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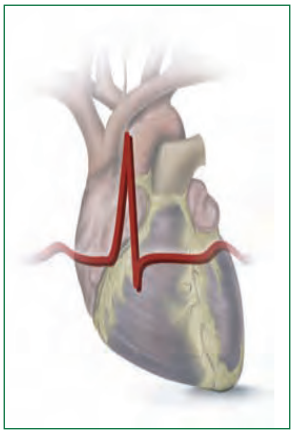

FAIR-HF: IV Iron Can Boost Kidney Function in HF With Iron Deficiency

Several months of intravenous iron therapy to correct iron deficiency in patients with systolic, NYHA class II-III heart failure not only made patients feel and exercise better, it apparently also improved renal function, in a post hoc look at findings from a randomized trial.

The renoprotective effect, as measured by changes in estimated glomerular filtration rate (eGFR), was independent of age, heart-failure severity, LVEF and, notably, whether the patient had anemia or poor renal function at the outset.

The observations from the **Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial** can't be considered conclusive, according to Dr Piotr Ponikowski (Medical University, 4th Military Hospital, Wroclaw, Poland), "and we are fully aware that further studies are required to determine the potential clinical benefits of our findings."

However, the results are potentially important because there are currently no evidence-based treatments specifically for the syndrome of heart failure with renal dysfunction, he said when presenting the analysis here at the Heart Failure Congress 2010 meeting of the Heart Failure Association of the European Society of Cardiology. Ponikowski is the association's president-elect.

It is an innovative therapy for a chronic problem that is very common. It is hard to think of how raising eGFR would not be helpful. The epidemiology is very, very sound.

But pointing out the surrogate and subjective end points that were the focus of FAIR-HF, Pfeffer presented a long list of clinical trials that found significant positive effects on such end points that were also associated with harm or lack of clinical benefit.

His list included the **African American Study of Kidney Disease (AASK),** a predominantly hypertension trial with calcium-channel-blocker (CCB), ACE-inhibitor, and beta-blocker randomization arms. The CCB arm of the trial was prematurely stopped when its patients showed an increase in mortality or need for dialysis.

In the trial's first three to six months, according to pfeffer, "the GFR - in that study they actually measured the glomerular filtration rate was increased in the calcium-channel-blocker arm compared with the ACE-inhibitor arm, but the clinical result was the opposite."

Researchers also cautioned that the follow-up in FAIR-HF was too short to disclose any late adverse effects of IV iron. There is no substitute for long-term trials to give you the safety of the intervention.

In the FAIR-HF primary analysis, patients treated with the injectable iron preparation ferric carboxymaltose (Ferinject, Vifor Pharma) over 24 weeks responded with significantly improved symptom status, NYHA functional class, six-minute-walk distance, and quality of life. The study, conducted at 75 centers around the world, had randomized 459 patients with depressed serum ferritin levels to receive either IV iron (n=304) or a saline placebo (n=155).

In the renal-function analysis, which hadn't been prospectively defined, the trial's primary findings of significant, steady improvements in both NYHA functional class and patient global assessment over 24 weeks held true regardless of whether the baseline estimated eGFR was above or below 60 mL/min/1.73 m^2. The same was found for the secondary end points six-minute-walk distance and quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Patients treated with placebo tended to show a fairly constant renal function throughout the study. In contrast, those treated with IV iron showed very favorable results and very significant improvement at the end of the trial. Even more important, there was evidence that this improvement was already seen very early in

Table: Increment in Mean eGFR* Among Patients Treated With IV Iron vs Placebo by Duration of Treatment in FAIR-HF

Treatment duration (wk)	eGFR increase (mL/min/1.73m^2)	P
4	2.8	0.054
12	3.0	0.049
24	4.0	0.017

*Estimated glomerular filtration rate was about 64 mL/min/1.73 m^2 at baseline in both treatment groups.

the trial, at week four, a treatment effect of about 3 mL/min/1.73 m^2.

Among actively treated patients, eGFR went up an average of about 2 mL/min/1.73 m^2 for patients with baseline levels <60 mL/min/1.73 m^2 and by about 5 mL/min/1.73 m^2 for those with higher baseline eGFR both significant improvements that remained so across a range of prospectively defined subgroups by age, sex, NYHA class, HF etiology, diabetic status, body-mass index, and baseline levels of hemoglobin and ferritin.

Significantly more patients taking IV iron showed improved renal function, and significantly fewer showed deterioration by week 24 (p=0.03). In particular, 50% of them had a >2 mL/min/1.73 m^2 rise in eGFR, vs only 33% for those given placebo. The increase was >5 mL/min/1.73 m^2 for 35% and 25% of the two groups, respectively. And eGFR slid by at least 2 mL/min/1.73 m^2 in 34% of actively treated patients and 50% of controls.

Dr John J McMurray (University of Glasgow, Scotland), who is the current Heart Failure Association president but not a FAIR-HF investigator, echoed in saying the trial "is so very encouraging, but we have seen so many trials mislead in the past." That has happened, "no matter how obvious, how logical, how mechanistic, how pathophysiologically sensible" their surrogate end points may have been.

McMurray went on to point out yet another potential limitation of the trial, which its investigators describe as double-blind for its clinicians and patients: that the placebo and the dark-brown IV iron were administered from syringes that had been blacked out in an attempt to hide their contents and preserve the blinding.

But because of that irregularity, "the blinding here was suspect." It could have been easily compromised, inadvertently or otherwise, he said.

He would like to see another study, even one with soft end points, that replicates the FAIR-HF findings but uses a tighter, more conventional system for blinding the treatment groups, "rather than going straight to a large morbidity-mortality trial." Two independent trials showing symptom improvement from IV iron therapy in such patients would strengthen its case for approval in the absence of a trial with hard clinical end points, McMurray said.

FAIR-HF was sponsored by Vifor Pharma. Ponikowski reports consulting for Amgen and consulting for and receiving honoraria for speaking from Vifor Pharma. Pfeffer reports receiving research grants from or consulting for Amgen, AstraZeneca, Baxter, Biogen, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Celadon, Centocor, CVRx, Genentech, Genzyme, Medtronic, Novartis, Roche, Sanofi-Aventis, Via, and Zensun and being coinventor of a patent awarded to Brigham and Women's Hospital regarding the use of renin-angiotensin-system inhibitors in selected survivors of acute MI.

Table: Levels of Iron-Metabolism Markers and Hemoglobin at Week 24 According to Study Treatment.*

Variable	Ferric Carboxymaltose (N = 305)	Placebo (N = 154)	P Value
All patients			
Ferritin (µg/liter)	312±13	74±8	<0.001
Transferrin saturation (%)†	29±1	19±1	<0.001
Hemoglobin (g/liter)	130±1	125±1	<0.001
Mean corpuscular volume (µm^3)	97±0	94±1	<0.001
Patients with anemia (hemoglobin ≤ 120 g/liter)			
Ferritin (µg/liter)	275±18	68±11	<0.001
Transferrin saturation (%)†	29±1	17±1	<0.001
Hemoglobin (g/liter)	127±1	118±2	<0.001
Mean corpuscular volume (µm^3)	98±1	93±1	<0.001
Patients without anemia (hemoglobin >120 g/liter)			
Ferritin (µg/liter)	349±19	80±11	<0.001
Transferrin saturation (%)†	30±1	22±1	<0.001
Hemoglobin (g/liter)	133±1	132±1	0.21
Mean corpuscular volume (µm^3)	96±1	95±1	0.91

* Plus–minus values are means ±SE. The P value is for the mean treatment effect, adjusted for the baseline value. One patient who had been randomly assigned to the placebo group received ferric carboxymaltose.

† The percent transferrin saturation was calculated as iron (in micromoles per liter) ÷ transferrin (in grams per liter) × 25.1.

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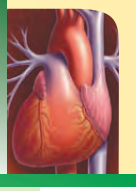

A review of dyspnea in acute heart failure syndromes

In acute heart failure syndrome (AHFS), dyspnea is one of the most common but least understood presenting symptoms for hospitalization. For this reason, dyspnea relief is increasingly becoming a focus in the development of therapies for the treatment of AHFS, and currently stands as an acceptable primary end point for regulatory approval by governmental agencies. This raises the question of how best to measure such a subjective symptom. In this review, we will describe the basis for dyspnea, provide a detailed description of the strengths and weaknesses of the current best tools used to measure it, and describe future directions for future development of dyspnea measurement in AHFS.

Breathing discomfort, and its varying degrees of severity, is the most disturbing symptom patients with an acute heart failure syndrome (AHFS) can experience; and it often serves as the impetus to seek medical care. *Acute heart failure syndrome* is collectively defined as a gradual or rapid change in heart failure (HF) signs and symptoms resulting in a need for urgent therapy. This same sensation of breathlessness is what also drives patients with asthma and chronic obstructive pulmonary disease (COPD) to seek medical attention, and it would be helpful to describe the pathophysiology of dyspnea in AHFS. *Dyspnea*, as defined by the American Thoracic Society in their consensus on the mechanisms, diagnosis, and treatment of dyspnea, is “a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses”. Although this is an agreed upon definition of the symptom, it is experienced differently by every patient and depending on the etiology. Patients with congestive HF will describe their dyspnea as “suffocating at rest” or “air hunger” or express the quality of rapid breathing rather than describe an increase in work of breathing that is commonly seen with pulmonary disease (ie, asthma, COPD).

Table I. Components of pathophysiology of dyspnea

Components	
Afferent signals	Mechanical receptors in the airways, lungs, chest wall structures, and chemoreceptors in the blood
Efferent signals	Efferent motor activity of the respiratory center in the brain descending to the diaphragm, and accessory respiratory muscles
Central processing	Perceived mismatch or dissociation between afferent sensation and efferent motor
Physiologic factors	Intrinsic dysfunction of the respiratory system caused by the burden of cardiac, pulmonary, or cardiopulmonary disease

Pathophysiology

The pathophysiology is theorized to result from a patient's perceived mismatch or dissociation between the efferent motor activity of the respiratory center in the brain and the incoming afferent signals from mechanical receptors in the airways, lungs, chest wall structures, and chemoreceptors in the blood (Table I). Thus, it has less to do with the status of intrinsic respiratory function and more to do with the unresolved and disjointed interpretation of information within the controls of the respiratory system. That is not to say that physiologic factors are spectators and not integral components. It has clearly been documented that the burdens of advanced age, malnutrition, anemia, and cardiopulmonary disease including congestive HF will initiate a cyclical and deleterious cascade of events that disrupts respiratory muscle function leading to a ventilatory challenge the system is unfit to meet, which further deteriorates respiratory function. If these factors could be modulated, then perhaps a better outcome could be achieved. Likewise, there is also an effort to identify the area of the cortex that processes information related to dyspnea with the goal of identifying a pathway that could be interrupted to prevent the uncomfortable sensation; however, it remains unidentified as evidenced by the lack of a cortical lesion that abolishes the sensation of dyspnea or a cortical area that causes it when stimulated.

Evaluation of dyspnea

Because the understanding of the pathophysiology of dyspnea is limited as well as the technology to determine it, the best current measurements of dyspnea involve using quality of life measurements. These instruments can be divided into 3 categories based on how they assess dyspnea during activities of daily living, during exercise, and on the overall impact on health status (Table II).

Quality of life measurements have been used for years to measure qualities such as pain, anxiety, and stress that could not otherwise be directly quantified. These

Table II. Dyspnea measurement tools

Components	Name of instrument
Rate dyspnea using scales in the chronic setting with ADLs as the benchmark for degrees of dyspnea	MRC Dyspnea Scale OCD BDI TDI UCSD SOBQ
Rate level of dyspnea during cardiopulmonary exercise testing	Modified Borg scale
Rate the impact of dyspnea on the overall well-being of a patient	SGRQ CRQ CHFQ

instruments have also been shown to be valid and reliable, meaning they have both the ability to measure a patient's dyspnea and the quality of reproducible measurements. Currently, these are considered objective measurements of the subjective symptom of dyspnea; and because they come directly from the patient, they are clinically relevant to therapy management.

The first category of quality of life measurement involves using scales in the chronic setting with activities of daily living as the benchmark for degrees of dyspnea. These are the Medical Research Council (MRC) Dyspnoea Scale, the Oxygen Cost Diagram (OCD), the Baseline and Transition Dyspnea Indexes (BDI/TDI), and the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ).

The MRC Dyspnoea Scale is the work of Sir Walter Morley Fletcher and the MRC in Wales in the 1940s. It was created in response to the problem of quantifying breathlessness in Welsh coal mine workers suffering from pneumoconiosis. Patients are asked to rate their degree of dyspnea on a scale from 1 to 5, with 1 being “not troubled by breathlessness except on strenuous exercise,” 2 being “short of breath when hurrying on the level or walking up a slight hill,” 3 being “walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace,” 4 being “stops for breath after walking about 100 yards or after a few minutes on level ground,” and 5 being “too breathless to leave the house, or breathless when undressing.” This scale has been validated for use in COPD patients. The main strength of this scale was that its repeated use during follow-up visits could be used to track changes in dyspnea; however, it has since been established that it is not sensitive enough to track responses to therapy during a single hospital stay. For this reason, there is uncertainty about its use in hospitalized HF patients, as the length of stay in hospital does not equate to the time between follow-up visits for outpatients with COPD.

The OCD asks patients to rate their level of dyspnea corresponding to the oxygen requirements of 13 different activities ranked in ascending order from 0 to 100 according to the number of calories expended in performing these activities and represented as a value along a vertical 100-mm line. Sleeping, sitting, and standing as less calorie intense and therefore less oxygen demanding activities are ranked closer to 0, while walking, briskly or not, uphill is ranked as 100. Patients are asked to mark the point at which they believe they are when they are at their best. The score is tabulated as the distance from 0 in millimeters. A score of 100 noted no impairment at all. The main strength of this instrument is in its use as a description of a patient's perceived exercise tolerance—it does not correlate well with objective changes in exercise tolerance. The overwhelming limitation of the OCD is that not all dyspneic patients can carry out the breadth of activities listed on the diagram. The frame of reference of the people incapable of performing all of the activities nullifies the widespread implementation of this particular instrument.

The BDI was developed to characterize the degree of activity that provokes dyspnea, the magnitude of effort necessary to carry out an activity, and the functional limitations in work and activities of daily living. The questionnaires were conceived for use in respiratory assessment; therefore, they are usually administered by health care providers familiar with history taking in respiratory disease. A cumulative grade is assigned to the patient's baselines status and is based on the individual scores of the categories of functional impairment, magnitude of task, and magnitude of effort, which are assigned a grade from 0 to 4 (0 being significant impairment and 4 being no impairment). A cumulative grade closer to 0 corresponds to more severe impairment. The BDI is used in tandem with the TDI, which tracks changes from baseline. The same open-ended questionnaires are used with the same categories, but changes are logged on a scale from -3 (significant deterioration) to +3 (significant improvement). Overall, a cumulative grade from -9 to +9 is produced for changes from baseline, with a score closer to -9 marking a more significant deterioration. Although this instrument has been demonstrated to be valid and reliable and sensitive to changes in dyspnea levels in patients with respiratory disease, it has shortcomings in assessing HF patients. The major weaknesses with this instrument are that the questions asked by interviewers are not standardized and timely administration of the questionnaire requires some proficiency in its use. This instrument is very user dependent; therefore, significant interinterviewer variability can occur depending on the experience of the health care provider administering the questionnaire. To reduce variability when used in a clinical trial, the same interviewer would have to conduct every interview. In addition, the instrument has not been validated for use in assessment of dyspnea secondary to HF.

The UCSD SOBQ consists of 21 questions about the severity of dyspnea associated with activities of daily living and 3 questions about the extent of limitations in these activities caused by the dyspnea itself or the fear of dyspnea on an average day during the week leading up to answering these questions. Each question is rated from 0 (no breathlessness) to 5 (unable to complete a particular activity of daily living because of shortness of breath), producing an overall score from 0 to 120. The main weakness in using this instrument to measure dyspnea in HF patients is that patients are asked to rate their level of dyspnea with respect to certain activities they may no longer perform. In addition, it has not been proven to be sensitive enough to changes that take place in less than a week.

The second category involves the Borg scale, which gauges the level of absolute dyspnea by asking patients to rate their level of dyspnea during cardiopulmonary exercise testing. The original Borg scale was from 6 to 20, but the American College of Sports Medicine modified it to a scale from 0 to 10. A numerical score of 0 corresponds to a verbal qualifier of “no perceived dyspnea” after testing, whereas a score of 10 is considered “maximal” perceived dyspnea. In a study that measured expiratory flow and orthopnea in left ventricular HF, the Borg scale was shown to accurately measure dyspnea in both the seated and supine positions before and after treatment with vasodilators and diuretics until hospital discharge. The main weakness of the Borg scale in HF patients is that most of these patients would be incapable of performing the necessary cardiopulmonary testing when acutely hospitalized with AHFS.

The final category involves using question inventories that rate the impact of dyspnea on the overall wellbeing of a patient. These are the St. George's Respiratory Questionnaire (SGRQ), the Chronic Respiratory Disease Questionnaire (CRQ), and the Chronic Heart Failure Questionnaire (CHFQ).

The SGRQ measures respiratory symptoms and activities that potentiate or are limited by dyspnea as well the overall impact of dyspnea on health status. The questionnaire asks 76 questions across the categories of symptoms (frequency and severity), activity (activities that cause or are limited by breathlessness), and impact (social functioning, psychological disturbances resulting from airways disease). The symptom category is rated on a 5-point Likert scale, and the activity and impact categories are yes/no responses. Each section is scored and weighted according to empirical data to produce a cumulative score from 0 to 100, with a higher score indicating worse health. The CRQ and CHFQ take a similar approach to assessing the impact of disease on quality of life. The CRQ and CHFQ questionnaires differ by only a single question and assess the disease limitations of activities of daily living using a 7-point scale (1 being extremely short of breath, 7 being not at all short of breath) to measure the domains of dyspnea, emotional function, mastery, and fatigue. The emotional function, mastery, and fatigue domains have standardized questions. The dyspnea domain is rated using the 7-point scale across 5 activities the patient has selected from memory or suggestion as being most important to their daily living. All of these questionnaires have been shown to accurately quantify the levels of dyspnea, with the scores on the questionnaires even demonstrating correlation to physiologic data yielded from pulmonary function tests. However, their main weakness, which prevents their use in clinical trials for HF patients, is that they are not sensitive enough to track the changes in dyspnea that can occur in a patient during their hospital stay.

Dyspnea scales in AHFS clinical trials

The most basic of requirements that new drugs must achieve to receive approval by the regulatory agencies is the demonstration that they improve either symptoms or clinical outcomes. The heterogeneity of symptoms, characteristics, and presentations of AHFS has limited the ability for creation of end points that satisfy the needs of the clinical community as well as regulatory agencies such as the Food and Drug Administration or European Medicines Agency. Because dyspnea is of the most common and disturbing experiences an AHFS patient encounters and because it satisfies one of the approved requirements, its relief has been targeted as a clinical end point. However,

Table III. Dyspnea measurement as an end point for studies focusing on HF

Type of instrument used for dyspnea assessment	Name of study (y)	Study Intervention (no. of subjects)
Likert scale	VMAC (2002)	Nesiritide versus nitroglycerine versus placebo (489)
	SURVIVE (2007)	Levosimendan versus dobutamine (1327)
	RITZ-1/RITZ-2 (2001/2003)	Tezosentan versus placebo (669/292)
	PROTECT (2009)	Rolofylline versus placebo (301)
	REVIVE-2 (2005)	Levosimendan versus placebo (600)
	EVEREST (2007)	Tolvaptan versus placebo (2048)
	ASCEND-HF	Nesiritide versus placebo (Enrolling)
VAS	VERITAS (2005)	Tezosentan versus placebo (1448/1760)
Borg scale	(2005).	Vasodilators, diuretics (9)
Composite HF score	OPTIME-CHF	Milrinone versus placebo (951)

there is no current standardization to the measurement of dyspnea. And unfortunately, most of the aforementioned quality of life measurements have been validated for use in patients with chronic dyspnea secondary to pulmonary disease such as COPD or cystic fibrosis, or in lung patients undergoing pulmonary rehabilitation; thus, their application for use in the acute setting with AHFS patients not capable of exercise is limited at best. In addition, although these instruments have been validated and proven reliable, they have not been demonstrated, for the most part, to be sensitive enough to track changes in dyspnea in HF patients over their average length of hospital stay. Furthermore, many of the questionnaires are time-consuming endeavors even for health care providers seasoned in their use.

All of these factors into the rationale of why the Visual Analog Scale (VAS) and Likert scales have been the most widely used and accepted measures of dyspnea in AHFS patients (Table III). Likert scales consist of 3-, 5-, or 7-point scales that ask patients to rate their level of improvement in response to therapy on a categorical spectrum ranging from markedly better to markedly worse or an appropriate variation. Moreover, the VAS asks patients to rate their level of breathing difficulty on a vertical numerical continuum with 0 at the bottom and 100 at the top, with 100 being the best imaginable ability to breathe and 0 being the worst conceivable dyspnea. The Likert scales and VAS have been established in multiple AHFS clinical trials such as VERITAS, RITZ-1/RITZ-2, VMAC, EVEREST, SURVIVE, and REVIVE-II as being valid and reliable instruments capable of discriminating the degree of a patient's dyspnea (Table III). In the MEASURE-HF trial, Likert and VAS scores were compared. The study found that Likert measures of dyspnea initially improved rapidly with no significant improvement thereafter, whereas VAS measurements of dyspnea improved continually throughout hospital stay.

Minimal clinically important difference

Although the VAS and Likert scores have proven themselves to be the best tools among the quality of life measurements in measuring dyspnea in HF, they too suffer from shortcomings that can limit their use. For example, intersubject comparisons of VAS scores are hard to make because the maximum and minimum levels of breathlessness can be different for each individual— one person's 50 is only another person's 20. Although these scores will never be the same for everyone, the changes in perceived dyspnea scores before and after treatment in HF are most important and deserve more attention. The minimal clinically important difference (MCID) is “the smallest difference between scores in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management.” The MCID in dyspnea scores in HF has not yet been fully explored.

The MCID for VAS has been investigated in 2 trials. In one prospective, observational study, the MCID in dyspnea was evaluated by assessing 156 patients before and after they received initial asthma therapy in an emergency department. During reassessment, subjects were asked to describe their asthma symptoms as “much better,” “a little better,” “no change,” “a little worse,” or “much worse.” The “mean VAS change among the ‘a little better’ subjects was 2.2 cm (95% CI 1.1, 3.4) which was significantly greater than the -0.4 cm (95% CI -2.1, 1.4) change in the ‘unimproved’ subjects.” Thus, a change of 2.2 cm or (22 mm) was found to be the minimal clinically significant improvement in VAS dyspnea scores. In another prospective observational study, 79 patients with diagnosed HF were asked to rate their level of dyspnea on a VAS before and after they received therapy. The study found that patients who had a higher recorded VAS score also had a significantly greater change in VAS. However, for all patients, the mean for a meaningful change in VAS was 21.1 mm (or 2.11 cm) (95% CI 12.3-29.9 mm). In essence, these studies, although well conducted, represent a first step in defining the MCID in dyspnea that HF patients experience as measured on VAS in response to therapeutic intervention. The consensus for the MCID appears to be between 21.1 and 22 mm. Moving forward, large randomized controlled trials are needed to form a more substantiated MCID. The MCID has also been established in the CHFQ, TDI, and UCSD SOBQ. The CHFQ was established in a retrospective study that compared the results of 3 previous studies that used the CHFQ. Patients were asked in the CHFQ to rate their shortness of breath during day-to-day activities, their level of fatigue, and how they were feeling emotionally and then compared that with how they had improved overall on a 15-point global rating scale that ranged from -7 (a great deal worse), through 0 (no change), to +7 (a great deal better). A global rating scale change from either -3 to -1 or +1 to +3 corresponded to a significant decrease in dyspnea. This corresponded to a mean change in 3 points per question in the dyspnea domain of the CHFQ, which averaged out to be 0.5 point per question within each domain. The MCID for the TDI was established with a multinational clinical trial of 997 patients with COPD. In this study, they found that a mean change of 1 unit in the TDI focal score corresponded to a clinically significant decrease in dyspnea. The MCID for the UCSD SOBQ was established in a study of 164 chronic lung disease patients before and after pulmonary rehabilitation. A mean change of 5 units corresponded to a clinically significant decrease in dyspnea.

Future methods for dyspnea evaluation

For any drug to receive US Food and Drug Administration approval, it has to demonstrate in a clinical trial either a decrease in mortality or relief of symptoms associated with a particular disease or condition. For this reason, the outcome end points for the development of therapies for AHFS have included decreased mortality, decreased hospital stay and rehospitalization, decreased use of special interventions, and relief of symptoms, as well as combinations of some or all of these. Among the relief of symptoms, dyspnea is the most important to patients. The improvement a patient reports in the assessment of his or her own dyspnea is one of the most important standards by which efficacy of therapy in AHFS is ascertained. Moreover, dyspnea relief serves as a viable reflection for physicians of patient improvement in the short term. Immediate relief of dyspnea mere hours after presentation can lead to more rapid stabilization of patients that can theoretically be discharged with a reduced length of stay. Consequently, this affects data collection for other clinical end points, underscoring the importance of furthering the evolution of dyspnea relief as a clinical end point in the treatment of AHFS. Despite the crux of improvement in a patient's clinical course being placed on dyspnea relief and the development of new AHFS therapies being based on it also, the measurement of dyspnea itself has not been well defined in the clinical setting and remains the next priority in AHFS end points. A concerted effort is needed to accurately gauge the dyspnea continuum and its MCID to allow for accurate tracking of quantifiable changes in response to therapy that will help guide the development of new therapies for this burdensome disease.

One potential direction is development of a combination of methods that relate to dyspnea. These new approaches must for instance take into account the potential effect of a patient's position on dyspnea assessment. This issue was explored in the recently published URGENT-dyspnea study. In this trial, HF patients were initiated on the standard of care in European medical centers (ie, intravenous diuretics) and underwent dyspnea assessment 6 hours after initiating therapy. The majority of patients were evaluated in the sitting position, but those with less severe dyspnea in this position were graduated to dyspnea assessment in the supine position. It was found that orthopnea may be refractory to treatment in the acute setting, as patients evaluated in the supine position reported less improvement in their dyspnea than their upright counterparts. With these and multiple other considerations in mind, the Dyspnea Severity Score (DSS) has been developed as a way to standardize dyspnea measurements. The DSS consists of asking patients to rate their level of dyspnea on a 5-point Likert scale in each category of the Provocative Dyspnea Assessment, which has patients sitting upright with oxygen, sitting upright without oxygen, lying supine without oxygen, walking 50 m as fast as possible, and a post–6-minute walk test. The DSS ranges from 1 to 25 and essentially measures when patients can no longer progress in performance. Although the DSS does well to incorporate objective measures, its overall scoring is still entirely reliant on patient reporting. It incorporates no concrete objective data and, as a result, is subject to the variation that is inherent in most other dyspnea assessment tools. The DSS, although quantifiable, still lacks a tangible MCID and is tedious and hence challenging to ascertain in large clinical trials. A mega clinical trial (ASCEND-HF) assessing dyspnea relief in AHFS is under way and may advance our understanding of pathophysiologic correlates of dyspnea relief. Dyspnea will be measured using the 7-point Likert scale in all patients at 6 and 24 hours after initiation of therapy. Change in weight, urine volume, biomarkers including natriuretic peptides (in a subset), and a respiratory substudy measuring peak expiratory flow rate will provide additional data to help ascertain an MCID in these patients. As promising as the DSS is, it has not been validated for use in any clinical trials to date.

Conclusion

Dyspnea is a complex pathophysiologic state that is not well understood and is deeply disturbing to patients who suffer from it. The best efforts to measure dyspnea to provide a basis upon which clinical trials for the development of new therapies for AHFS can be conducted or patients' improvement can be clinically judged are aimed at using quality of life measurements. Among these quality of life measurements, the Likert scale and VAS have been established as being the best combination of valid, reliable, and easy to use instruments for measuring dyspnea in the clinical setting; with the DSS being the first promising, yet untested, step in standardizing dyspnea assessment. Quantifying the exact significance in degree of change in dyspnea with these quality of life measurements needs future attention; however, initial steps have been taken by exploring the MCID for the VAS, in particular. In improving the evaluation of dyspnea relief as a benchmark for AHFS intervention efficacy, additional steps may be needed. To date, as dictated by the understanding of the pathophysiology, dyspnea measurements have relied almost entirely on subjective data from either the patient or the health care provider. Future studies may consider incorporating objective data in addition to subjective measures, although symptom relief is at the heart of the problem from a patient's perspective.

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Cardiology News

Early Age at Menopause Linked to Angina Post MI

Women who have an early menopause, at 40 years or younger, are at higher risk for angina after a myocardial infarction (MI) vs women who experience menopause at 50 years or older. According to the researchers, women who experience early menopause may be at risk for cardiovascular disease morbidity and mortality because of a deprivation of estrogen after menopause; however, no descriptions of its prognostic importance among women with known coronary heart disease have been reported. In addition, the study authors note that angina symptom-driven care for women accounts for most costs associated with care in women with coronary heart disease. In the current study, 493 women were interviewed by telephone 1 year after discharge from the hospital for MI on aspects of behavioral, treatment, and health status measures. Mean age at menopause (AAM) was 45.2 ± 7.8 years.Of the women, 132 (26.8%) experienced early menopause at 40 years or younger. However, the rate of 1-year angina in women with an AAM of 40 years or younger (32.4%) was double that of women with an AAM of 50 years or older (12.2%) in a multivariable analysis, as was the severity of angina.

Menopause. Published online July 21, 2010.

Rising Furosemide Doses in Heart Failure Patients Don't Bode Well

A rising need for furosemide is linked with a rising risk for death in elderly heart failure patients. Researchers studied 4270 heart failure patients (mean age 78.4 years), tracking changes in furosemide dose for up to 5 years after hospital discharge. A "dynamic" daily dose of furosemide - the most common medication used in heart failure treatment, was classified as low dose (up to 59 mg), medium dose (60-119 mg), or high dose (at least 120 mg). "The 'dynamic furosemide dose' reflects both the dose of the drug and the amount of time exposed to higher doses of this diuretic over time, and is important because changes in furosemide dose occurred in nearly two-thirds of all patients. Overall, 46% of patients changed dose categories within one year, and 63% changed categories over the course of the study. The adjusted mortality hazard ratios with dynamic time-varying furosemide dose were 1.96 with medium-dose furosemide and 3.00 with high-dose furosemide, using low-dose furosemide as the referent. They also observed a "prominent" increase in the risk of renal dysfunction and arrhythmias with furosemide exposure. The team concludes, Furosemide dose can serve as a powerful, dynamic, and easily used marker of prognosis in heart failure.

Am Heart J. August 2010.

Increased CVD Risk Associated With Shorter and Longer Sleep Durations

Sleep duration, both less than and more than the standard 7 hours, may be an important marker of cardiovascular disease (CVD). The researchers analyzed information from 30,397 respondents. The reported amount of sleep was subdivided into 5 categories: 5 hours or less, 6 hours, 7 hours, 8 hours, and 9 hours or more. Compared with the group having, on average, 7 hours of sleep a night, the risk for CVD in the other groups, who either had more sleep or less sleep, was increased by approximately 23% to 220%. The greatest risk was associated with 5 hours or less of sleep per night. For sleep duration of 6 hours, 8 hours, and 9 hours or more, the multivariate ORs were 1.33, 1.23, and 1.57, respectively. The mechanisms underlying the association of short duration of sleep with CVD may include sleep-related disturbances in endocrine and metabolic functions, whereas longer duration of sleep could be related to an underlying sleep-disordered breathing or poor sleep quality.

Sleep. 2010;33:1037-1042.

Editorial Note

Dear Doctor,

We are happy to present the 19th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on " ***Dyspnea in acute heart failure syndromes*** ". We will appreciate your thoughtful comments.

Thanks and regards.