State-of-the-Art Article

A new clinical entity: multi-etiological heart failure in the elderly and its therapeutic implication

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Heart failure (HF) is a major health problem for the geriatric population. In the United States, most of the 5 millions patients with HF are elderly.1 Seventy-five percent of HF hospitalizations occurred in patients older than 65 years and 50% in patients 75 years and older.1 In the Framingham population, the prevalence of HF increased eightfold among men from the fifth decade of life to the seventh decade.2 However, despite of considerable improvement in the treatment, the mortality of HF patients remained relatively constant between 1948 and 1997. Large epidemiologic surveys, such as the ongoing Framingham Study, have not documented any meaningful change in the HF patients’ overall death rate.1,2,3 Between 1994 and 1997, in Ontario, approximately 33% of patients diagnosed with HF on the first admission died within 1 year.4 The mortality rate increased exponentially after age 65 in both men and women.4 Reduction in mortality demonstrated in randomized clinical trials of pharmacological agents, such as β-receptor blockers (BB) and angiotensin-converting enzyme inhibitors (ACEI), have been slow to be translated into substantial reductions of death and hospitalization rates in community-based HF populations.5 In more recent clinical trials, the addition of newer agents has had little, if any, impact on the high mortality of optimally treated patients.1,6 Accordingly, some authors have raised the concern that there may be limits to the benefits achievable through conventional pharmacological strategies.7,8 Therefore, there remains a need to develop novel, widely applicable, and cost-effective approaches in the management of HF.

For patients with heart failure, especially in the elderly, use of multidisciplinary teams in the treatment has been shown to reduce substantially the rate of hospitalizations, as well as to reduce mortality and improve functional status.9 We had previously proposed a new clinical entity: multi-etiological heart failure in the elderly (MHFE) and defined it as heart failure that occurred in the elderly and caused by two or more concomitant etiologies.10 In this review, we discuss the therapeutic implications of the concept of multi-etiological causes of HF, highlighting the impact of some newly recognized, age-related coexisting conditions on the progress and prognosis of HF in the elderly.

Diversity of heart failure etiologies in the elderly

Why did new modalities of management fail to result in further reduction of mortality in HF patients? It is important to recognize that HF, especially in the elderly, is a clinical syndrome arising from diverse etiologies.3 Although there is similarity in signs and symptoms of HF between the young and elderly population, the most common causes of heart failure in the elderly are a combination of coronary artery disease (CAD), hypertensive cardiovascular disease, and valvular heart disease, while in the young population HF is usually caused by a single etiology.11 In our series of 1000 elderly patients (aged 65 years or over) admitted for HF, only 21.5% were caused by a single etiology, whereas two or more causes could be identified in 81.5% of these patients.10

The reasons behind this difference are multifactorial. First, advanced aging produces major cardiovascular changes, which compromise the reserve capacity of the cardiac function in the elderly.11 These changes are listed in Table 1.

Table 1. Changes in the cardiovascular system due to advanced aging

| Loss of myocytes in left and right ventricles |
| Progressively increased cell volume per nucleus |
| Decreased elasticity and compliance of aorta and the great arteries |
| Decreased rate of myocardial relaxation |
| Loss of pacemaker cells in the sinus node |
| Increased fibrosis of the atio-ventricular anuli and in other conduction tissue |
| Thickened and calcified valves |

Second, many of the primary causes of HF are age-related. The prevalence of systemic hypertension, atherosclerosis, diabetes mellitus increases with advanced age, and calcific aortic stenosis, which is one of the most common cause of HF in the elderly, rarely occurs in the younger population.12

Third, HF is more frequently precipitated or exacerbated by associated medical problems in the elderly than in younger patients.13 These problems include uncontrolled atrial fibrillation and arrhythmias, acute myocardial infarction, poorly-controlled hypertension (HTN), infections, fluid overload,13 acute blood loss, pulmonary embolism, anemia, occult thyrotoxicosis, renal insufficiency, acute lower urinary

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tract obstruction in men, major dietary indiscretions, and obstructive sleep apnea (OSA). Of these problems, OSA, anemia, and chronic renal insufficiency have attracted great attention by clinicians, and extensive investigations have been undertaken on their relationship with HF. Therefore, here we provide a brief review of OSA, anemia, renal insufficiency and their clinical relevance and therapeutic implications in elderly patients with HF.

**Obstructive sleep apnea**

OSA and hypopneas is defined as hypoxia resulted from complete or partial collapse of a narrowed pharynx. The reported prevalence of OSA in otherwise healthy adults is approximately 4% in women and 9% in men. In two recent cross-sectional studies of Chinese urban community population aged 30 years or over, the prevalence of OSA was estimated to be more than 3-4%. Increasing age is a major risk factor for OSA, with prevalence as high as 62% in community-dwelling elderly. Cross-sectional data from the Sleep Heart Health Study showed an adjusted odds ratio of 2.2 for self-reported heart failure among subjects with OSA. Two clinical studies in the pre β-blocker treatment era found the prevalence of OSA to be 11-37%. Although whether OSA alone is sufficient to cause heart failure is still in controversy, there is still an ample reason to believe that it could adversely affect left ventricular function in those with a failing heart. OSA elicits a series of mechanical, hemodynamic, chemical, neural, and inflammatory responses with adverse consequences on the cardiovascular system. Large negative swings in intrathoracic pressure increase left ventricular afterload. Reflex sympathetic activation secondary to hypoxia and hypercapnia, and arousal from sleep, causing acute surges in blood pressure and heart rate, further increases left-ventricular afterload and wall stress. Increased venous return, plus acute hypoxic pulmonary vasoconstriction, would increase right-ventricular volume and pressure, which may compromise left-ventricular filling. Vascular pressor responses to hypoxia are increased in patients with OSA. Also, patients are more likely to have elevated daytime sympathetic activity and systemic blood pressure, which may further perpetuate heart failure.

**Anemia**

The prevalence of anemia in the elderly is greater than that of young adults, ranging from 5% to 51%. It is considered not to be due to aging alone, but to a greater extent, due to chronic diseases accumulated during the aging process. However, the elderly are more susceptible to anemia-inducing events because of an age-associated impairment of the marrow’s ability to appropriately increase red cell production.

Although anemia is a well-recognized co-morbidity in a variety of conditions, including myocardial ischemia, its role in heart failure has only recently been appreciated. Many studies during the last decade showed that in the elderly, anemia is much more common than what was expected before in patients with heart failure. For example, Silverberg et al. reported that the 9% prevalence of anemia in New York Heart Association (NYHA) functional class I patients increased to 79% in class IV patients. In a more recent study, anemia was found in 17% of the 12065 community-dwelling patients with CHF, and older age was associated with the higher prevalence (odds ratio [OR] 1.01 per year). Furthermore, many studies have demonstrated that anemia is associated with worse symptoms as well as greater impairment in functional capacity in patients and also is an independent prognostic factor for heart failure mortality.

The relationship of anemia and heart failure is interactive. Anemia may either cause heart failure or make it worse. Potential mechanisms by which anemia could worsen HF include exacerbation of myocardial and peripheral tissue hypoxia, increased venous return and cardiac work, and consequent left ventricular hypertrophy. Hypoxia could also potentially lead to activation of neurohormones and cytokines. In turn, excessive cytokine production [for example, tumor necrosis factor-alfa (TNF-alfa) and interleukin-6 (IL-6)], which is common in CHF, can reduce erythropoietin (EPO) secretion, interfere with EPO activity in the bone marrow and decrease iron supply to the bone marrow, leading to anemia. However, the most likely common cause of anemia in HF is chronic renal insufficiency (CRI), which is present in about half of all CHF cases. The CRI is likely to be due to the renal vasocostriction that often accompanies CHF and can cause long-standing renal ischemia. This reduces the amount of EPO produced in the kidney and leads to anemia, forming a vicious cycle, the recently named cardio-renal-anemia syndrome.

**Renal insufficiency**

The changes in renal function during normal aging are among the most dramatic of any organ system. From the middle of the fourth decade of life on, the overall glomerular filtration rate (GFR) declines by about 8mL/min/1.73 m² per decade. In general, however, renal reserve function, a measure of the ability of the kidney to increase GFR in response to an elevated protein or amino acid load, appears to be well preserved in elderly people. The prevalence of renal dysfunction rises with age, particularly after age 70. Individuals with end-stage renal disease have a cardiovascular mortality rate 10 to 20 times greater than that in the general population. However, the association of mild to moderate renal insufficiency with the outcome of heart failure has been under-appreciated until recently. In a recent study, Akhter et al. showed that renal insufficiency, as represented by elevated serum creatinine >1.5mg/dl on admission, was common and found in almost half of patients hospitalized with decompensated heart failure, and this finding is associated with prolongation of length of stay and rate of rehospitalizations after discharge, and also has an independent unfavorable effect on 6-month mortality. Similarly, an increase in serum creatinine (>0.5 mg/dl) in the hospital results in a significantly longer length of stay and has an independent effect on long-term mortality.

Why is renal insufficiency associated with poorer outcomes in patients with heart failure? It has been speculated that this may be attributable, at least in part, to more advanced heart failure, excess co-morbidities, and/or therapeutic nihilism.
in patients with concomitant renal sufficiency who are less likely to receive proven efficacious therapies for either the index condition or the co-morbidities. However, most of studies to date show that even after adjustment for all other prognostic factors, HF survival is still significantly associated with renal function in patients with either systolic or diastolic dysfunction.\textsuperscript{35-36} In addition, in patients with primary kidney diseases or renal transplantations, their cardiac function could improve.\textsuperscript{41} All these suggest that renal insufficiency may be more than a marker of the severity of heart failure, and may play a causative role in the progression and deterioration of heart failure, although the mechanisms are still not fully understood. Renal insufficiency is associated with multiple changes in vascular pathology that may worsen cardiovascular outcome, including abnormalities in the coagulation/fibrinolytic systems, abnormal vascular calcification, endothelial dysfunction, hyperhomocysteinemia, insulin resistance, elevated C-reactive protein, disruption in the endothelin/nitric oxide balance, electrolyte perturbations predisposing to arrhythmias, and hyperactivation of the sympathetic nervous and renin-angiotensin systems.\textsuperscript{42}

Therapeutic implications: treating heart failure in the elderly with a multidisciplinary approach

Treatment of heart failure in the elderly presents a special challenge. As mentioned above, many newer therapies failed to result in a meaningful reduction in the mortality of these elderly patients. There are many reasons behind this gap. Major clinical studies of heart failure have generally excluded older patients, and the majority of patients are in the age range of 50-70 years. In such patients, the etiology of left ventricular systolic dysfunction is usually coronary artery disease and myocardial infarction, and in most clinical trials the compliance of patients is good. But typical elderly patients with heart failure, by contrast, often have multiple etiologies, as well as multiple pathologies and variable compliance.\textsuperscript{5,11}

The concept of multifactorial heart failure in the elderly has its great clinical relevance, and could potentially provide new opportunities for novel therapeutic strategies in the management of these patients. It emphasizes the importance of identifying and correcting all treatable factors that could adversely affect the quality of life or survival of the patients with heart failure. Compared with those in younger patients, these factors play a more important role in the progression of heart failure and in causing exacerbation and rehospitalizations of these patients. For instance, non-compliance with medical therapy, excessive salt intake and volume overload contribute to 30 to 50 percent of recurrent episodes of HF in the elderly.\textsuperscript{43}

Recent studies on the relationship of OSA and anemia have showed that OSA and anemia are potential therapeutic targets in heart failure. Although to date no randomized trials in HF have evaluate the impact of treating OSA on important clinical cardiovascular outcomes, several studies showed that acute abolition of OSA by continuous positive airway pressure (CPAP) in patients with HF prevents recurrent hypoxia, reduces nocturnal blood pressure and heart rate,\textsuperscript{44} and increases arterial baroreflex sensitivity.\textsuperscript{45} The first study to examine the effects of treating OSA with CPAP on left ventricular function in patients with HF was not a controlled study. Eight patients with idiopathic dilated cardiomyopathy and coexisting OSA were studied. After 1 month of CPAP, mean left ventricular ejection fraction increased from 37% to 49%, and dyspnea was reduced significantly.\textsuperscript{46} In a randomized trial, Kaneko et al. reported that patients with HF and OSA treated with CPAP for 1 month experienced a significant reduction in daytime heart rate and systolic blood pressure. Their mean left ventricular ejection fraction increased by 9%. In contrast, those in the control group experienced no improvement in these variables.\textsuperscript{47} In another more recent study, fifty-five patients with CHF and OSA were randomized into CPAP or control groups in a 3 months trial. Compared with the control group, the CPAP group had significant improvements in LVEF, reductions in overnight urinary norepinephrine excretion, and improvement in quality of life.\textsuperscript{48}

The consistent association of anemia with adverse clinical outcomes in HF has led to substantial interest in taking anemia as a potential therapeutic target.\textsuperscript{29} Potential treatment for anemia include the use of blood cell transfusions and treatment with erythropoietin analogs to increase red blood cell production. Given the risks and costs of red blood cell transfusion and its uncertain benefit showed in several studies on critically ill patients (including those with cardiovascular diseases such as myocardial infarction),\textsuperscript{49,50} it does not appear that transfusion represents a sound therapeutic strategy for the routine treatment of anemia in HF.

However, three studies published recently have showed the benefit of recombinant human erythropoietin (rHuEPO) in the treatment of patients with HF and mild to moderate anemia. In an uncontrolled study, Silverberg et al. demonstrated an improvement in ejection fraction, NYHA functional class, and hospitalization after treatment with erythropoietin and intravenous iron in a group of 26 patients with NYHA functional class III to IV HF.\textsuperscript{51} In this study, the dosage of EPO was adjusted to maintain a hemoglobin (Hb) level of 12g/dl. The same group subsequently conducted a small randomized trial of rHuEPO and intravenous iron in 32 patients with NYHA functional class III to IV HF, which demonstrated that treatment of anemia in this patient population resulted in improved functional class and a decrease in the need for hospitalization.\textsuperscript{51} Our study on 48 patients with NYHA functional class III to IV HF and mild to moderate anemia showed similar results.\textsuperscript{52} A randomized, single-blind, placebo-controlled study by Mancini et al.\textsuperscript{53} evaluated the effect of 3 months of erythropoietin treatment on exercise capacity in patients with anemia and NYHA functional class III to IV HF. This study demonstrated significant improvements in peak oxygen consumption (VO\textsubscript{2max}) with EPO treatment. A significant correlation was observed between elevations in Hb with EPO treatment and increased VO\textsubscript{2max}. Although these pilot studies are preliminary and limited, they demonstrated the potential of therapies targeted at anemia to improve clinical outcomes in heart failure.
Conclusions

HF in the elderly is often caused by more than one etiology, and multiple factors and coexisting conditions play an important role in its progression. The concept of multifactorial HF in the elderly provides new insight not only into our understanding of the pathophysiology of this global and growing epidemic, but may also into the development of different novel treatment strategies.

References


