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Comorbid Conditions Impacting the Patient with HF – Obesity, Anaemia, Depression

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ABSTRACT:

Chronic heart failure (CHF) is a condition caused by structural or functional abnormalities in the heart, leading to reduced cardiac output and/or increased cardiac pressure during rest or stress. The prevalence of CHF in developed countries is estimated to be around 1-3% of the adult population exceeding 10% in individuals over 70 years old and even higher, at 30%, in those over 85. This trend is expected to continue due to the aging population, with an estimated 46% increase in CHF prevalence projected for 2030 compared to 2012 in the United States. Patients diagnosed with CHF often experience multiple comorbidities, both cardiovascular and non-cardiovascular, which accelerate disease progression and worsen response to treatment.1 The presence of these comorbidities is associated with higher rates of hospitalization and prolonged hospital stays, leading to a significant decline in functional capacity and health-related quality of life (HRQoL) for individuals with CHF.1 Comprehensive management of CHF patients should include addressing these comorbidities. Proper treatment and management of these conditions can have a positive impact on the prognosis, reduce hospitalization rates, and improve the overall health-related quality of life for affected individuals.2

Keywords: Chronic heart failure, Comorbidities, Cardiac output, Health-related quality of life, Disease progression

HF is the leading cause of hospitalization, with a striking three-month readmission rate of up to 35% among this group. Although there has been some progress in reducing readmission rates in recent years, over 20% of patients still face readmissions within just 30 days, and this figure rises to a concerning 50% within six months.[3] While cardiovascular causes are the main contributors to mortality in CHF patients, it is worth noting that non-cardiovascular factors account for the majority of hospitalizations. Furthermore, patients with non-cardiovascular comorbidities are at a significantly higher risk of mortality and experience longer hospital stays compared to those with CHF but no comorbidities or only cardiovascular-related ones.[1] Among the non-cardiovascular comorbidities commonly observed in CHF patients, iron deficiency is prevalent in 53-65% of cases, anemia in up to 37%, diabetes mellitus in 23-47%, and depression in up to 61%, among others. [2]

The key focus should be placed on improving the HRQoL of patients with CHF so that the comorbidities are also targeted and not CHF alone. However, given that some comorbidities have a higher prevalence than others, these should be prioritized when caring for the patient.[1] Obesity & anaemia emerge as prominent comorbidity, and efforts should be made for prevention and treatment.[5] Iron deficiency and anemia are key and independent factors that contribute strongly to the worsening of the HRQoL of patients with CHF. [1]

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Management of comorbidities represents a critical step in optimal treatment of heart failure (HF) patients. However, minimal attention has been paid whether comorbidity burden and their prognostic value changes over time. Despite major advances in HF treatment over the past decades, comorbidity burden remains high in HF and influences outcome to a large extent.[5]

OBESITY

Obesity is a widely accepted risk factor of HF. Globally, more than two-thirds of deaths attributable to high body mass index (BMI) are due to cardiovascular diseases (CVD). BMI >30 Kg/m^2 is an independent risk factor for HF readmissions. Obesity, diabetes, and hypertension (metabolic syndrome) are prevalent in the HF population and contribute to the pathophysiology of congestive HF (CHF) with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Morbid obesity [body mass index (BMI) ≥40.0 kg/m^2] is a risk factor for patients with CHF and contributes to an increased risk of readmissions among HF patients. HF and obesity are increasingly prevalent and associated with high morbidity, mortality, and healthcare costs worldwide. Obesity increases the CVD burden by various physiological mechanisms. It increases insulin resistance, hyperlipidemia, obesity-induced hypertension, development of systemic inflammation, obstructive sleep apnea (OSA), and eventually congestive failure. BMI is a valid and acceptable tool to quantify the severity of obesity; however, it does not account for the content of body or abdominal fat. Regardless, higher BMI has been associated with CVD and poor outcomes. Studies have suggested an inverse relationship between obesity and mortality due to HF. This concept is called the obesity paradox, which refers to lower mortality in obese HF patients than patients who have normal or higher BMI.[3]

Obesity is associated with poor outcomes in hospitalized patients with HF. A study indicated an increased 30- day readmission rate in obese patients (BMI >30 kg/m^2) with a higher incidence of positive pressure ventilation use and increased length of stay (LOS; five days vs. three days) compared to non-obese patients. Studies have suggested that HF patients with morbid obesity (>40 Kg/m^2) also have a higher mortality rate. Obesity is a potentially expanding public health issue and contributes to high morbidity and mortality. Obesity or increased BMI is associated with increased risk and severity of HF. Increased BMI is considered a risk factor for other CVD including hypertension, diabetes, and hyperlipidaemia, and all of these increase the risk of myocardial infarction, which in turn augments the risk of HF. Elevated BMI is associated with left ventricular remodelling, and the activation of the renin-angiotensin-aldosterone axis increases sympathetic drive and inflammation. Studies have indicated that non-invasive positive pressure ventilation (NIPPV) methods, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP) can effectively treat CHF exacerbations. A significant decline in HF hospitalization is observed in patients after bariatric surgery. A grade associated between increasing weight loss and HF reduction has been observed secondary to improvement in diabetes, hypertriglyceridemia, and hypertension. Continuation of guidelines-directed medical therapy (GDMT) for HF exacerbation, a low threshold for the use of NIPPV in obese patients, promotion of lifestyle modific ations including weight loss, and early follow-up after discharge to prevent HF readmissions is suggested in the obese population.[3]

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ANAEMIA

Anemia is a very common comorbidity in subjects affected by HFrEF and HFpEF.[2] A study reported that patients with both anemia and iron defciency were 2.2 times more likely to have a worse HRQoL than patients without anemia or iron deficiency. Moreover, patients with iron defciency who had not developed anemia were 1.6 times more likely to have a worse HRQoL than patients without anemia or iron defciency[1]. Anaemia is justified in HF patients by nutritional deficiencies, loss of blood through the gastrointestinal system, reduced iron absorption, and reduced release of stored iron. It is an independent predictor of recurrent hospitalizations and it may negatively affect reduced exercise capacity and the quality of life. After the RED-HF trial results (increasing hemoglobin to 12–13 g/dl with erythropoietin does not improve outcomes in HF patients with anemia) the focus has been shifted to the role of iron deficiency. Iron deficiency (ID), frequent in patients with HF, is characterized by insufficient iron stores to meet the body requirements. There are different forms of ID: absolute and functional ID, both with or without anemia. In absolute ID, ferritin levels are <100 μg/ml. In functional ID, typical in chronic inflammatory diseases and CKD, ferritin is normal with a transferrin saturation <20%. This condition may increase hemodynamic instability, re-hospitalization, and mortality rates in patients with HF. The results of the IRON-HF and IRONOUT-HF (The Iron Repletion Effects on Oxygen Uptake in Heart Failure) trials have demonstrated that oral iron supplementation is unsuccessful.[2]

Ferric carboxymaltose (FCM) intravenous (IV) treatment seems to improve both ID and symptoms in HF patients. The FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) trial results demonstrated an improvement of functional class and a decreased impairment of renal function after 24 weeks of treatment with FCM. The CONFIRM-HF (CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) trial showed an exercise capacity improvement and a relevant decrease in the hospitalization rate after 12 months of FCM therapy in HF patients with ID and normal hemoglobin levels. Recently, a study demonstrated that FCM therapy was safe and able to decrease the risk of HF hospitalizations, without apparent effect on the risk of cardiovascular death, in stabilized patients after AHF with ID and LVEF <50%. Data from a sub study of the Myocardial-IRON trial in patients with HFrEF with ID, showed FCM was related to short-term improvement in LVEF and right ventricular ejection fraction. According to the latest ESC HF guidelines recommendations, all newly diagnosed HF patients should be routinely tested for ID and FCM IV administration should be considered in HF patients (if serum ferritin <100 μg/l, or if ferritin between 100 and 299 μg/l and transferrin saturation <20%) in order to improve HF symptoms, and increase exercise capacity and quality of life (Class recommendations: IIa, Level of evidence: A).[2]

The FAIR-HF 2 trial was designed in order to further evaluate the possible benefit of IV iron in HF patients with ID. The IRON-CRT trial aimed at studying the effect of FCM on cardiac reverse remodeling and cardiac contractility in HFrEF patients.[2] The trial concluded that treatment with FCM in HFrEF patients with iron deficiency and persistently reduced LVEF after CRT results in an improvement of cardiac function measured by LVEF, LVESV, and cardiac force-frequency relationship.[4] Furthermore, an ongoing FAIR-HFpEF trial will

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verify any benefits of IV iron in relation to survival in HFpEF patients. These results may suggest that ID could be a new therapeutic target for HF therapy.[2]

DEPRESSION

Depression (also called major depressive disorder) is a mental disorder characterized by a persistent feeling of sadness and loss of interest. It may lead to different emotional problems.[2] Mental and behavioral disorders, mainly depression, have a statistically signifcant and negative impact on HRQoL.[1] Depression is a common comorbidity in HF, above all in CHF and advanced HF. The prevalence rates are similar in studies of HFrEF and HFpEF (24% vs 25%). Depression is associated with poor prognosis (and all-cause mortality and rehospitalization) in both HFrEF and HFpEF. Pharmacological therapy for depression in HF has not affected the prognosis. Tricyclic antidepressants should be avoided because they might lead to significant hypotension, arrhythmias, and decompensation of HF. The association between antidepressants and HF prognoses remains controversial.[2] A study that assessed patients at a 3-month follow-up found that those with a clinically meaningful improvement in their depression scores were 4.3 times more likely to report a clinically meaningful improvement in their HRQoL.[1]

Recently, a meta-analysis demonstrated that patients with HF and depression taking antidepressants had increased risks of all-cause death and CV death. Compared with non-users, the use of selective serotonin reuptake inhibitors, tricyclics and selective serotonin reuptake inhibitors significantly increased the rate of all-cause death. Instead, the combination of cognitive behavioural therapy with a selective serotonin reuptake inhibitors was reported as the best management of depression in HF patients in a position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. Recently, a reduction in depressive symptomatology in heart transplant waiting list patients treated with sacubitril/valsartan was demonstrated. In HFpEF patients enrolled in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial, randomization to spironolactone was related to a mild decrease in depressive symptoms. According to the ESC HF guidelines recommendations, psychosocial intervention, behaviour cognitive therapy and exercise training (low- to moderate-intensity aerobic training) might be helpful in patients with HFrEF and depression.[2] Patients with CHF and iron deficiency can benefit from intravenous treatment with ferric carboxymaltose, reaching a HRQoL at least similar to that of patients with CHF without this comorbidity. The integrated management of CHF from its diagnosis and that of associated non-cardiovascular comorbidities is relevant in the context of clinical practice to increase the HRQoL of patients but it can also be essential in reducing the economic burden on society.[1]

Multi-morbidity, generally defined as the co-occurrence of more than one chronic condition, frequently accompanies heart failure (HF). It has been put forward that comorbid conditions are important determinants of HF outcomes and have major impact on quality of life. In today's ageing society, comorbidities are the rule rather than the exception, making healthcare professionals face the challenge of simultaneous management of HF and underlying conditions. For years, the European Society of Cardiology (ESC) Heart Failure guidelines emphasize routine testing for coexisting comorbidities in all patients suspected for HF. Also in the 2021 guidelines, assessment and treatment of comorbid conditions has a prominent position. [5]

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CONCLUSION:

The impact of non-cardiovascular comorbidities on the HRQoL of patients with CHF is consistently negative and significant. The comorbidities whose impact has been studied most frequently in the literature are anaemia and iron deficiency, respiratory diseases, mental disorders, and diabetes. The presence of comorbidities whose impact on HRQoL has been less studied (renal insufficiency, thyroid dysfunction, neoplasms, obesity) also showed a significant association with a worse HRQoL. It is essential to include comorbidities associated with a worse HRQoL in the integrated clinical management of CHF, with special emphasis on treating or adequately controlling comorbidities of greater prevalence in these patients. Control of these comorbidities can contribute not only to significantly increasing the HRQoL of patients but it can also provide other social benefits. Further studies are needed to clearly estimate the impact that non-cardiovascular comorbidities have on HRQoL in patients with CHF.[1]

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