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CARDIOVASCULAR CARE (L ROEVER, SECTION EDITOR)

Heart Failure and Comorbidities—Part 1

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Abstract

Purpose of Review The main objective of the 1st part of this review is to demonstrate that a better understanding of comorbidities such as COPD, obstructive sleep apnea, thyroid dysfunction, cardiorenal syndrome, its pathophysiological and therapeutic implications, impact on the management of FH by interfering with its survival, and quality of life of patients.

Recent Findings The prevalence of heart failure will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age. This disease has a large burden of noncardiovascular comorbidities, which may increase the risk of mortality and decrease quality of life. There is a perception that patients hospitalized for HF are also becoming more medically complex. In this review, we highlight important comorbidities often found in patients with heart failure.

Summary Approximately one-third of patients with heart failure also have chronic obstructive pulmonary disease. Obstructive sleep apnea syndrome is a highly prevalent disorder in HF patients, occurring in 46–80% of patients. It is known that changes in thyroid metabolism have been associated as an independent risk factor regarding the progression and development of heart failure (HF). Understanding cardiorenal syndrome facilitates the management of FH.

Keywords Heart failure · Comorbidities · COPD · Renal failure

Introduction

The prevalence of heart failure (HF) will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age with HF. Additionally, the total percentage of the population with HF is predicted to increase from 2.42% in 2012 to 2.97% in 2030. Data from the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Chicago Heart Association Detection Project in Industry, Atherosclerosis Risk in Communities (ARIC), and Cardiovascular Health Study (CHS) cohorts indicate that HF incidence approaches 21 per 1000 population after 65 years of age [1••].

Data from Kaiser Permanente indicated an increase in the incidence of HF among the elderly and improved HF survival, resulting in increased HF prevalence, with both trends being more pronounced in males. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, for example, hypertension, obesity, and systolic dysfunction were important risk factors that may be targets for prevention. HF risk factors vary substantially across world regions, and hypertension is highly associated with HF in all regions, but most commonly in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa, with a minimal association of IHD with HF in sub-Saharan Africa [1••, 2, 3].

HF has a large burden of comorbidities, which may increase the risk of mortality and decrease quality of life. Among US Medicare beneficiaries, 40% of patients with HF had more than 5 comorbidities, and these patients accounted for the majority of days spent in the hospital. There is a perception that patients hospitalized for HF are also becoming more medically complex [4, 5]. Therefore, awareness of these comorbidities, including prognostic implications and nuances for therapeutic adjustment, is essential (Fig. 1).

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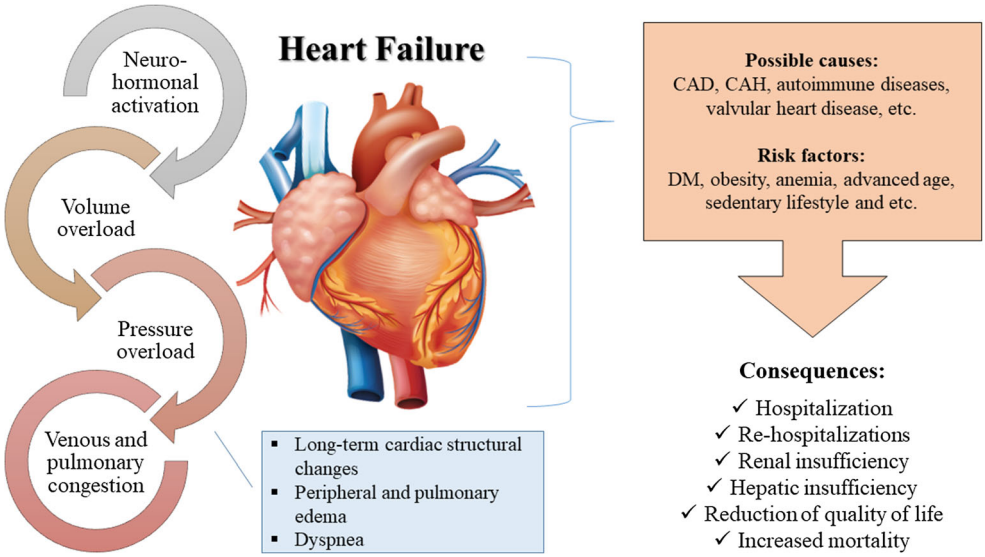

Fig. 1 Evolution of Heart Failure: From risk factors to outcomes

Methods

A literature search was performed for the present study. The electronic search included three databases, PubMed, EMBASE, and Google Scholar, and used these search terms: "heart failure", "heart failure and comorbidities", "heart failure and pulmonary disease", "heart failure and anemia", "heart failure and diabetes", "heart failure and renal failure", "heart failure and coronary disease", "heart failure and cachexia". "heart failure and cancer", "heart failure and cognitive dysfunction", "heart failure and thyroid dysfunction", and "heart failure and obesity" between January 1, 2000, and January 31, 2020. The inclusion criteria were all types of articles, articles published in PubMed, and related only to humans. The exclusion criteria were articles for which full text was not available, were not in English, or were gray literature. From the articles retrieved in the first round of search, additional references were identified by a manual search among the cited references.

Due to the extent and relevance of the theme, we chose to divide this paper into 2 parts. In the first part, we will be addressing simultaneous occurrence of HF with chronic obstructive pulmonary disease (COPD), cardiorenal syndrome (CRS), obstructive sleep apnea syndrome (OSAS), thyroid dysfunction, cognitive dysfunction, and cancer. Already in the 2nd part sarcopenia, cachexia, diabetes, peripheral arterial disease (PAD), anemia, coronary arterial disease (CAD), and chronic renal disease (CKD) will be addressed, respectively.

Chronic Obstructive Pulmonary Disease

Unlike previously thought, there is cumulative evidence showing a high rate of coexistence of COPD and HF, particularly in the elderly population. The prevalence of HF in COPD patients varies between 7.2 and 20.9%, with the highest estimates coming from studies that have used standardized HF diagnostic criteria. Considerable variation of COPD prevalence in patients with HF is also found across studies, with estimates ranging from approximately 10.0 to 39.0% [6].

Mortality in COPD is more often due to cardiac rather than respiratory causes. The coexistence of HF and COPD is frequent but remains underdiagnosed. Both conditions share several similarities, including the age of the population affected, the fact that both are risk factors associated with smoking, and symptoms of exertional dyspnea (Fig. 2). There is also a strong possibility of COPD promoting atherosclerotic vascular disease through systemic inflammation. An active search for the second disease using clinical examination supplemented with specialized investigations, including plasma natriuretic peptides, lung function testing, and echocardiography, should be carried out, followed by appropriate management. Issues such as adverse effects of drugs on cardiac or pulmonary function need to be sorted out by studies in patients with both COPD and HF. Caution is advised with the use of beta2-agonists in COPD when HF is also present, and more so in acute exacerbations.

Based on current evidence, the beneficial effects of selective beta1-blockers should not be denied in stable patients who have coexistent COPD and HF. The prognosis of coexistent COPD and HF is poorer than that in either disease alone. A favorable response in a patient with coexistent COPD and HF depends on proper evaluation of the severity of each of the two and appropriate management with judicious use of medication [7].

The use of beta blockers is part of the therapeutic arsenal for HF with reduced ejection fraction (HFREF). Regardless of their unequivocal morbidity and mortality benefits, these agents remain underused and are frequently withdrawn in

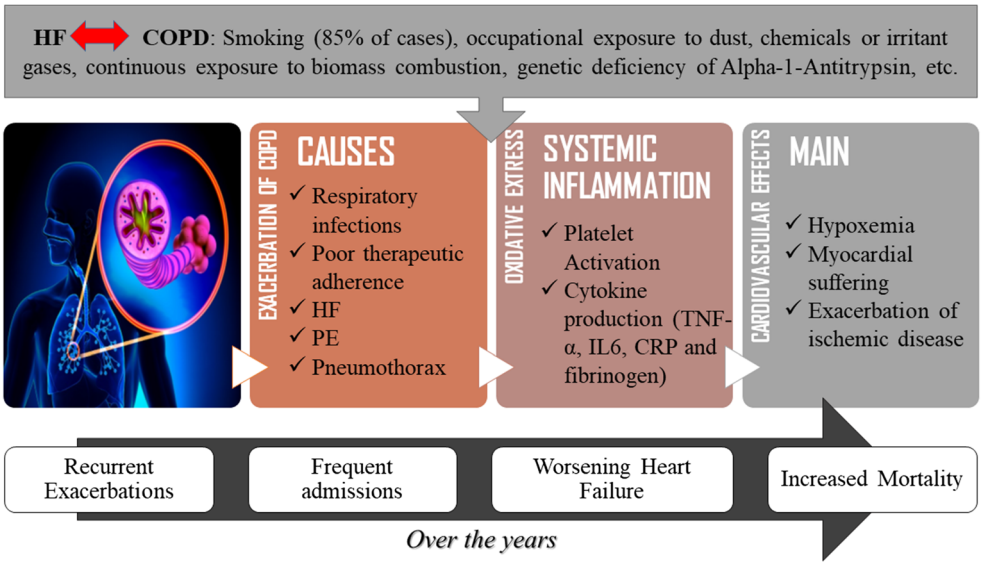

Fig. 2 Evolution of COPD and its interaction with heart failure

HF patients with concomitant COPD due to fear of precipitating bronchospasm [12]. Groove et al. published a European survey noting that COPD was the most powerful predictor of the under-prescription of beta-blockers in HF patients [8]. Close follow-up with a cardiologist in conjunction with a pulmonologist may benefit patients with these mutual conditions.

Cardiorenal Syndrome

CRS comprises a wide interface of disorders involving both the heart and kidneys, in which acute or chronic dysfunction in one organ may induce or exacerbate acute or chronic dysfunction in the other [9]. CRS is divided into 5 subtypes according to which organ is primarily involved. The goal of this classification is to facilitate characterization of the primordial clinical presentation for diagnostic, therapeutic, and epidemiological data and to develop new treatment strategies [10•]. Nevertheless, identification of the initial insult that results in decompensated CRS can be difficult to achieve (Table 1).

Sometimes, subclinical dysfunction in one or another organ may cause malfunction of the other without a clear link showing the problem with the first organ. Three major mechanisms participate in the development of cardio-renal dysfunction: neurohormonal, hemodynamic, and cardiovascular disease–associated mechanisms. All are interconnected and affect both cardiac and renal function. Neurohormonal mechanisms include activation of both the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system. The hemodynamic mechanisms include salt and water retention leading to fluid overload, resulting in cardiac and renal venous congestion. Renal venous congestion might be the cause for the acceleration of renal dysfunction in this clinical context. CV disease–associated mechanisms are related to several pathways that contribute to the development of cardiovascular disease, including the development of systemic and local inflammatory mechanisms, acid–base disorders, anemia, bone–mineral disorders, and acid–base disorders.

Normal potassium (K) homeostasis involves maintenance of the plasma K concentration within a narrow range, and it is achieved by matching the K intake with excretion and proper distribution between intracellular and extracellular fluid compartments. About 2% of total body K is found in the extracellular fluid, whereas 98% of exchangeable K is in the intracellular compartment [11•]. In a large cohort of patients with newly diagnosed of HF, hypokalemia was more frequent at baseline than hyperkalemia (HK), with 3% versus 0.9%, respectively [12]. In a retrospective observational cohort study, both hypokalemia and HK were associated with increased mortality risk, and HK was associated with increased likelihood of RAAS inhibition discontinuation [13]. HK is the most common electrolyte disturbance observed in patients with advanced stages of CKD, causing a significant burden, and even mild HK has been associated with increased morbidity and

Table 1 Cardiorenal syndrome classification

Type 1: acute	Acute deterioration of cardiovascular disease leading to acute kidney injury
Type 2: chronic	Chronic cardiac dysfunction resulting in CKD
Type 3: acute	Acute renal dysfunction resulting in chronic cardiac dysfunction
Type 4: chronic	CKD resulting in chronic cardiac dysfunction
Type 5: secondary	Diseases affecting both heart and kidney

mortality in patients with chronic diseases, such as HF, CKD, hypertension, and diabetes mellitus (DM).

While RAAS inhibition involves the most cardio-nephroprotective drugs used in clinical practice, treatment with these drugs increases serum K values, particularly when DM and HF coexist. Usual strategies aimed at preventing/treating chronic HK are still insufficient. Indeed, dietary potassium restriction, the use of sodium bicarbonate or diuretics, the withdrawal or down-titration of RAAS inhibition, or the administration of former potassium binders (sodium polystyrene sulfonate and calcium polystyrene sulfonate) have limited efficacy and are barely tolerated. Therefore, these treatments are not suitable for long-term control of K levels [14]. Two new potassium binders, patiromer and sodium zirconium cyclosilicate, have been approved by the US Food and Drug Administration for the management of HK.

Patiromer is an organic, non-absorbed polymer that increases fecal excretion of potassium by exchanging it for calcium through the gastrointestinal tract [15]. Using calcium as the counter-ion makes it a more adequate choice in patients with HF and CKD to avoid volume overload and hypertension. The recommended starting dose is 8.4 g per day, which can be up-titrated to a maximum dose of 25.2 g per day. The PEARL-HF (Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multiple-Dose to Evaluate the Effects of RLY5016 in Heart Failure Patients) Trial [16], the AMETHYST-DN (Patiromer in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy) [17], the OPAL-HK (Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors), with concomitant CKD [18].

One ongoing trial in subjects with HF with reduced ejection fraction (HFREF) and HK while receiving RAAS inhibition medications with the purpose of determining if patiromer treatment will result in the maintenance of the treatment and reduce CV death and CV hospitalizations [19]. Sodium zirconium cyclosilicate (SZC) is an inorganic, selective cation that exchanges K for sodium and hydrogen, thus capturing K in the intestine. The HARMONIZE trial was designed to evaluate the safety and efficacy of SZC for up to 4 weeks in patients with HK, with good results obtained within 48 h, where there was a higher proportion of patients with normal potassium levels for up to 28 days when compared with the placebo [20]. In the long-term open label extension of the HARMONIZE trial (effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia), for up to 11 months, the results remained steady [21]. This agent has very recently been approved for non-emergent treatment of HK in the USA.

Obstructive Sleep Apnea Syndrome

OSAS is a highly prevalent disorder in HF patients, occurring in 46–80% of patients, with HFREF [22], HF with intermediate reduced ejection fraction (HFMREF), and HF with preserved ejection fraction (HFPEF) [23•, 24]. Sleep disorder breathing (SDB) is classified as obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is characterized by periods of apnea/hypopnea with sustained respiratory effort, while CSA presents the same apnea/hypopnea without respiratory effort [25, 26•]. In HF, the worse the ejection fraction (EF), the more frequent CSA occurs instead of OSA [23•]. Conceptually, apneas are considered to be respiratory pauses that are > 10 s and hypopneas as reduction in respiration with O2 desaturation > 4% [26•, 27].

The relationship between OSAS and HF is not well established. In a prospective analysis of patients who underwent polysomnography without a diagnosis of HF, it was noted that in male patients with apnea-hypopnea (AHI) with > 30 events per hour, there was a relative increase of 58% of developing HF compared with the AHI group (< 5 events per hour) [28].

One explanation for the appearance of OSA in HF patients could be the redistribution of body fluid when in the supine position, causing edema in the peripharyngeal region, favoring its obstruction and consequent airway occlusion, triggering OSA, and mechanisms such as accumulation of intra-alveolar fluid [29]. The mechanism of CSA is quite different; the abnormality is in the regulation of breathing in the respiratory centers of the brainstem [30•]. SDB is common in people with HF. HFREF occurs in about 50% of the individuals [31]. OSA occurs more frequently in HFPEF and CSA more often in HFREF. Both entities produce distinct cardiovascular changes. In HFMREF, CSA is more frequent in males and with elevated pulmonary systolic pressure [23•].

OSA is related to a higher number of readmissions and mortality in patients discharged after hospitalization for HF [32]. The fact that SDB is present is deleterious in both chronic and acute HF patients. The diagnosis of OSA in patients with HF is different from patients without the disease. Apnea scales, such as Epworth, do not correlate well with AHI, in which individuals with HF are less symptomatic [33].

In individuals with HFREF, CSA is more frequent than OSA during sleep, and CSA is also present during the daytime. In addition, the CSA burden is higher than OSA [34]. Thus, patients are exposed to an increased number of periods with apnea and their deleterious triggers. The most frequent phenotype for this presentation is male, elderly, presence of kidney disease, worse systolic ventricular function, and more symptomatic. In addition, this population has a worse prognosis than OSA patients.

The treatment of OSA in patients with HF is based on the use of CPAP. In a Canadian study, there was an improvement in secondary outcomes, such as improved nighttime oxygenation and increased 6-min walking distance, but there was no effect on survival [27].

The CAT-HF trial randomized patients with acute heart failure, HFREF, and SDB to servo ventilation plus optimal medical therapy (OMT) versus exclusive OMT. Both treatment arms showed improved EF at 6 months [35], but the trial was stopped because the results of the study for central apnea treatment (SERVE-HF). In the SERVE-HF, comparing medical treatment associated or not with positive pressure, there was a significant increase in the risk of cardiovascular mortality [36]. In patients with HFREF and CSA, treatment should be avoided [37•], at least until the result of the ongoing ADVENT-HF trial, designed to assess the effectivity of servo-ventilation on SBD in these patients [38]. There are currently no studies of the effect of CPAP on patients with HFPEF and OSA.

One study of transvenous phrenic stimulation showed a reduction in the number of episodes of CSA [39]. A multicenter trial found improvement in AOS, CSA, and apnea indices [40]. A study on phrenic stimulation was performed to treat moderate to severe CSA with results consistent for 36 months of therapy [41].

Thyroid Dysfunction

Often, specific thyroid dysfunctions (particularly hypothyroidism and hyperthyroidism) can be diagnosed after cardiovascular changes, such as arrhythmias, hypertension, and reduced cardiac performance, with an impact on systolic or diastolic functions since thyroid hormones play a role in the regulation of cardiac function and cardiovascular hemodynamics.

It is known that changes in thyroid metabolism have been associated with the development and progression of HF, as well as with low levels of triiodothyronine (T3), an active physiological form of the thyroid hormone tetraiodothyronine (T4). T4 is fundamental to the normal function of cardiomyocytes (contractility and chronotropism) and peripheral vasculature (reduces the arterial resistance), and it is also associated with increased incidence and worse prognosis of chronic heart failure (CHF). It is recognized as "low T3 syndrome." The high TSH levels are also associated with similar outcomes [42, 43].

Table 2 describes the main effects of hypo/hyperthyroidism on the cardiovascular system, as well as the main symptoms and laboratory diagnosis. In the case of hyperthyroidism, CHF is a rare event, occurring especially in patients with severe hyperthyroidism or previous cardiovascular changes (ischemia, hypertensive disease, etc.), causing prolonged hemodynamic changes with progressive ventricular dysfunction [42].

Among the cardiovascular changes that occur in thyrotoxicosis, atrial fibrillation occurs in about 10–15% of patients with hyperthyroidism, causing an increased risk of cardioembolic events [44], with a negative impact on morbidity and mortality. Sinus rhythm (SR) restoration can be completed through cardioversion. Chemical or electrical cardioversion in hyperthyroidism is still controversial. In contrast, it is estimated that 60–70% of patients return spontaneously to RS after a return to euthyroidism [45]. Restoration of SR reduces thromboembolic events and improves ventricular function.

In addition to the use of antithyroid drugs to control heart rate and thyrotoxic effects on systemic vasculature, propranolol, a non-cardioselective beta-adrenergic blocker, is

Table 2 Effects of hypo/hyperthyroidism on the cardiovascular system

	Hypothyroidism	Hyperthyroidism
Signs/symptoms	Fatigue, drowsiness, weight gain, reduced intestinal rhythm, dyslipidemia	Agitation, anxiety, tremors in the extremities, palpitation, increased intestinal rhythm, weight loss, heat intolerance, sweating
Laboratory diagnosis	↑ TSH + ↓T4L	↓ TSH + ↑ T4L
Pathophysiological changes of hormonal dysfunction	Reduction of cardiac chronotropism and inotropism, increased systemic vascular resistance	Myotoxicity related to significant increase in thyroid hormones, resulting in myocyte necrosis; hypermetabolism; reduction of systemic vascular resistance
Cardiovascular effects	Increased afterload and reduction in systolic volume and cardiac output (systolic hypotension); diastolic hypertension; bradycardia	Volume overload (RAAS activation); Increased preload; high ventricular filling pressure; resting tachycardia; exercise intolerance with exertional dyspnea; PH
Possible electrocardiographic changes	Sinus bradycardia	Sinus tachycardia; atrial fibrillation (most common)
Therapeutic options	Thyroid hormone replacement (levothyroxine)	Antithyroid drugs (tapazole, methimazole, propylthiouracil), beta-blockers (1st line - non-selective, such as Propranolol)
Suggestions of clinical practice		In patients with HF, the first goal to be achieved is the adjustment of thyroid dysfunction; Echocardiography should be performed routinely. Attention to the treatment of cardiovascular symptoms and hemodynamic stabilization.

RAAS: renin-angiotensin-aldosterone system (RAAS); PH: Pulmonary hypertension

commonly used. Oral or venous diuretics may also be used in patients with volume overload. Digoxin in the context of ventricular dysfunction and atrial fibrillation, with poorly controlled ventricular response, or in the presence of moderate to severe HF symptoms [42]. In patients on antiarrhythmic drugs such as amiodarone, we should not forget that the use of the drug may lead to the development of thyroid dysfunction (hyperthyroidism). Thus, it should be used with caution.

In contrast, in relation to hypothyroidism, such a clinical condition can cause cardiac atrophy, chamber dilation, and reduction of myocardial blood flow [46]. In small placebo-controlled studies, oral replacement of the thyroid hormone (L-thyroxine) results in improved cardiac function and performance in CHF patients, and it is capable of reducing disease-induced cardiomyopathy (when present) [47].

Because they are considered reversible causes of HF, the American College of Cardiology's guidelines for HF (The American College of Cardiology Foundation/American Heart Association—ACCF/AHA, 2009) recommend that patients who are newly diagnosed with ventricular dysfunction undergo laboratory testing of thyroid hormones as routine screening [48].

Cognitive Dysfunction

Cognitive impairment (CI) is common in older adults with HF. The prevalence of CI is higher among patients with HF than in those without it. The spectrum of CI in HF patients is similar to that observed in the general population and may range from delirium to isolated memory or non-memory-related deficits to dementia [49].

Despite optimizing the treatment of HF, favoring a better prognosis and quality of life, in clinical practice with an aging population, we often find patients with CI, either due to the natural aging process or due to the presence of ischemic microvascular changes, cerebral hypoperfusion due to HF, and diseases such as Alzheimer's, both with the possibility of evolving into dementia.

A full neuropsychological assessment is required to determine a diagnosis of cognitive impairment and to identify the specific areas of cognitive deficit. In patients with HF, there appears to be differing clusters of cognitive deficits [50]. CI, which is frequently undocumented, may indicate a greater risk of readmission for individuals with HF than those without. Screening for CI and involving family and caregivers in discharge education may help reduce readmissions [51].

The diagnosis of cognitive dysfunction can be made through clinical devices, such as the Mini-Mental State Examination or the Montreal Cognitive Assessment [52]. It should be acknowledged that patients with cognitive dysfunction may have impaired daily activities, reduced ability to follow medical procedures, and even reduced ability to maintain medical adherence. Therefore, follow-up with a multidisciplinary team and family support is necessary to prevent cardiovascular outcomes.

Cancer

The combination of cancer and HF represents a major clinical problem because each disease impinges on the treatment of the other disease and, consequently, has a detrimental impact on quality of life and survival. In recent years, a previously unappreciated connection between cancer and cardiovascular disease emerged from epidemiological studies reporting an increased risk of incident cancer in HF patients. In addition, anticancer therapies are burdened by the risk of cardiovascular toxicity [53, 54•, 55, 56].

HF represents the most common cardiovascular adverse event from cancer therapy. Both classical and novel cancer therapies contribute to the development of this condition [57, 58]. In a metal-analysis, Totzeck et al. [59] showed that patients under anthracycline-based chemotherapy had a moderate yet significant benefit in left ventricular ejection fraction (LVEF) from beta-blockers or angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs). However, throughout the studies, the beneficial effects were variable.

The most frequent cancer sites in patients with HF were the lung and skin, but the most common tumor types, including hematologic malignancies, were detected more often in the HF group, with the exception of prostate cancer [55]. Common risk factors, such as diabetes and obesity, leading to a pro-inflammatory state and oxidative stress, may justify this mutual occurrence of cancer and HF [60].

On the other hand, chronic inflammation with ensuing cellular oxidative stress, in addition to hyperactivation of the sympathetic nervous system and the RAAS, may boost cancer initiation and progression, not only when it is organ specific, but also when it is diffuse [61]. Thus, a good interaction between the cardiologist and the oncologist becomes essential in the management of this important comorbidity.

Conclusion

Despite a progressive fall in incidence, the prevalence of HF continues to rise, demonstrating an overall aging of the population. And an advanced age carries a higher risk of other comorbidities, making managing this interaction a growing challenge for everyone. A better understanding of the most common comorbidities and their various interactions will facilitate the management of this complex clinical condition.

Compliance with Ethical Standards

Conflict of Interest The authors of this article declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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