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Symptom burden in heart failure: assessment, impact on outcomes, and management

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Abstract

Evidence-based management has improved long-term survival in patients with heart failure (HF). However, an unintended consequence of increased longevity is that patients with HF are exposed to a greater symptom burden over time. In addition to classic symptoms such as dyspnea and edema, patients with HF frequently suffer additional symptoms such as pain, depression, gastrointestinal distress, and fatigue. In addition to obvious effects on quality of life, untreated symptoms increase clinical events including emergency department visits, hospitalizations, and long-term mortality in a dose-dependent fashion. Symptom management in patients with HF consists of two key components: comprehensive symptom assessment and sufficient knowledge of available approaches to alleviate the symptoms. Successful treatment addresses not just the physical but also the emotional, social, and spiritual aspects of suffering. Despite a lack of formal experience during cardiovascular training, symptom management in HF can be learned and implemented effectively by cardiology providers. Co-management with palliative medicine specialists can add significant value across the spectrum and throughout the course of HF.

Keywords

Heart Failure; Palliative Care; Symptoms; Quality of Life; Supportive Care

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INTRODUCTION

The prevalence of heart failure (HF) in the U.S. has reached epidemic proportions and is expected to increase another 30% to a total of 8 million Americans by 2030 (1). Advances in pharmacologic therapy and implantable cardiac devices have revolutionized HF management and improved survival(2). Unfortunately, these therapies rarely prove curative, and more patients with HF endure a terminal disease state for a longer period of time. As a result, both cardiovascular providers and their patients are now exposed to greater symptom burden and, ultimately, more suffering as an unintended consequence of increased longevity.

Patients with severe chronic illness, including those with HF, identify symptom management as a top priority, particularly at the end of life.(3,4) In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, over half of patients with advanced HF were willing to trade survival time for improved symptom control, and more than a quarter stated they would trade nearly all of their remaining time to feel better.(5) Among patients awaiting heart transplantation, symptoms represent the most significant stressor.(6) Symptoms cause suffering and negatively impact both quality of life and will to live.(7) Not only is symptom control critical to quality of life, but patients cite symptom management as a critical component of a good death as well. (3,8) Unfortunately, providers often fail to address their patients' symptomatic concerns, and this problem may be worsening. By some accounts, patients at the end-of-life are suffering more and complaining of greater pain, depression, and confusion compared to those from even fifteen years ago.(9)

Adequate symptom management consists of two key components: comprehensive symptom assessment and sufficient knowledge of the available approaches to alleviating the physical, emotional, social and spiritual aspects of the symptoms.(10) Some disciplines are attacking the problem more aggressively than others. For example, cancer patients die with less shortness of breath, fill more symptom-directed prescriptions prior to death, and receive more frequent palliative care consultations than cardiac patients.(11–13) Despite a lack of formal palliative care experience during cardiovascular training, symptom management in patients with advanced HF can be learned and implemented effectively by cardiology providers.

SYMPTOMS – SCOPE OF THE PROBLEM

A symptom is defined as the patient's "perception of an abnormal physical, emotional, or cognitive state."(14) Patients with HF experience physical, psychological, social, and existential distress that crescendos in the final six months of life.(15,16) The sheer magnitude of symptoms among patients with HF is striking, with a similar burden to that seen in patients with advanced malignancy and AIDS.(17,18) In survey-based studies, the mean number of symptoms in patients with HF ranged from 7 in a study that excluded psychological symptoms to 19 in one that included them.(19–22) This wide distribution highlights variability introduced by inconsistent definitions, disparate methods of detection, and varying degrees of sampling bias.(17) Simply counting symptoms, however, is

insufficient. It fails to acknowledge other contributing factors such as symptom intensity and symptom-related distress.

Defining the underlying cause of a symptom in a patient with HF can direct the appropriate treatment strategy. First and foremost, symptoms often arise from HF itself. Patients with HF and a preserved ejection fraction (HFPEF) experience the same classic HF symptoms as those with reduced ejection fraction (HFREF).(23) Even following implantation of a ventricular assist device or heart transplantation, HF symptoms can persist.(24–29) Guideline-directed medical therapy remains the cornerstone of symptom control, although it is important to note that these therapies can produce unintended side effects that contribute to suffering.(30,31) In addition to the symptoms caused by the HF itself, patients also experience symptoms due to comorbid illnesses, which are quite common given that the average patient with HF in the developed world at the time of hospitalization is more than seventy-five years old. (32)

Even with optimal HF therapy, patients often experience an increase in symptom burden over time as the underlying disease progresses.(33) Symptoms worsen both with increasing New York Heart Association (NYHA) functional class and with closer proximity to death. (34,35) Life-saving therapies such as the implantable cardioverter defibrillator (ICD) prolong the course of HF by successfully treating previously fatal malignant arrhythmias. (36) As a result of the increasing usage of ICDs, there has been a shift from sudden cardiac death to protracted, more predictable pump failure and its associated symptoms. As more patients with HF decline gradually towards their deaths, there is an accompanying loss of autonomy, an inability to engage in self-care, and a heightened need for complex shared decision-making.(37,38) Caregivers, too, are not immune to the downstream consequences of these symptoms, which reduce caretaker quality of life as well through increased fear and anxiety.(39,40)

Symptoms matter—not only for the patient and their family but also for the healthcare system at large. Symptoms correlate in a dose-dependent fashion with adverse clinical events, as defined by a composite of all-cause mortality, hospitalization, emergency room admission, ventricular assist device implantation, and heart transplantation. In one study, when compared to patients with HF with low overall symptom burden, those with moderate symptom burden were 82% more likely to have such an adverse event within a year, while patients with severe burden were more than twice as likely to have one.(41) In the Carvedilol or Metoprolol European Trial (COMET) study, a patient-assessed symptom profile similarly predicted all-cause hospitalization and five-year mortality.(42) Thus, symptoms experienced by patients with HF drive significant healthcare costs through resource utilization in the emergency room and beyond.(43)

SYMPTOM ASSESSMENT TOOLS

Providers and patients with HF must share the responsibility for symptom recognition. It has been observed that patients with HF with the highest symptom burden are not those most likely to attend clinic visits, suggesting a mismatch between providers and those patients most in need.(20) Even if patients are evaluated by a provider, symptoms are not always

identified. As one example, pain is conspicuously absent from descriptions of symptoms in major HF textbooks.(44) While 2/3 of patients reported pain in one study, only 1/4 of visits provided documentation of it.(45) Simply put, providers are not good at recognizing symptoms, and when they do note them, their perception often deviates markedly from that of the patient.(46,47) Such patterns remain until the end, as providers struggle to accurately predict terminal symptoms in the days leading up to death as well.(35,48–50) Patients, too, can fail to recognize their own symptoms and frequently normalize daily fluctuations or ignore them long enough for their symptoms to become severe.(51) Efforts to improve patient literacy may encourage greater patient involvement in symptom recognition, and maintenance of a symptom diary can allow a patient to track subtle changes.(52) Unfortunately, some patients have comorbid cognitive dysfunction that impairs their ability to interpret or express symptoms.(51,53,54) Similarly, at the end of life, many patients cannot engage altogether, thus requiring providers to recognize nonverbal cues of suffering. (55)

Numerous validated tools are available for symptom assessment; however, many of them were developed for research purposes and are quite cumbersome to use in the clinical arena. Clinically, most symptoms can be adequately assessed and followed over time using a numeric rating scale, which is more user-friendly than a visual analog scale. For a comprehensive symptom assessment using numeric rating scales, the Edmonton Symptom Assessment Scale (ESAS) is both effective and efficient. The ESAS is a ten question symptom survey initially designed for cancer patients that can be self-administered (e.g., in the waiting room).(56) Patients score from 0–10 their level of distress from pain, fatigue, nausea, depression, anxiety, sleepiness, appetite, dyspnea, and ‘other’ symptoms, with overall well-being scored in reverse with 0 denoting best and 10 being worst possible well-being. The summary ESAS score (0–100) provides complementary information about ‘non-classical’ HF symptoms but also correlates with NYHA functional class and the Kansas City Cardiomyopathy Questionnaire (KCCQ), a frequently used measure of global health status in patients with HF.(56–58) The 32-item modified Memorial Symptom Assessment Scale is more comprehensive than the ESAS but at a cost of being significantly more time consuming. (59)

PAIN

In the words of Albert Schweitzer, “Pain is a more terrible lord of mankind than even death itself.”(60) Pain among patients with HF is both common and undertreated, representing an opportunity for improvement in symptom control.(19) More than half of all patients with HF —up to 84% in one study—acknowledge that pain consistently contributes to their suffering. (18,45,61–63) Fourteen percent report “horrible or excruciating” pain, and a substantial proportion attribute “at least quite a bit” of distress to pain.(61–63) Pain increases with NYHA Class, affecting 89% of those with Class IV symptoms, and worsens over time, afflicting up to 75% of patients with HF in the final six months of life.(19,33,44) Over time, pain that persists becomes more closely tied to psychosocial and emotional factors.(64) Eloquently stated in a textbook of nursing, “pain that is diminished, ignored, or doubted is pain that leads to suffering.”(65)

With the exception of the relatively small proportion of patients with HF with angina, pain localization in patients with HF is the same as in age-matched controls without HF.(61,62,66) As expected based upon the advanced age of many patients with HF, musculoskeletal pain is extremely common and tends to be worsened by physical inactivity as HF progresses. In one study, musculoskeletal pain afflicted 75% of veterans with HF who were lacking concomitant edema (62). Other types of non-cardiac pain commonly reported by patients with HF include headaches, abdominal pain, and pain due to comorbid illnesses such as diabetic neuropathy.(62)

The morbidity generated by uncontrolled pain is profound. Patients with pain have lower medication adherence, provide worse self-care, and are four times as likely to have depression and anxiety.(67–69) Other distressing sequelae include sleeplessness, fear, reduced cognitive functioning, hopelessness, and increased suicidal ideation.(67,70) All of these ramifications of uncontrolled pain may lead to increased hospital admissions. Pain leads to a greater dependency for activities of daily living and diminished quality of life.(67) There is even evidence to suggest that pain can worsen underlying HF by triggering an already overactive sympathetic nervous system and activating the renin-angiotensin-aldosterone cascade.(67) Pain frequently clusters with other symptoms in patients with HF, and adequate treatment of pain can lead to improvement in those non-pain symptoms as well.(45)

Pain can be subdivided in multiple ways, and an awareness of the complex classification system can guide prescriptive therapy. Total pain is comprised of physical, emotional, social, existential, and spiritual components.(66) Physical pain can be nociceptive, resulting from damage to non-neuronal tissue, or neuropathic, resulting from damage to the body's peripheral sensors. Nociceptive pain can be further subdivided into somatic pain and visceral pain. Somatic pain is usually musculoskeletal or superficial in nature, causing throbbing, aching, or stabbing. In contrast, visceral pain, an internal pain brought on by stretch, ischemia, or inflammation, manifests as deep, diffuse, and dull discomfort.(66,71) An adequate assessment of pain should include questions of frequency, location, duration, qualities, precipitants, and alleviating factors.(71) Using a numeric pain intensity scale ranging from 0 (no pain) to 10 (worst pain possible) provides the clinician with a metric to gauge response to treatment as well.

Arguably the most straightforward pain control for cardiac providers is the management of angina using both pharmacologic and revascularization strategies.(72) Other etiologies of pain, however, often prove more challenging to cardiologists, as the underlying cause is often unclear, and some common analgesics are relatively contraindicated in the HF population. The World Health Organization Pain Relief Ladder recommends an initial approach to pain using non-opioid medications, reserving consideration of opioids only when non-opioids alone are ineffective.(73) It is also important to note that non-pharmacologic therapies can be quite effective adjuvants in treating pain including acupuncture, physical therapy, biofeedback, mindfulness-based stress reduction, exercise, and music.(74–76)

While effective for nociceptive pain, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) are usually contraindicated in patients with HF due to their propensity to cause worsening fluid retention, kidney injury, and gastrointestinal bleeding.(72) Some studies suggest that oral NSAIDs may increase HF hospitalizations more than ten-fold.(77,78) Although the data on efficacy in palliative care populations are scant, topical NSAIDs are a safe alternative to trial in these patients given that plasma concentrations following administration are less than 1% of oral systemic levels.(79) Other non-opioid medications that can be considered for nociceptive pain include acetaminophen and topical lidocaine preparations, although the latter have only been shown to be effective for non-neuropathic pain in case reports and open-label non-randomized trials.(80)

For neuropathic pain there are several different classes of medications available, though they all must be considered carefully in the HF population due to their potential for significant side effects. Topical lidocaine is effective for localized peripheral neuropathic pain and causes very few side effects. Anti-epileptics, such as gabapentin, are often effective for neuropathic pain at adequate doses, but they must be dose-adjusted for patients with renal insufficiency, may increase fluid retention, and often have significant potential for drug-drug interaction. Tricyclic antidepressants can also be quite effective for neuropathic pain but are usually a poor choice in patients with HF because they can be negative inotropes, QT-prolonging proarrhythmics, and potent antimuscarinics.(71,81,82)

If non-opioid medications are inadequate analgesics, then opioids can be a useful addition for pain management in the HF population. Tramadol, oxycodone, hydromorphone, and fentanyl are generally viewed as the safest options and provide versatility through oral, intravenous, and transdermal formulations. Tramadol, which is a weaker opioid, also has serotonergic activity that may limit its use when given concomitantly with antidepressant medications.(83) For chronic use, morphine and codeine can be more problematic for pain management because they break down into neurotoxic, renally-excreted metabolites that can accumulate in patients with HF with concomitant renal dysfunction.(71,72) Methadone use is discouraged without palliative care consultation because it accumulates in tissues over time, has frequent drug interactions, and prolongs the QT interval, thereby lowering the threshold for life-threatening arrhythmias in a population that is already at heightened risk.(71,72) Regardless of agent selected, all patients on opioids need to be monitored for constipation, nausea, urinary retention, and mental status changes.(55)

Additional barriers to effective pain management in the HF population include under-recognition, concerns about polypharmacy and drug-drug interactions, and worries that opioid use in particular might potentiate addiction or hasten death.(62,84) Yet cardiac providers should be reassured that true addiction in terminally ill patients is rare and that behavior perceived to be deceitful often instead signals inadequate treatment that will respond to better analgesia.(8,64,72) Although limited data suggest that chronic opioid administration slightly increases adverse cardiovascular events in healthy patients, expert consensus argues that the benefits of using opioids to effectively manage symptoms in the HF population outweigh the risks of undertreated pain.(85) Additionally, the concern over opioids as agents that hasten death has not been validated in the literature.(86,87)

DYSPNEA

Dyspnea or breathlessness is defined by the American Thoracic Society as a “subjective experience of breathing discomfort.”(88) Braunwald defines dyspnea as an “uncomfortable awareness of breathing” that demands increased effort.(89) However, it is worth noting that the patient vernacular for dyspnea often differs from common medical terminology and also varies based on underlying disease.(90,91) Some patients note feelings of “suffocating”, “air hunger”, or “somebody…clutching [their] throat,” while others admit that their breathing “requires effort” and that “words [get] stuck in [their] mouth.”(43,54,91,92) Elucidation of dyspnea is further complicated among patients with HF because many normalize shortness of breath as an accepted part of everyday life and therefore only affirm breathing difficulties when in the midst of an acute exacerbation. When a patient is unaware of or denies seemingly obvious shortness of breath, a helpful question is, “Do you have to think about your breathing?” Another strategy for assessing breathlessness in patients who have become acclimated to chronic dyspnea is to ask about functional limitations and lifestyle changes, including abandoned hobbies.(90)

Like pain, dyspnea is consistently reported in more than half of patients with HF and peaks in the last six months of life.(18,19,22,34,35,61) Also like pain, uncontrolled dyspnea has been shown to negatively impact outcomes of patients with HF. In the COMET study, patient-reported breathlessness predicted death and all-cause hospitalization independent of many other factors, including investigator-assigned NYHA class.(42) Dyspnea is also the symptom that most frequently motivates patients to present to the emergency room and has consistently been shown to negatively impact a patient’s will to live.(7,43,93,94)

Dyspnea may be continuous or episodic, punctuated by a clear onset and offset with a sometimes identifiable trigger.(95,96) Assessment of dyspnea is not only plagued by its difficult recognition but also by its lack of an objective gold standard for validation.(97,98) Studies have repeatedly failed to link patient-reported dyspnea to objective measurements such as pulmonary-capillary wedge pressure, left ventricular ejection fraction, and cardiac output.(18,31,99) Similarly, dyspnea does not correlate well with spirometry or pulse oximetry, though one trial suggested that the use of peak expiratory flow rate may be helpful.(95,97) Many assessment tools rely on visual analog scales, Likert scales or numerical rating scales to quantify dyspnea or instead try to quantify the impact of dyspnea on quality of life rather than measure the dyspnea itself.(92) For practical purposes, a numerical rating scale for dyspnea is a valid measure of present dyspnea severity and correlates with many of the other available tools.(92,100,101)

There are many potential explanations of dyspnea in patients with HF, including lungs stiffened by elevated left ventricular pressures, diaphragmatic skeletal muscle weakness, comorbid obstructive lung disease, obesity, deconditioning, and malnutrition.(99) Treatment, it follows, must also be multifaceted.(102) Intracardiac filling pressures can be optimized through inotropy, vasodilation, and volume removal with dietary changes, diuresis, and even ultrafiltration. Pulmonary disease can be optimally managed with guideline-directed medical therapy. Nutrition and physical therapy can counter the effects of cardiac cachexia.(103) Cardiac rehabilitation can improve self-reported health status in patients with HF, as

measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). In a similar vein, a recent study from Europe demonstrated that patients with HF randomized to inspiratory muscle training on top of baseline aerobic training reported significantly less dyspnea after a twelve-week program.(104)

Other interventions can successfully target the breathlessness sensation itself rather than its underlying etiology. While supplemental oxygen has failed to demonstrate benefit over ambient room air at rest, it may provide benefit during exertion.(105–108) Opioids can act centrally to blunt the perception of dyspnea and may be particularly useful in patients with advanced disease.(88,109) When used at usual doses, opioids can be safely used for the management of dyspnea in patients with cardiopulmonary disease.(110) Benzodiazepines are generally not recommended for the management of dyspnea given that they have not been shown to be more effective than placebo and have many detrimental side effects.(88,111) Often, anxiety in a dyspneic patient is driven by the breathlessness itself and will resolve when the dyspnea is appropriately treated. Simple non-pharmacological adjunctive therapies can sometimes be quite helpful. Oscillating fans, which are both inexpensive and safe, can decrease breathlessness by 40% on a visual analog scale.(112) Open windows may provide a similar benefit.(113) Physical accommodations, such as an adjustable bed or the use of a motorized scooter, can offer additional benefit. Non-traditional treatment approaches to dyspnea include biofeedback, neuroelectrical muscle stimulation, chest wall vibration, exercise training, hawthorn extract, and diets enriched in lycopene and omega-3.(114–118) Recognizing the need for a multipronged approach, two separate studies in the United Kingdom found preliminary success with the creation of multi-professional, interdisciplinary outpatient breathlessness clinics that improved breathlessness and positively impacted performance status, physical state, and emotional health.(102,117,119)

DEPRESSION

Depression is extremely common in the general population but occurs even more frequently among patients with HF.(120) Studies document that 21–36% of patients with HF have a mood disorder, though this number may rise as high as 70% when limited to inpatients suffering from HF.(72,82,120–122) Depression in HF has profound consequences, as it is associated with increased symptom burden, rehospitalization, mortality, and healthcare costs.(34,82,121–123) Depression can heighten sensitivity to other preexisting symptoms, interfere with self-care, and impair adherence to therapy.(21,34,82,122,124–126) As depression worsens, there is a dose-dependent rise in both the total number of symptoms reported as well as the relative distress that each of them causes.(21) Such an increase in symptoms then causes a greater need for outpatient and inpatient care, doubling the combined endpoint of hospital readmission and all-cause mortality in several studies.(82,121,127) When mortality is isolated as an endpoint, depression has been reported to increase mortality by as much as five-fold.(128)

Many have tried to elucidate the link between depression and worsening HF. Proposed mechanisms include a heightened sympathetic tone and/or inhibited parasympathetic tone among patients with depression as well as increased cortisol levels, higher rates of platelet aggregation, and the development of a pro-inflammatory milieu.(82,121,122) In contrast,

worsening HF brings with it declining functional status and increasing awareness of burdening others, more frequent hospitalizations, erosion of identity, and the embarrassment of using supplemental oxygen and motorized scooters.(50,82,129–131) Moreover, a large subset of the sickest patients with HF have ICDs and are susceptible to appropriate defibrillation discharges as well as the aftermath of such a shock. As many as 20% of patients with devices have severe post-traumatic stress disorder precipitated by a shock, and this may increase susceptibility to depression as well.(132)

Depression in patients with HF can be particularly challenging to diagnose. Symptoms of depression are often unmasked only when pursued by heightened suspicion, as the fatigue, poor appetite, and sleep disturbances of depression may all be attributed to the comorbid HF. In fact, patients with HF and depression report fewer symptoms such as depressed mood, worthlessness, and guilt than depressed persons without HF.(120) Any time that there is a disconnect between subjective HF complaints and objective data, depression should be strongly considered. Similarly, when a typically vocal patient stops complaining entirely, depression should also be entertained.(120) The Patient Health Questionnaire-2 (PHQ-2) inquires about the frequency of anhedonia and hopelessness over the past two weeks and is an efficient and sensitive screening instrument for depression.(133)

Importantly, depression is inextricably linked to other symptom domains, and worsening in one often produces a setback in the other.(21,122) Although depression negatively affects symptom burden, hospitalization rate, and mortality in patients with HF, treatment of that depression may also stand to improve the totality of symptoms.(134) The most commonly used antidepressants, selective serotonin reuptake inhibitors (SSRIs), improve platelet function, stabilize the endothelium, and provide anti-inflammatory benefit, all of which should benefit HF pathophysiology.(135) Moreover, SSRIs have a favorable side-effect profile and low risk of complications of overdose, particularly in the elderly.(136) Initial excitement was sparked by a study in which nearly six hundred patients with comorbid HF and major depression receiving an SSRI showed an improvement in physical symptoms at four weeks.(134) Unfortunately, these results have not been reproduced in larger studies.(135,137) One theory to explain this discrepancy proposes that depressed patients with multiple comorbidities, as often found in the depressed HF population, are inherently less likely to derive benefit from antidepressants.(136) Given these inconsistent study results and their relatively benign side effect profile, SSRIs are still worth trialing in depressed patients with HF. When starting an SSRI, though, it is important to monitor patients with renal dysfunction for worsening hyponatremia and fluid retention.(138) Among the SSRIs, sertraline, fluoxetine, fluvoxamine, and paroxetine appear to be the safest to use in patients with HF because they are unlikely to prolong the QT interval.(139) When choosing which of these SSRIs to use, it is important to consider possible drug interactions via cytochrome P450 enzymes 3A4 (fluvoxamine) and 2D6 (fluvoxamine, fluoxetine, and paroxetine). In general, sertraline is a good choice in patients with HF because it is unlikely to cause QT prolongation and has a lower potential to interact with concomitant medications.(140) Although serotonin-norepinephrine reuptake inhibitors (SNRIs) and mirtazapine are effective treatment for depression in the general population, these medications have not been formally studied in patients with HF. SNRIs are not considered first-line treatment for mood disorders in patients with HF because of case reports of SNRI-induced tachycardia and HF

exacerbations in previously stable patients.(141) Mirtazapine can be useful in some patients who are also experiencing concomitant poor appetite or sleeping difficulties with their mood disorder.(142) However, mirtazapine is considered a second-line treatment because doses of 15mg per day or greater are indicated for depression, and increased noradrenergic activity at these doses could theoretically lead to worsening of HF. Also, mirtazapine has been associated with mild increases in the QT interval. As noted above, tricyclic antidepressants are only recommended with expert consultation due to the possibility of negative inotropy, QT-prolongation, and significant antimuscarinic side effects.(81,82)

In addition to pharmacologic therapy for depression, there are several non-pharmacologic therapies that should be considered.(143) O'Connor argues that the first step to successful treatment of depression in a patient with HF is the normalization of the symptom.(144) Psychotherapy and cognitive behavioral therapy are effective treatments for depression, but logistical issues and patient reluctance can limit implementation.(145,146) Spiritual well-being should be promoted if the patient is amenable.(18,147) In addition, a regular exercise routine, acupuncture, and mindfulness have all been shown to be effective.(148,149) Improved patient education, deliberate efforts at creating patient-centered, family-focused care, and discussion of advance directives can reduce anxiety.(53,54,150,151) Specific to the subpopulation of patients with an ICD, shared decision-making regarding the device functionality is welcomed by patients as end-of-life approaches.(152) Preparation for a shock may also lessen a patient's distress should the device actually discharge (132). Lastly, there is some evidence that a multidisciplinary team--similar to the model successfully employed for dyspnea as mentioned above—can reduce symptoms of depression as well in patients with HF.(153)

GASTROINTESTINAL DISTRESS

Patients with HF frequently experience a wide variety of gastrointestinal (GI) distress. In one study, upper GI symptoms were noted in 27% of patients; while anorexia due to tasting or swallowing difficulties has been observed in up to half of patients with HF. Constipation and poor appetite are also common.(57,154)

Nausea and vomiting can be attributed to low forward cardiac output and poor intestinal blood flow, as well as right-sided volume overload, hepatic congestion, and gut wall edema.(155) Nausea can be measured and followed over time using a numeric rating scale.(156) Nausea can be exacerbated by cardiac medications such as aspirin, spironolactone, amiodarone, and digoxin, not to mention symptom-directed therapy such as opioids.(57) When comorbid renal failure is present, nausea can be further worsened by uremia. Improved HF management and removal of offending medications when possible are important approaches to reducing nausea. Many of the commonly used anti-emetics, including prochlorperazine, promethazine, ondansetron and metoclopramide, can be effective at reducing nausea, but they necessitate close monitoring of the QT interval when not outright contraindicated by baseline QT prolongation. When QT interval does limit traditional antiemetic use, a trial of dronabinol may be reasonable. Dronabinol is generally well tolerated, though psychoactive side effects and sleep disturbances can occur.(157) Unfortunately, it has not been explicitly studied in patients with HF, and its efficacy is

extrapolated from that established among patients with chemotherapy-induced nausea and vomiting.(157) Although benzodiazepines are frequently utilized in patients with HF with nausea and a prolonged QT interval, they are not desirable due to their unfavorable side effect profile and lack of efficacy in all but anticipatory nausea.(158)

Constipation is also problematic among patients with HF, and fluid restriction, diuretic use, comorbid diabetic gastroparesis, and opioid analgesia can all contribute. Constipation is the only common symptom seen in patients with HF that is not included in the ESAS. The simplest assessment tool which has been validated for clinical measurement of constipation is the Bowel Function Index (BFI), which asks patients to rate over the prior week their ease of defecation, feeling of incomplete bowel evacuation and subjective rating of constipation from 0–100.(159) Dietary changes, osmotic agents, stool softeners, stimulant laxatives and motility agents may be useful for constipation in patients with HF. One popular osmotic agent, polyethylene glycol, has to be administered with 8 ounces of fluid which makes it difficult for some patients with HF to tolerate. In patients with opioid-induced constipation, colonic opioid antagonists such as methylnaltrexone may also be trialed if other treatments are unsuccessful, though its use is often limited by cost.(55)

Diminished oral intake results from anorexia, early satiety, and uncontrolled HF symptoms that can interfere with completion of a meal.(57) The ESAS includes an item which assesses poor appetite using a numeric rating scale. Although there are many different medications which are FDA approved for appetite stimulation, none have been formally studied in this population. Metoclopramide, a first-line prokinetic agent, is the safest agent to consider in the population of patients with HF with symptoms of early satiety.(160–162) Mirtazapine can stimulate the appetite in some patients. Although it can be used as an appetite stimulant at doses less than 15mg per day to avoid noradrenergic side effects, it can actually be sedating due to its increased affinity for histamine receptors at these lower doses and should be given at bedtime.(163) Both metoclopramide and mirtazapine may cause QT prolongation and should be monitored closely. Dronabinol is another drug that could be considered in the HF population, but it can cause psychoactive side effects and sleep disturbances.(164) Megestrol should be avoided, because it increases thromboembolism risk in this already sedentary population.(165) Prednisone is also not recommended due to its propensity to cause fluid retention. Calorically dense supplements could be considered, though there is no evidence that they translate into significant clinical benefit. (103)

FATIGUE

Fatigue affects up to 85% of patients with HF and has many contributing factors beyond just low cardiac output.(18,22,34,45,61) Fatigue can be assessed using a numeric rating scale such as the one located within the ESAS. Patients with HF have abnormal skeletal muscle structure at baseline and, as the disease progresses, further lose muscle bulk and strength in a similar manner to that seen in sarcopenia of aging or in detraining.(31,99,115) End-stage HF is a severely catabolic state that promotes cardiac cachexia and protein-calorie malnutrition. (166) In addition, patients with HF frequently experience orthopnea and paroxysmal nocturnal dyspnea, which can interfere with sleep and contribute to fatigue. Other sleep-disturbing comorbidities include sleep-disordered breathing, which afflicts roughly half of

patients with advanced HF, as well as anemia, infection, thyroid abnormalities, and electrolyte disturbances.(72,167,168) Depression, outlined previously, can also worsen fatigue by causing psychomotor retardation or insomnia. Finally, cardiac medications may produce fatigue directly, such as beta-blockers, or through nocturia, such as diuretics.(22,34)

Unfortunately, many older patients with HF normalize their diminished stamina and do not attribute it to HF at all.(169) However, normalization only delays recognition and treatment, thus resulting in increased severity at the time of downstream diagnosis. Treatments for fatigue often focus on behavioral changes to directly target an underlying cause and may include exercise, scooter use, dietary modification, adjusted diuretic scheduling, upright sleep positioning with a wedge or hospital bed if necessary, use of a continuous positive airway pressure machine (CPAP), or nocturnal supplemental oxygen.(115,170–172) If behavioral modifications and good sleep hygiene practices fail to resolve sleep disturbance, medications such as trazodone should be considered. Daytime use of stimulants such as methylphenidate have not been formally studied in HF but carry an increased concern for independent cardiotoxicity and should be avoided in patients with HF.(173–177) Melatonin, which is commonly used to combat fatigue in the general population, should be considered and may even hold a special role in patients with HF through its putative anti-adrenergic effects.(178,179)

COLLABORATIVE MANAGEMENT AND A CALL TO ACTION

Although cardiologists should be empowered to assess and treat symptoms in patients with HF, it is also important to consider collaborative management with a palliative care specialist when symptoms are not easily controlled. One study showed that symptoms in patients with HF that were recognized at the start of a hospitalization were often not improved at discharge.(180) The consequences of uncontrolled symptoms while hospitalized is especially problematic for pain, as the level of pain during hospitalization is strongly associated with increased levels of pain following discharge home.(181) When symptom management is challenging, collaboration with palliative care for expert symptom management can benefit the patient.(182,183) The importance of formal palliative care involvement is increasingly recognized in HF care, given its positive impacts on symptom burden, quality of life, survival, caregiver outcomes, and potentially overall healthcare costs, too.(38,84,184)

In order to derive maximal benefit, patients with symptomatic HF should be referred to palliative care early in the course of their disease.(183–185) Multiple studies have shown that co-managed patients experience a decrease in symptoms such as pain, depression, and fatigue, which often recur shortly after the discontinuation of palliative care follow-up.(186,187) Co-management between cardiology and palliative care also allows patients to continue all beneficial cardiac medications and treatments while receiving medication for symptom palliation at the same time.(188) Ongoing studies are further evaluating the effect of palliative care on clinical and economic endpoints in advanced HF.(189)

Despite the benefits of palliative care consultation in patients with HF, a recent survey administered to members of the Heart Failure Society of America documented that more

than two-thirds of providers had never referred any patients to palliative care specialists, and an additional twenty percent had referred fewer than five patients.(190) One barrier to referral is easily corrected with education, as many providers and patients are surprised to learn that palliative care and curative care are not mutually exclusive and, additionally, that hospice care and palliative care are not synonymous.(191) Another barrier to palliative care referral is the relative shortage of palliative care providers, limiting the availability of expert consultation. In the US, there is only one board-certified palliative care physician for every 20,000 patients with chronic illness, and only 66% of hospitals have a palliative care program.(192) Perhaps even more worrisome is that palliative care provider shortages are unlikely to improve in the near future. More than half of the palliative care physicians in this country are over the age of fifty and only 265 fellowship-trained physicians are joining the national workforce annually.(192,193) These barriers to accessing specialty palliative care services make it even more important for cardiologists who care for patients with HF to become knowledgeable “primary” palliative care providers through ongoing education.(194)

As the HF epidemic continues to grow and life-prolonging treatments expand, some patients will unfortunately endure greater symptom burdens for even longer periods of time. In order to disrupt this trend, the evidence base for symptom assessment and management in HF must grow. Such strides can only be made by expanding HF clinical study endpoints beyond mortality and hospitalization to assess overall symptom burden and quality of life.(30,150) In order to achieve this goal, investigators must also commit to the pursuit of an ambitious, sophisticated research agenda.(195) Second, medical training must cultivate a new palliative-based skillset among providers other than palliative care specialists. Medical training curricula should be revised in such a way that all primary care providers, general cardiologists, and HF specialists are required to develop expertise in palliative medicine, including both symptom assessment and management. These efforts should be modeled on existing effective programs.(196–200) Access to palliative care providers should also be improved such that primary providers can avail themselves of this expertise when needed. Finally, goals of care discussions, including completion of advance directives, should become routine. In contrast to providers’ concerns of causing fear or eliminating hope, such discussions can unmask otherwise hidden symptom burden and reduce existential angst and anxiety.(201)

CONCLUSION

Patients with heart failure suffer an extensive symptom burden beyond the typical manifestations of HF such as dyspnea and edema. Providers may fail to ask the right questions, and patients often normalize their suffering as a necessary part of everyday existence. As a result, symptoms are under-recognized and, in turn, undertreated despite a predictable pattern of progression that parallels worsening of the HF syndrome. Heightened awareness, formal assessment, and empiric treatment of symptoms can markedly improve quality of life for patients with HF. Palliative medicine specialists can provide benefit to patients with HF and their caregivers throughout the course of their illness, not just near the time of death.

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TABLE

Symptoms, Recommended Treatments, and Precautions in Patients with Heart Failure

Symptom*	Recommended Treatments		Precautions in Patients with HF**
PAIN	Acetaminophen		Dose Adjustment with Hepatic Insufficiency
	Anti-Epileptics (e.g. Gabapentin)		Dose Adjustment with Renal Insufficiency
	Topical NSAIDs		Monitor for Hypervolemia (Possible Systemic Absorption)
	Opioids	Tramadol	Monitor for Serotonin Syndrome When Combined with Other Serotonergic Medications (e.g. SSRIs) Monitor for Constipation
		Oxycodone, Hydromorphone and Fentanyl	Dose Adjustment with Renal and Hepatic Insufficiency Monitor for Constipation
	Non-Pharmacologic Therapies (e.g. Acupuncture, Exercise and Mindfulness)		None
DYSPNEA	Optimization of HF Regimen		None
	Cardiopulmonary Rehabilitation		Proper Supervision Required
	Supplemental Oxygen with Exertion		None
	Opioids (e.g. Oxycodone, Hydromorphone and Fentanyl)		Dose Adjustment with Renal and Hepatic Insufficiency
	Oscillating Fan Directed at Patient's Face		None
DEPRESSION	Selective serotonin reuptake inhibitors (SSRI) (e.g. Sertraline, Fluoxetine, Fluvoxamine and Paroxetine)		Monitor for Hyponatremia Citalopram, escitalopram may prolong QT interval
	Mirtazapine		Monitor for QT Interval Prolongation Monitor for Worsening Heart Failure Symptoms at Doses ≥ 15mg
	Psychotherapy and Cognitive Behavioral Therapy (CBT)		None
NAUSEA	5-HT3 Receptor Antagonists (e.g. Ondansetron)		Monitor for QT Interval Prolongation
	Phenothiazines (e.g. Promethazine and Prochlorperazine)		Monitor for QT Interval Prolongation
	Prokinetic Agents (e.g. Metoclopramide)		Monitor for QT Interval Prolongation
	Dronabinol		Monitor for Psychoactive Effects and Sleep Disturbance
CONSTIPATION	Stool Softeners (e.g. Docusate)		None
	Osmotic Laxatives (e.g. Magnesium Hydroxide and Polyethylene Glycol)		Some Require 8 Ounces of Fluid
	Stimulant Laxatives (e.g. Senna)		Monitor for Abdominal Cramping
	Prokinetic Agents (e.g. Metoclopramide)		Monitor for QT Interval Prolongation

Symptom*	Recommended Treatments	Precautions in Patients with HF**
ANOREXIA	Mirtazapine	Monitor for QT interval prolongation Monitor for Worsening Heart Failure Symptoms at Doses ≥ 15mg
	Dronabinol	Monitor for psychoactive effects and sleep disturbance
FATIGUE	Trazodone	Monitor for QT Interval prolongation
	Melatonin	None
	Behavioral Changes (e.g. Sleep Hygiene)	None

*While each symptom above has a validated numeric rating scale, they are all included in the numeric Edmonton Symptom Assessment Scale (ESAS) with the exception of anorexia.

**These precautions are not comprehensive but reflect important considerations specific to patients with HF.