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Assessment of Dyspnea in Acute Decompensated Heart Failure

Insights from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) on the Contributions of Peak Expiratory Flow

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Objectives This study hypothesized that peak expiratory flow rate (PEFR) would increase with acute heart failure (AHF) treatment over the first 24 h, related to a Dyspnea Index (DI) change and treatment effect.

Background Dyspnea is a key symptom and clinical trial endpoint in AHF, yet objective assessment is lacking.

Methods In a clinical trial substudy, 421 patients (37 sites) underwent PEFR testing at baseline, 1, 6, and 24 h after randomization to nesiritide or placebo. DI (by Likert scale) was collected at hours 6 and 24.

Results Patients were median age 70 years, and 34% were female; no significant differences between nesiritide or placebo patients existed. Median baseline PEFR was 225 l/min (interquartile range [IQR]: 160 to 300 l/min) and increased to 230 l/min (2.2% increase; IQR: 170 to 315 l/min) by hour 1, 250 l/min (11.1% increase; IQR: 180 to 340 l/min) by hour 6, and 273 l/min (21.3% increase; IQR: 200 to 360 l/min) by 24 h (all $p < 0.001$). The 24-h PEFR change related to moderate or marked dyspnea improvement by DI (adjusted odds ratio: 1.04 for each 10 l/min improvement [95% confidence interval (CI): 1.07 to 1.10]; $p < 0.01$). A model incorporating time and treatment over 24 h showed greater PEFR improvement after nesiritide compared with placebo ($p = 0.048$).

Conclusions PEFR increases over the first 24 h in AHF and could serve as an AHF endpoint. Nesiritide had a greater effect than placebo on PEFR, and this predicted patients with moderate/marked improvement in dyspnea, thereby providing an objective metric for assessing AHF. (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure [ASCEND-HF]; NCT00475852) (J Am Coll Cardiol 2012;59:1441–8) © 2012 by the American College of Cardiology Foundation

Shortness of breath is 1 of the principal presenting symptoms of patients with acute decompensated heart failure (AHF) (1), and relief of this dyspnea is a commonly employed endpoint for clinical care and randomized clinical trials of AHF therapy (2). Yet assessment of dyspnea is subjective, difficult to validate, and the relationship to objective measures is unknown (1,3,4). Despite this shortcoming, 3 major clinical trials in AHF (supported by the European Medicines Agency and U.S. Food and Drug Administration) have used dyspnea as a primary endpoint, given the importance assigned to this symptom (5–7).

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Abbreviations and Acronyms

AHF = acute decompensated heart failure

BNP = B-type natriuretic peptide

CI = confidence interval

COPD = chronic obstructive pulmonary disease

DI = Dyspnea Index

FEV_1 = forced expiratory volume in 1 s

HF = heart failure

PEFR = peak expiratory flow rate

Whereas a recent study enrolling patients with AHF very early in the emergency department reported that patient-assessed visual analogue and Likert scales evaluating the change in dyspnea were highly correlated, these results differed when provocative orthopnea testing was introduced. Hence, the relationship between dyspnea and more objective measures remains unclear (1).

Although the mechanisms of dyspnea are multiple, bronchoconstriction is thought to be a key modulator (8). Peak expiratory flow rate (PEFR) is a measure that reflects airflow limitation and is primarily determined by large airway caliber, expiratory muscle strength, elastic recoil, and resistance of the smaller intrathoracic airways (9). Because PEFR is inexpensive, portable, and widely used for the assessment of asthma and chronic obstructive lung disease, it is frequently used as an endpoint in clinical trials of asthma control (10).

Three studies have evaluated the use of PEFR for the diagnosis of patients with AHF (11–13). All found that patients with AHF could be readily distinguished from those with chronic lung disease by PEFR; however, its value for the diagnosis of heart failure (HF) is limited. However, only baseline PEFR measures were used in these mixed cardiovascular and respiratory disease populations with the goal of demonstrating diagnostic utility, rather than potential as an objective clinical trial endpoint. To date, no studies to our knowledge have described change in PEFR from baseline over time in patients with AHF.

We evaluated the baseline and sequential change in PEFR over the first 24 h from admission in a prospective substudy of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), a large trial of patients with AHF. Additionally, we examined the relationship of PEFR to clinical outcomes, and the effect of nesiritide or placebo on PEFR. Finally, we explored the relationship of a subjective Dyspnea Index (DI) to PEFR.

Methods

Study design. The study design and results of the ASCEND-HF study have been previously published (2,5). Briefly, the ASCEND-HF study evaluated nesiritide versus placebo in 7,007 patients with AHF enrolled within 24 h of first intravenous HF–related treatment. Participants were required to have each of the following at time of randomization: dyspnea at rest or with minimal activity; ≥1 accompanying sign (respiratory rate ≥20 breaths/min or pulmonary congestion/edema with rales ≥1/3 base); and ≥1 objective measure of HF (evidence of congestion/edema on chest x-ray; B-type natriuretic peptide [BNP] ≥400 pg/ml or N-terminal pro-BNP ≥1,000 pg/ml; pulmonary capillary wedge pressure >20 mm Hg; or left ventricular ejection fraction <40% in the previous 12 months). Among others, 1 exclusion criteria germane to this substudy was severe pulmonary disease (full exclusion criteria are available elsewhere) (5).

Respiratory substudy design. Patients in the prospectively planned respiratory substudy were enrolled between May 2007 and August 2010 at 37 sites in Canada and the United States. Consecutive patients were approached for enrollment at the time of entry into the main trial. The institutional review board at each participating hospital approved the protocol, and patients were required to provide written informed consent. The study team at each site completed standardized training including how to perform PEFR, and the same type of PEFR meter was used across all sites along with standardized patient and study team instructions.

PEFR, that is, the maximal flow generated on expiration after full inspiration, was performed at baseline (after randomization, but before drug infusion) and at 1 h, 6 h, and 24 h thereafter. Three measurements were completed at each time point, with the highest PEFR recorded in l/min (11–13). Other data captured simultaneously included respiratory rate in breaths/min, oxygen saturation (%), and liters of oxygen delivered (in l/min).

Sample sizes were estimated from 3 prior studies of dyspneic patients with cardiovascular disease that showed baseline PEFRs of 224 l/min (SD: 82 l/min) (12), 253 l/min (SD: 93 l/min) (13), and 267 l/min (SD: 97 l/min) (11), and 1 study of patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD), which had a mean PEFR of 113 l/min (SD: 51 l/min) (14). An improvement in the PEFR between 10 to 25 l/min, or approximately 5% to 12%, was considered clinically significant based on asthma studies (15,16). We assumed that with a baseline mean PEFR of 200 l/min (SD: 80 l/min), 200 patients per treatment arm would provide 80% power to detect a clinically meaningful 20% change (between nesiritide and placebo groups) in PEFR with a p value <0.05. A total of 400 patients would also result in adequate measurements to ascertain the time course of change, detect any differences between groups, and allow for drop-outs and missing data of <10% of PEFR measurements.

Statistical analysis. Data for continuous variables are presented as medians with 25th and 75th percentiles, and categorical variables are presented as frequencies and percentages. Wilcoxon rank sum tests were used to measure differences for continuous variables, and the chi-square test was used for categorical variables. Differences in continuous variables over time followed a Gaussian distribution and are reported as means with confidence intervals (CI) using *t* tests for comparison. Adjustment for baseline differences was done using covariate adjustment. Repeated-measures

analysis of covariance was used to model the effects of treatment group and to control for baseline PEFR. The groups were defined by the intention-to-treat groups as per the main trial protocol for the principal analysis. An additional "on-treatment" group was used to evaluate effects of patients receiving study drug or placebo as a sensitivity analysis. Outliers were examined for PEFR using the methods of Shiffler (17). Log transformation was used to normalize the PEFR data for evaluation. A correlation analysis was used to evaluate the association of the DI score and the change in PEFR. Additionally, a series of parsimonious logistic regression models were developed for predicting both significant improvement in dyspnea score, and for the composite outcome of HF rehospitalization or death at 30 days. Candidate variables included age, sex, PEFR, and treatment assignment. A p value of <0.05 was used as the level of statistical significance for all tests. A statistical analysis plan was developed before data analysis; all analyses were pre-specified unless otherwise stated. All analyses were performed using R Software (version 2.12.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 430 patients enrolled in the respiratory substudy. PEFR data was available for 421, 406, 405, and 410 patients at baseline, hour 1, hour 6, and hour 24, respectively. The 9 patients without baseline PEFR data were excluded from further analyses. Of the 421 patients, 208 (49.4%) were in the nesiritide arm, and 213 (50.6%) in the placebo arm. Comparisons with the 7,007 patients in the overall trial as well as all the 2,728 ASCEND patients enrolled in Canada or the United States are shown in Table 1. As compared with patients from Canada or the United States not in the respiratory substudy, those in the respiratory substudy were older, weighed less, and had higher respiratory rates; however, measurements of BNP, N-terminal pro–BNP, creatinine, and ejection fraction were similar. Differences between patients in the nesiritide or placebo arms are shown in Table 1. Small differences between groups in the percent of patients on beta-blockers or creatinine clearance were not associated with PEFR ($p = 0.7$ and $p = 0.4$, respectively).

Peak expiratory flow rate. As shown in Table 2, Overall, median PEFR increased from 225 l/min (interquartile range [IQR]: 160 to 300 l/min) at baseline, to 230 l/min (IQR: 170 to 315 l/min) at hour 1, 250 l/min (IQR: 180 to 340 l/min) at hour 6, and 273 l/min (21% increase, IQR: 200 to 360 l/min) at hour 24 (Table 2). Compared with baseline, PEFR increased by hour 1 (per patient average: 8.39 l/min; 95% CI: 2.89 to 13.89), hour 6 (26.32 l/min; 95% CI: 19.09 to 33.61), and at 24 h (43.92 l/min; 95% CI: 36.39 to 51.47).

Respiratory rate and oxygen saturation. Median respiratory rate was 23.0 breaths/min at baseline and similar between the nesiritide and placebo groups (22 [IQR: 20 to 24] vs. 23 [IQR: 21 to 24]; $p = 0.30$). Respiratory rate declined per patient by 2.9 breaths/min (95% CI: 2.56 to 3.22) over the first 24 h in the overall group from a median of 23.0 (IQR: 21 to 24) to 20 (IQR: 18 to 22; $p < 0.0001$).

Median oxygen saturation was 96% (IQR: 95% to 98%) at baseline and remained similar over the next 24 h to a median of 97% (IQR: 95% to 98%); the mean per patient difference was 0.08% (95% CI: −0.19 to 0.34). Initially, patients were on a median of 2 l/min of oxygen (IQR: 0 to 2.8 l/min), which declined to a median of 0 l/min by 24 h; the mean per patient decrease was 0.36 l/min (95% CI: 0.20 to 0.53). The difference was similar between the nesiritide and placebo groups.

Nesiritide versus placebo. The change in PEFR from baseline to 24 h between the nesiritide and placebo arms was statistically significant, with greater improvement in the nesiritide arm compared with placebo (unadjusted mean difference: +52.4 l/min vs. +35.9 l/min; 95% CI of difference: 1.37 to 31.54; $p < 0.05$). Individual pairwise comparisons at each time point did not show any significant difference between nesiritide and placebo. However, a repeated measures model incorporating time and treatment group showed a significant result favoring an improvement in nesiritide versus placebo ($p = 0.05$) (Fig. 1) for the improvement in PEFR.

Respiratory rate tended to decline more following nesiritide treatment as compared with placebo, that is, nesiritide patients had an additional 0.67 breaths/min reduction at 24 h ($p = 0.07$) not evident earlier at baseline, 1 h, or 6 h. There were no significant differences between the nesiritide and placebo groups in either oxygen saturation or delivered oxygen over the 24 h.

DI and PEFR. Baseline PEFR was unrelated to the 6-h or 24-h DI result (rho = −0.017, $p = 0.73$; rho = −0.08, $p = 0.11$, respectively). Additionally, the change in PEFR from baseline to 6 h did not correlate with the simultaneous DI measurement at 6 h (rho = 0.03, $p = 0.5$). At 24 h, the DI showed a small but significant correlation with change in PEFR from baseline to 24 h (rho = 0.15, $p = 0.002$).

The relationship between PEFR and DI at 24 h was further explored to evaluate whether the improvement in PEFR predicted patients with a moderate or markedly improved response on the DI. The regression model at 24 h shows a significant relationship: an increased PEFR predicted improved DI at 24 h (C-index: 0.60; odds ratio: 1.04 for each 10 l/min improvement [95% CI: 1.01 to 1.07]; $p < 0.01$). Figure 2 shows the relationship divided into 2 groups: patients with an improvement in DI ($n = 272$) and those without improvement ($n = 127$) demonstrating an improving PEFR over time by group.

No relationship was seen between the change in DI and change in respiratory rate (i.e., the change in respiratory rate by 24 h was unrelated to the DI response at 24 h).

Clinical outcomes. Similar to the overall study, the 30-day mortality and HF re-hospitalization rate in the substudy was 2.8% ($n = 12$ events) and 10.0% ($n = 43$ events),

Table 1 Baseline Characteristics of Patients in Overall Trial, North America, and Respiratory Substudy

Variable	Overall Trial (N = 7,007)	North America			Substudy		
		Not Enrolled in Substudy (n = 2,728)	Enrolled in Substudy (n = 421)	p Value	Nesiritide (n = 208)	Placebo (n = 213)	p Value
Demographics							
Age, yrs	67 (56–76)	67 (56–78)	70 (59–79)	0.003	69 (58–80)	70 (59–79)	0.72
Female	34.1	34.9	34.2	0.83	34.1	34.3	1.00
Race				<0.001			0.52
White	55.9	64.0	68.2		65.9	70.4	
Black	14.8	33.0	24.9		25.5	24.4	
Asian	24.9	1.3	3.3		4.3	2.4	
Other	4.3	1.7	3.6		4.3	2.8	
Medical history							
Heart failure admission 1 yr before admission	38.9	46.1	42.3	0.16	42.8	41.8	0.84
Prior myocardial infarction	34.9	34.6	39.0	0.09	38.0	39.9	0.69
Ischemic etiology for HF	47.9	43.6	42.0	0.56	40.9	43.2	0.69
Hypertension	72.2	81.5	79.1	0.26	81.7	76.5	0.23
Atrial fibrillation or flutter	37.5	41.7	46.1	0.09	43.8	48.4	0.38
Diabetes mellitus	42.6	49.6	44.7	0.07	42.3	47.0	0.34
Chronic respiratory disease	16.4	25.3	21.4	0.09	20.3	22.5	0.64
Measurements							
Weight, kg	78 (64, 95)	88 (73, 106)	84 (73, 102)	0.03	84 (74, 101)	85 (72, 103)	0.97
Blood pressure, mm Hg							
Systolic	123 (110, 140)	124 (111, 141)	123 (110, 137)	0.08	125 (110, 138)	121 (110, 137)	0.61
Diastolic	74 (67, 83)	72 (64, 83)	71 (62, 84)	0.31	72 (62, 85)	71 (63, 84)	0.94
Heart rate, beats/min	82 (72, 95)	80 (70, 90)	78 (68, 91)	0.30	77 (68, 91)	79 (68, 91)	0.96
Respiratory rate, breaths/min	23 (21, 26)	22 (20, 24)	24 (20, 24)	<0.001	23 (20, 24)	24 (20, 25)	0.57
BNP, pg/ml	992 (548, 1879)	1,030 (603, 1,900)	1,106 (577, 1,914)	0.99	1,108 (633, 1,941)	1,040 (551, 1,914)	0.37
NT-proBNP	4,463 (2,108, 9,048)	4,799 (2,266, 9,331)	4,662 (2,707, 9,312)	0.90	4,268 (2,414, 9,509)	5,161 (2,967, 9,048)	0.54
Creatinine, μmol/l	108 (88, 141)	115 (92, 150)	115 (88, 150)	0.29	108 (88, 141)	120 (88, 155)	0.02
BUN/urea, mg/dl	9.0 (6.4, 13.8)	8.6 (6.1, 12.1)	8.2 (5.8, 12.3)	0.24	7.5 (5.4, 11.1)	9.0 (6.2, 13.6)	0.001
Hemoglobin, g/dl	12.7 (11.3, 14)	12.3 (11, 13.7)	12.5 (11.1, 13.6)	0.46	12.4 (11.2, 13.6)	12.5 (11, 13.7)	0.68
LVEF*				0.38			0.26
≤40%	79	71	74		77	71	
>40%	21	29	26		23	29	
Medical or device therapy							
ACE inhibitor or ARB	61	62	65	0.23	64	67	0.61
Beta-blocker	58	74	70	0.07	65	75	0.03
Aldosterone blocker	28	24	18	0.02	18	19	0.80
Nitrates (oral or topical)	24	25	25	1.00	26	24	0.57
Loop diuretic	95.1	97.9	96.9	0.22	96.2	97.7	0.37
Implantable cardioverter-defibrillator	8.5	17.5	10.9	0.001	12.0	9.9	0.53
Biventricular pacemaker	1.3	1.7	2.1	0.55	1.0	3.3	0.18

Continued on next page

Table 1 Continued

Variable	Overall Trial (N = 7,007)	North America			Substudy		
		Not Enrolled in Substudy (n = 2,728)	Enrolled in Substudy (n = 421)	p Value	Nesiritide (n = 208)	Placebo (n = 213)	p Value
Study drug administration							
Time from hospitalization to randomization, h	15.5 (5.4, 21.9)	16.9 (6.6, 22.1)	16.2 (6.7, 22.3)	0.94	16.7 (7.8, 22.9)	15.8 (6.2, 21.8)	0.16
Use of study drug bolus	62	58	68	<0.001	68	67.0	0.76

Values are % or median (25th, 75th percentiles). Measurements and medical and device therapy are at baseline before randomization. *LVEF as assessed within 12 months before index admission.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic protein; BUN = blood urea nitrogen; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

respectively, with the composite rate of 12.1% (n = 52 events) (5). Using a logistic regression model incorporating 4 variables (age, sex, treatment assignment, and PEFR), the effect of baseline PEFR (and change from baseline to 24 h in PEFR) on the 30-day composite outcome was evaluated. Each 10 l/min increase in baseline PEFR was associated with an adjusted odds ratio of 0.96 (95% CI: 0.92 to 0.98, $p < 0.01$), and the change from baseline to 24 h in PEFR was similar but nonsignificant (odds ratio: 0.95 for 10 l/min change over 24 h, 95% CI: 0.92 to 1.01; $p = 0.1$).

Other analyses. There was no effect of bolus (vs. no bolus) nesiritide use, baseline beta-blocker or other medication use, or other baseline characteristics (including chronic respiratory disease) on PEFR. Additionally, there was no effect on the overall results when time from presentation to the emergency department to enrollment in the trial was incorporated into the multivariable model.

Discussion

This prospective substudy in AHF provides 3 novel observations: 1) PEFR shows a similar, clinically important pattern of improvement within 24 h of admission, analogous to that seen in acute respiratory diseases such as asthma or exacerbations in COPD; 2) changes in PEFR over 24 h predicted those AHF patients with a significant (moderately or markedly) improvement in their subjective DI; and 3) changes in PEFR demonstrated a small difference in respiratory function between nesiritide and placebo.

The minimal clinically important difference was postulated by Jaeschke et al. (18) to help place statistical differences in clinical context. In patients with asthma, the minimal clinically important difference for a PEFR has been proposed to be an absolute value of 18 l/min (16) or a 12% increase over baseline value (15), and for COPD trials, between 10 to 32 l/min (19–21). Hence, our observation of a mean increase of 44 l/min over 24 h falls well within this range and thus appears to reliably demonstrate an objective difference. Further studies will be required to establish whether the minimal clinically important difference in AHF should be expected to be greater, given the placebo group, on top of background medical therapy that included diuretics, also had an improvement in both PEFR and dyspnea. Additionally, PEFR should be examined over a longer duration of time (e.g., 5 days after admission) to see whether these findings correlate with other clinical improvements.

There are a number of potential mechanisms by which dyspnea may improve in patients with AHF with nesiritide, and objective measurements such as PEFR improvement may reflect 1 or more possibilities. For example, infusion of nesiritide to stable outpatients with asthma has been shown to increase forced expiratory volume in 1 s (FEV_1) and forced vital capacity by 36% and 24%, respectively, indicating a significant direct bronchodilator effect of nesiritide (22). Intravenous and inhaled atrial natriuretic peptide have both been shown to improve FEV_1 in patients with asthma

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Table 2 Respiratory Measurements

Variable	Patient Group	Baseline	Hour 1	Hour 6	Hour 24
Respiratory rate, breaths/min	All	22.5 (20, 24)	22 (20, 24)	20 (18, 22)	20 (18, 22)
	All	23.2 (22.8–23.5)	21.9 (21.6–22.3)	20.9 (20.5–21.2)	20.3 (20.0–20.7)
	Placebo	23.4 (22.7–23.9)	21.9 (21.4–22.3)	20.8 (20.3–21.2)	20.7 (20.2–21.3)
	Nesiritide	23.0 (22.5–23.5)	22.0 (21.5–22.5)	20.9 (20.4–21.4)	20.0 (19.6–20.4)
Oxygen saturation, %	All	96 (95, 98)	96 (95, 98)	96 (95, 98)	97 (95, 98)
	All	96.1 (95.9–96.3)	96.0 (95.8–96.3)	96.0(95.8–96.2)	96.2 (95.9–96.4)
	Placebo	96.0 (95.7–96.3)	96.0 (95.7–96.4)	96.1 (95.9–96.4)	96.4 (96.0–96.7)
	Nesiritide	96.2 (95.8–96.5)	96.0 (95.7–96.4)	95.8 (95.5–96.2)	95.9 (95.6–96.3)
Oxygen delivered, l/min	All	2 (0, 2.5)	2 (0, 2.5)	1.5 (0, 2)	0 (0, 2)
	All	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.5 (1.3–1.7)	1.2 (1.0–1.4)
	Placebo	1.4 (1.1–1.7)	1.4 (1.1–1.6)	1.3 (1.0–1.6)	1.1 (0.8–1.4)
	Nesiritide	1.8 (1.5–2.1)	1.8 (1.5–2.1)	1.7 (1.4–2.0)	1.4 (1.1–1.7)
Peak expiratory flow rate, l/min	All	225 (160, 300)	230 (170, 315)	250 (180, 340)	272.5 (200, 360)
	All*	221 (211–231)	228 (218–239)	244 (233–255)	263 (252–275)
	Placebo*	224 (210–238)	226 (212–242)	244 (228–261)	260 (244–276)
	Nesiritide*	219 (206–233)	231 (216–246)	243 (229–259)	267 (251–285)

Values are median (interquartile range) or mean (95% confidence interval). *Means and 95% confidence intervals are back transformed from log.

(23,24). The significant 18 l/min PEFR improvement with nesiritide in our study is consistent with the impact of nesiritide in these studies, albeit in a different population, and should be put in context of the overall ASCEND-HF trial result. The overall mechanism of how nesiritide and other current therapies affect peak flow limitation and dyspnea improvement is poorly understood.

The measurement of the symptom of dyspnea is clinically important in AHF as it constitutes a treatment goal that is subjectively assessed by both clinician and patient on a day-to-day basis. Dyspnea is complex and has been defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. . .derived from interactions among multiple physiological, psychological, social, and environmental factors" (8). Within clinical trials, dyspnea has been challenging to measure as evident from the use of multiple different dyspnea instruments seeking to internally "validate" a specific scale without external validation of the mechanisms, psychometric properties, or objective measurement of dyspnea. Given the absence of a gold standard, clinical trials have frequently used simple 5- or 7-point Likert scales without further validation (25). Our findings, albeit only when predicting improvement (as few subjects worsened), demonstrate an objective correlate for the subjective measure of the 7-point DI.

Assessment of "soft" endpoints such as symptomatic changes used in clinical trials of AHF therapy are difficult to evaluate and deserve careful scrutiny. Until recently, the DI (as assessed by visual analogue scale or Likert scale) had yet

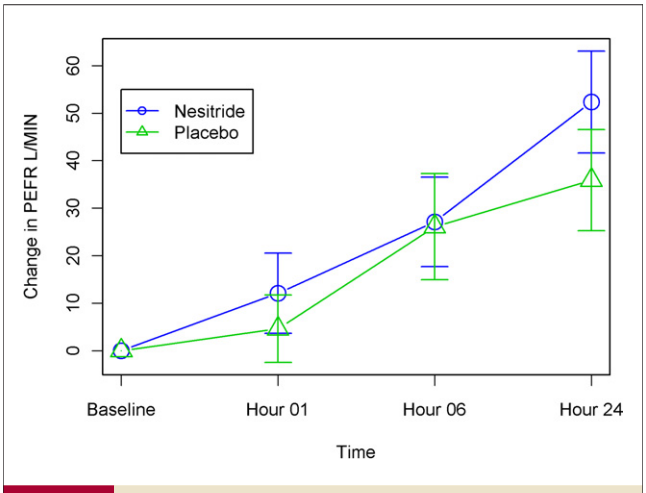

Figure 1 Change in PEFR Over Time With Nesiritide and Placebo

Error bars indicate 95% confidence intervals. PEFR = peak expiratory flow rate.

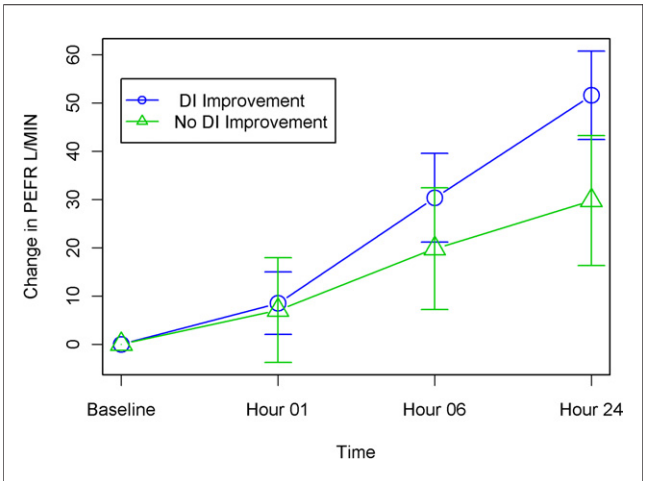

Figure 2 Change in PEFR Over Time and 95% CI (Values Back Transformed From Log)

Patients were divided into those with 24-h Dyspnea Index (DI) moderate or marked improvement (DI improvement, n = 272) versus those without improvement (No DI improvement, n = 127). *p = 0.01. CI = confidence interval; PEFR = peak expiratory flow rate.

to be linked to improved clinical endpoints such as re-hospitalization, mortality, or other established surrogates such as BNP within clinical trials (26). However, in a recent large randomized clinical trial enrolling patients with AHF, those with early dyspnea relief had a greater weight loss and a lower 30-day mortality than patients without dyspnea relief as measured by a 7-point Likert scale (27). When other surrogates such as pulmonary capillary wedge pressure are measured, they are perceived to be of clinical value since they can be re-assessed, standardized between patients, sites, and trials, and provide objective evidence of improvement. Given the disconnect between the measurement of dyspnea as a symptom and clinical outcomes, we contend that PEFR provides an improved approach for evaluating respiratory function (25). Prior studies evaluating respiratory flow limitation have demonstrated a relationship between posture and airflow limitation consistent with our overall results and may help explain the relationship between dyspnea, posture, pulmonary edema, and PEFR (28). Further work should refine the role of the provocative dyspnea test as a clinical trial endpoint (3) in the context of objective measures of respiratory function including PEFR and FEV_1. In order for PEFR to be effectively used as a surrogate in a large clinical trial, further efforts to define the pathophysiology of peak flow limitation, measurement characteristics of the instrument used (e.g., visual analogue scale), and susceptibility of symptom measures to small variations in positioning are required (29).

Study limitations. Our study has both limitations and strengths. First, PEFR was used rather than FEV_1. FEV_1 has been shown to be an independent predictor of mortality (30) and have a modest improvement in response to diuresis (31). PEFR was selected because we sought to test a simple, portable, reproducible, and inexpensive measurement that could be applied in the acute setting across multiple sites with minimal additional training. FEV_1 and forced vital capacity are also now available in portable units (albeit at a greater expense), and both metrics are used clinically in acute respiratory disease, with PEFR favored for asthma and FEV_1 for COPD. Although FEV_1 and PEFR are correlated, PEFR underestimates the degree of respiratory impairment (32), and further studies should test both PEFR and FEV_1 in the same cohort to determine the relative merits of each measure. The baseline PEFR of 230 l/min in our study is lower than previously reported in a stable outpatient HF population of 420 l/min, likely reflecting the acute presentation of these patients with symptoms of dyspnea (33)—further PEFR data from a broad AHF cohort with repeated measures would aid the generalizability of our study. Second, our substudy was of modest size, but similar to the size of many phase II trials, and the largest study of PEFR in patients with AHF. This further highlights the modest sample size required for demonstrating change in a clinical study with PEFR. Further exploration of the dosing and timing of diuretics will need to be explored in the overall trial as well as in this cohort to examine what effect, if any, is present. Third, the DI used in ASCEND-HF had few patients who worsened, and significant interpatient variability existed, requiring the creation of a model highlighting moderate or marked improvement prediction rather than using the entire scale. Further work will be required to understand the patient population who deteriorated, and what, if any, subjective or objective measurement should be used to predict this population.

Conclusions

PEFR is a useful objective measure that improves over the first 24 h of treatment for AHF. In this substudy of the ASCEND-HF trial, the improvement in PEFR was greater with nesiritide compared with placebo, and PEFR was linked to the primary clinical outcome at 30 days. However, the change in the DI was only modestly correlated with the change in PEFR. Additional validation in cohorts using multiple patient-reported symptom instruments and serial measures of PEFR are required for the demonstration of efficacy before use as an endpoint in clinical trials.

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REFERENCES

1. Mebazaa A, Pang PS, Tavares M, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J 2010;31:832–41.
2. Hernandez AF, O'Connor CM, Starling RC, et al. Rationale and design of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF). Am Heart J 2009;157:271–7.
3. Pang PS, Cleland JG, Teerlink JR, et al. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. Eur Heart J 2008;29:816–24.
4. Gheorghiade M, Follath F, Ponikowski P, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail 2010;12:423–33.
5. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.
6. McMurray JJ, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 2007;298:2009–19.
7. Teerlink JR, Metra M, Felker GM, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. Lancet 2009;373:1429–39.
8. Dyspnea. Mechanisms, assessment, and management: a consensus statement. Am J Respir Crit Care Med 1999;159:321–40.
9. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. Eur Respir J Suppl 1997;24:2S–8S.
10. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59–99.

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11. Ailani RK, Ravakhah K, DiGiovine B, et al. Dyspnea differentiation index: a new method for the rapid separation of cardiac vs pulmonary dyspnea. Chest 1999;116:1100–4.
12. McNamara RM, Cionni DJ. Utility of the peak expiratory flow rate in the differentiation of acute dyspnea. Cardiac vs pulmonary origin. Chest 1992;101:129–32.
13. Malas O, Caglayan B, Fidan A, Ocal Z, Ozdogan S, Torun E. Cardiac or pulmonary dyspnea in patients admitted to the emergency department. Respir Med 2003;97:1277–81.
14. Emerman CL, Cydulka RK. Use of peak expiratory flow rate in emergency department evaluation of acute exacerbation of chronic obstructive pulmonary disease. Ann Emerg Med 1996;27:159–63.
15. Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. Acad Emerg Med 2000;7:327–34.
16. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999;14:23–7.
17. Shiffler RE. Maximum Z scores and outliers. Am Stat 1988;42:79–80.
18. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407–15.
19. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA 1995;273:957–60.
20. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74–81.
21. Vestbo J, Pauwels R, Anderson JA, Jones P, Calverley P. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax 2005;60:301–4.
22. Akerman MJ, Yaegashi M, Khiangte Z, Murugan AT, Abe O, Marmur JD. Bronchodilator effect of infused B-type natriuretic peptide in asthma. Chest 2006;130:66–72.
23. Angus RM, McCallum MJ, Thomson NC. Effect of inhaled atrial natriuretic peptide on methacholine induced bronchoconstriction in asthma. Clin Exp Allergy 1994;24:784–8.
24. Angus RM, McCallum MJ, Hulks G, Thomson NC. Bronchodilator, cardiovascular, and cyclic guanylyl monophosphate response to high-dose infused atrial natriuretic peptide in asthma. Am Rev Respir Dis 1993;147:1122–5.
25. Allen LA, Hernandez AF, O'Connor CM, Felker GM. End points for clinical trials in acute heart failure syndromes. J Am Coll Cardiol 2009;53:2248–58.
26. West RL, Hernandez AF, O'Connor CM, Starling RC, Califf RM. A review of dyspnea in acute heart failure syndromes. Am Heart J 2010;160:209–14.
27. Metra M, O'Connor CM, Davison BA, et al. Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study. Eur Heart J 2011;32:1519–34.
28. Duguet A, Tantucci C, Lozinguez O, et al. Expiratory flow limitation as a determinant of orthopnea in acute left heart failure. J Am Coll Cardiol 2000;35:690–700.
29. Allen LA, Metra M, Milo-Cotter O, et al. Improvements in signs and symptoms during hospitalization for acute heart failure follow different patterns and depend on the measurement scales used: an international, prospective registry to evaluate the evolution of measures of disease severity in acute heart failure (MEASURE-AHF). J Card Fail 2008;14:777–84.
30. Iversen KK, Kjaergaard J, Akkan D, et al. The prognostic importance of lung function in patients admitted with heart failure. Eur J Heart Fail 2010;12:685–91.
31. Pison C, Malo JL, Rouleau JL, Chalaoui J, Ghezzo H, Malo J. Bronchial hyperresponsiveness to inhaled methacholine in subjects with chronic left heart failure at a time of exacerbation and after increasing diuretic therapy. Chest 1989;96:230–5.
32. Aggarwal AN, Gupta D, Jindal SK. The relationship between FEV1 and peak expiratory flow in patients with airways obstruction is poor. Chest 2006;130:1454–61.
33. Evans SA, Kinnear WJ, Watson L, Hawkins M, Cowley AJ, Johnston ID. Breathlessness and exercise capacity in heart failure: the role of bronchial obstruction and responsiveness. Int J Cardiol 1996;57:233–40.

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