically, NYHA class[11,39] for HRQOL models and comorbidities[40,41] for symptom models were used as the theoretical covariates. New York Heart Association class was not used as a covariate in the symptom models to avoid overlap in symptoms assessed with NYHA class and symptoms measured in the current study (fatigue and dyspnea).

Results

Participants in the study were on average 62 ± 13.5 years old, predominantly white (86%), and married or living with their partners (63%) (Table 1). Women comprised 39% of the sample. Most participants had moderate to severe functional limitation due to HF (63% NYHA III/IV) and a non-ischemic HF etiology (80%).

Table 1
Characteristics of the sample

		Threshold (TH) crossings		
	Sample (n = 49)	+TH crossing (n = 22)	−TH crossing(n = 27)	p value
Age (in years)	62.4 ± 13.5	63.0 ± 13.1	62.0 ± 14.0	0.801
Female	19 (38.8)	10 (45.5)	9 (33.3)	0.386
Caucasian	42 (85.7)	20 (90.9)	22 (81.5)	0.624
Educational status				
High School or less	15 (30.6)	6 (27.3)	9 (33.3)	0.659
Financial status				
More than enough	8 (17.4)	3 (13.6)	5 (18.5)	0.429
Marital status				
Married or living with partner	31 (63.3)	14 (63.6)	17 (63.0)	0.961
Charlson co-morbidity category				
low (score of 1 or 2)	27 (55.1)	9 (40.9)	18 (66.7)	
medium (score of 3 or 4)	17 (34.7)	10 (45.5)	7 (25.9)	
high (score of 5 or more)	5 (10.2)	3 (13.6)	2 (7.4)	0.174
BMI	30.9 ± 6.7	31.0 ± 5.6	30.8 ± 7.6	0.914
MOCA	25.8 ± 2.3	25.5 ± 2.6	26.0 ± 2.2	0.473
Heart failure characteristics:				
NYHA III/IV	31 (63.3)	15 (68.2)	16 (59.2)	0.519
Ejection Fraction %	33.8 ± 14.2	29.4 ± 14.1	37.4 ± 13.4	0.048
LVID	5.8 ± 1.2	5.9 ± 1.1	5.8 ± 1.3	0.856
Primary etiology				
Ischemic	10 (20.4)	7 (31.8)	3 (11.1)	0.090
Systolic BP	113.6 ± 15.3	112.9 ± 13.9	114.2 ± 16.6	0.763
Aldosterone antagonist	28 (57.1)	11 (50.0)	17 (63.0)	0.362
Diuretic	39 (79.6)	19 (86.4)	20 (74.1)	0.288
ACE/ARB	43 (87.8)	17 (77.3)	26 (96.3)	0.077
Beta blocker	46 (93.9)	20 (90.9)	26 (96.3)	0.581
Hemoglobin	90.013.3 ± 2.0	13.5 ± 1.8	13.1 ± 2.1	0.722
Serum sodium	138.0 ± 3.1	138.5 ± 3.0	137.5 ± 3.2	0.143
Years with HF				
>7 years	24 (49.0)	15 (68.2)	10 (37.0)	0.030

Sample characteristics comparing those with a threshold crossing (+) to those with no threshold crossings in the previous 90 days (−). Threshold crossing = exceeding the 60 Ω Opitvol® Index threshold in the 3 months prior to study enrollment. Abbreviations: ACE/ARB - angiotensin converting enzyme inhibitor/angiotensin receptor blocker, BMI – body mass index, HF - heart failure, LVID- left ventricular internal diameter MOCA – Montreal cognitive assessment, NYHA - New York heart association functional class.

Table 2
Unadjusted differences in HF symptoms and Health-related Quality-of-life (HRQOL) as a function of the presence and duration of TH-threshold

A . Presence of threshold crossing in previous 90 days

		TH crossings			Effect size
	Sample (n = 49)	+ TH crossing (n = 22)	−TH crossing(n = 27)	p value	Hedge's g
Symptoms:					
Fatigue	20.3 ± 11.7	22.9 ± 13.6	18.3 ± 9.8	0.210	0.39
Dyspnea	7.4 ± 6.7	9.4 ± 7.5	6.0 ± 5.7	0.102	0.51
Early/Subtle	13.3 ± 5.8	14.7 ± 6.6	12.1 ± 4.8	0.140	0.44
Depressive	7.3 ± 5.8	9.3 ± 7.4	5.8 ± 3.6	0.061	0.62
Anxiety	12.3 ± 5.8	12.8 ± 6.4	11.9 ± 5.4	0.644	0.39
HRQOL (KCCQ summary score)	55.39 ± 20.0	49.7 ± 20.3	59.8 ± 18.8	0.091	0.51

B. Duration of threshold crossings in previous 90 days

	Duration of TH crossings				Effect size	
	0 days (n = 27)	4–22 days (n = 11)	23–56 days (n = 11)	p value	Hedge's g (0 vs 4–22 days)	Hedge's g (0 vs 23–56 days)
Symptoms:						
Fatigue	18.3 ± 9.8	25.4 ± 13.25	20.4 ± 14.1	0.270	0.64	0.18
Dyspnea	6.0 ± 5.7	10.7 ± 8.5	8.0 ± 6.5	0.156	0.71	0.34
Early/Subtle	12.1 ± 4.8	16.4 ± 6.0	13.1 ± 6.4	0.139	0.77	0.17
Depressive	5.8 ± 3.6	9.8 ± 8.4	8.8 ± 6.7	0.119	0.74	0.64
Anxiety	11.9 ± 5.4	14.7 ± 7.6	10.8 ± 4.5	0.292	0.45	0.21
HRQOL (KCCQ summary score)	59.8 ± 18.8	43.9 ± 20.5	54.4 ± 19.7	0.114	0.81	0.28

Effect sizes in 2B show the mean comparisons between 0 days and 4–22 days above threshold and 0 days above threshold and 23–56 days above threshold. Threshold crossing = exceeding the 60 Ω Opitvol® Index threshold in the 3 months prior to study enrollment. Abbreviations: KCCQ-Kansas City Cardiomyopathy Questionnaire, HF-heart failure, HRQOL-health-related quality of life, TH-threshold crossing.

Table 3
Generalized linear models of objective marker of cardiopulmonary congestion associated with health-related quality of life (KCCQ) in patients with HF

A. KCCQ summary score	β ± Standard error	*p* value
Threshold crossing	−11.78 ± 5.08	0.020
>7 years with HF	9.99 ± 4.89	0.041
NYHA III/IV	−23.92 ± 5.09	<0.001
LVEF	−0.11 ± 0.19	0.539
B. KCCQ Summary Score	**β ± Standard error**	***p* value**
<median days above threshold (4–22 days)[1]	−16.16 ± 6.32	0.011
≥median days above threshold (23–56 days)[1]	−7.90 ± 6.05	0.193
>7 years with HF	9.32 ± 4.90	0.057
NYHA III/IV	−23.76 ± 5.07	<0.001
LVEF	−0.11 ± 0.19	0.562

Estimates are in units of the KCCQ summary score. Higher values indicate better HRQOL. An empirical and theoretical approach was used to identify model covariates for adjusted analysis. Empirical covariates were shown to be significantly different between those with and without threshold crossings (years of HF and LVEF) in the current study. The theoretical covariate was NYHA class, which has been shown by others to be consistently associated with HRQOL in HF. Threshold crossing = exceeding the 60 Ω Optivol® Index threshold in the 3 months prior to study enrollment. Abbreviations: HF-heart failure, KCCQ-Kansas City Cardiomyopathy Questionnaire, LVEF = left ventricular ejection fraction, NYHA-New York Heart Association.

A slight majority (55%) of the sample did not have a threshold crossing in the previous three months from enrollment. Having ≥ one threshold crossing in the previous three months was significantly associated with lower ejection fraction and longer duration of HF (Table 1). There were no statistically significant diffeernces in physical and psychological symtpoms comparing patients with and without threshold crossings (Table 2A), or among patients with 0, 4–22 or 23–56 days above threshold (Table 2B) in the previous 90 days.

In multivariate models, the presence of at least one threshold crossing and a duration of 4–22 days above threshold were associated with worse HRQOL (Table 3). Adjusted multivariate models of physical and psychological symptoms showed that dyspnea, early & subtle, depressive and anxiety symptoms were significantly worse for those who experienced threshold crossings or had threshold crossings between 4 and 22 days (Table 4). Only depressive symptoms were also significantly worse for participants with threshold crossing of 23 days or more.

Discussion

In this prospective observational study of 49 patients with symptomatic HF and Optivol®-enabled pacemarker/ICDs, we found that the presence and duration of a device-detected cardiopulmonary congestion event in the previous 3 months was associated with higher physical and psychological symptom burden and worse HRQOL. Highlighting the need to better understand objective indicators of HF symptoms, a recent study by Riegel et al.[42] showed that the perception of fluid retention in 44% of patients with symptomatic HF did not match objective measures of fluid congestion with the Optivol® Index. The results of our study, on the other hand, with a larger sample shows a strong relationship (Hedge's *g* as high as 0.82) between both physical and psychological symptoms and threshold crossings of the Optivol® Index. This study adds to our understanding of HF symptomology by identifying an objective measure of HF pathophysiology associated with worse hallmark HF symptoms and HRQOL. Furthermore, our study suggests monitoring of intrathoracic impedance may be a valuable tool in addressing symptom burden and quality of life in patients with symptomatic HF.

Intrathoracic impedance, quantified using the Opitvol Index, has been used to detect fluid retention events in patients with HF.[42] Although lower intrathoracic impedance (higher Optivol® Index) has been associated with less engagement in HF self-care behaviors, higher clinical event risk and mortality, our study demonstrated a significant relationship between intrathoracic impedance and patient-reported outcomes of physical and psychological HF symptoms and a clinically meaningful difference in HRQOL.[8,26] Thus, this is an important finding in our understanding of symptom biology in HF. First, physical symptoms such as dyspnea are the primary reasons patients with HF seek care.[6] Physical and psychological symptoms are also significant drivers of HRQOL. Furthermore, patients often delay seeking treatment for worsening symptoms due to difficulty in the detection or interpretation of symptoms.[15] Since the Optivol data can be reviewed by providers prior to or during clinical visits, our data suggests assessment of the Optivol® Index by clinicians may provide additional information regarding underlying changes in physiology that may portend worsening symptoms and allow for earlier detection and treatment of worsening HF, particularly in patients who may struggle to detect or report their symptoms. In other words, remotely reviewing trends in impedance data may earlier identify patients experiencing worsening congestion and potentially worse symptoms. Alternatively, reviewing impedance data as part of the HF clinic visit may elucidate previous episodes of congestion and symptoms that may provoke further discussion regarding symptoms burden and patient self-management difficulties that may have gone unaddressed.

Second, our study suggests intrathoracic impedance may not be a reliable indicator of fatigue in HF. Cardiopulmonary congestion

Table 4
Generalized linear models of an objective marker of cardiopulmonary congestion associated with patient-reported symptoms

A. HF symptoms	Fatigue Relative difference (95% CI)	Dyspnea Relative difference (95% CI)	Early/Subtle Relative difference (95% CI)	Depressive Relative difference (95% CI)	Anxiety Relative difference (95% CI)
Threshold crossing	+34.7% (−6.0%, 93.1%)	**+130% * (15.8%, 356%)**	+25.0% (−5.4%, 65.1%)	**+95.0% ** (25.9%, 202%)**	+20.0% (−9.3%, 59.0%)
B. HF symptoms	**Fatigue Relative difference (95% CI)**	**Dyspnea Relative difference (95% CI)**	**Early/Subtle Relative difference (95% CI)**	**Depressive Relative difference (95% CI)**	**Anxiety Relative difference (95% CI)**
<median days above threshold (4–22 days)	+47.3% (−1.8%, 121%)	**+143% * (10.2%, 437%)**	**+40.0% * (3.4%, 89.7%)**	**+83.9% * (6.40%, 218%)**	**+40.1% * (3.7%, 89.1%)**
≥median days above threshold (23–56 days)	+15.3% (−28.0%, 84.6%)	+114% (−6.60%, 390%)	+10.2% (−21.9%, 55.5%)	**+106% ** (19.1%, 257%)**	−1.0% (−32.2%, 44.5%)

In order to facilitate comparisons across symptoms, the relative difference in symptoms are reported for differing levels of the presence and duration of threshold crossings. The relative differences are reported as a percentage increase or decrease in the symptom score compared to 0 threshold crossings. An empirical and theoretical approach was used to identify model covariates for adjusted analysis. Empirical covariates were shown to be significantly different between those with and without threshold crossings (years of HF and LVEF) in the current study. The theoretical covariate was co-morbidities, which has been shown by others to be associated with symptom perception in HF. Threshold crossing = exceeding the 60 Ω Optivol® Index threshold in the 3 months prior to study enrollment. Abbreviations: HF-heart failure, KCCQ-Kansas City Cardiomyopathy Questionnaire, LVEF = left ventricular ejection fraction, NYHA-New York Heart Association.

* <0.05,

** ≤0.01.

events in our sample were not significantly associated with the experience of fatigue. One explanation for the lack of association between an objective measure of cardiopulmonary congestion and fatigue may be that intrathoracic impedance is simply not particularly sensitive to fatigue. Although the pathophysiology of fatigue has not been fully elucidated, it is believed to stem from both physiological sources (inflammation, muscle dysfunction and anemia) and from psychological sources such as depression.[43,44] For example, our data suggests that fatigue may be more strongly associated with depression than device-detected cardiopulmonary congestion as depression was highly correlated with fatigue (data not shown). Cardiopulmonary congestion, on the other hand, results from elevated pressures in the heart and pulmonary system that often result in dyspnea.[45] Additionally, fatigue is a common and generalized symptom that may be less HF-specific.[46,47] Further research is needed to identify objective HF-related measures associated with fatigue in patients with HF.

Third, an unexpected finding from our study was that patients with the most severe marker of cardiopulmonary congestion (longest duration of threshold crossings) did not report the worst physical or psychological symptom burden or worst HRQOL. Although comparisons were not statistically significant at a p value of 0.05 (likely due to small sample sizes and large standard deviations), based on substantial differences in effect sizes patients who experienced more severe congestion (23–56 days above threshold) reported, on average, milder physical symptoms and anxiety and better HRQOL compared to patients with less severe cardiopulmonary congestion (4–22 days above threshold).

This intriguing finding is consistent with two recent studies which found a mismatch between objective metrics of HF pathophysiology and subjectively-reported HF symptoms.[22,42] Both studies showed that there are substantial proportions of patients whose perception of HF symptoms are discordant with objectively measured metrics of HF pathophysiology including intrathoracic impedance.[42] Of particular importance was the observation that those, with what Lee et al. termed “symptom-hemodynamic mismatch”, were at higher risk for adverse clinical events than those with concordant symptoms and hemodynamics.[22] Our study may reflect a similar mismatch between an objective metric of worsening cardiopulmonary congestion and patient-reported symptoms and HRQOL. One reason for the mismatch may be related to response shift bias.[48] Response shift bias may occur as individuals learn to adapt and compensate for declines in physical or psychological function that often occur in the trajectory of HF. As function declines over time, people with HF may continually develop a “new normal” from which they evaluate symptoms that eventually results in a mismatch between the patient’s subjective interpretation of symptoms and the worsening HF pathophysiology. Interestingly, depressive symptoms were the only symptoms significantly associated with more severe congestion. This may reflect the high levels of distress associated with depression and that more severe depressive symptoms may be less amenable to a response shift bias. Simply put, developing a “new normal” with depression may be difficult due to the negative influence depression has on many aspects of a patient’s life. Further research is needed to more clearly determine the causes, characteristics and outcomes associated with symptom-hemodynamic mismatch.

Finally, this study suggests the use of instruments that assess patient-reported symptoms as a varied rather than homogenous experience may enhance the research of symptom biology in HF. In multiple previous studies, using predominantly single-item symptoms measures that narrowly define symptoms such as dyspnea and fatigue (e.g. present or not) have shown little to no association between metrics of cardiopulmonary function and subjectively-reported HF metrics of symptoms and HRQOL.[16,18,19] Since this study is one of the first to show moderate to strong effect sizes, although non-significant unadjusted findings, between an objectives metric of cardiopulmonary congestions and patient-reported symptoms in HF, it may offer insights into the study of HF symptomology that may enhance future research. For example, the use of symptom measures that assess physical symptoms in multiple ways may have enhanced the ability of our study to detect significant associations. A number of recent publications have shown significant relationship between objective metrics of HF pathology and physical symptoms using measurement tools that assess symptoms in multiple ways.[49–51] The HF symptom experience is heterogeneous[52] and can be experienced differently by differing patient populations.[53] Single-item descriptions of symptoms may capture a narrower range of the symptom experience making it more difficult to detect associations with physiologic markers. In short, it may be useful in clinical practice and research for the assessment of symptoms to reflect the differing ways in which patients experience symptoms. The collection of patient-reported data with instruments that capture a more diverse symptom experience may facilitate the identification of objective markers of HF that may better predict burdensome and heterogeneous HF symptoms.

Strengths and limitations

Our study had several strengths. First, the study examined the association of intrathoracic impedance with both physical and psychological symptoms. The use of physical and psychological symptoms provides a more comprehensive understanding of the patient symptom experience. Second, the use of generalized linear modeling allowed non-normally distributed variables to be used without transformation. Transforming non-normally distributed symptom variables would have made direct comparisons between symptoms difficult in this study. In addition to strengths, there a number of limitations to the study. The sample size was small, limiting the statistical power in some models, the number of covariates and the ability to detect significant smaller effects. Additionally, the sample had little variation in self-reported race and the use of certain medications such as beta-blockers and ACE/ARBs. This prevents our study from making inferences about how these variables may have affected the results. Finally, the sample was comprised predominantly of non-ischemic, married, self-described white participants with more severe functional limitations. These characteristics of the sample hinder the generalizability of the results to the general HF population.

Conclusion

Optivol® fluid index threshold crossings over 3 months were significantly associated with physical and psychological HF symptoms and HRQOL. Optivol® threshold crossings can provide additional information regarding symptom burden and HRQOL that may enhance clinical assessment of symptoms and facilitate earlier treatment to improve patient outcomes. Additional research with larger sample sizes and longitudinal designs are needed to further our understanding of the association between intrathoracic impedance and patient-reported outcomes.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2018.12.003.

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