

Review Article



Understanding Obesity-Related High Output Heart Failure and Its Implications

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ABSTRACT

Morbid obesity remains most common cause of high output failure. The prevalence of the obesity is growing when two-thirds of American adults already are overweight or obese. Obesity is the risk factor for heart disease and eventually leads to heart failure. High output heart failure is common in obese patients and is characterized by high cardiac output, decreased systemic vascular resistance, and increased oxygen consumption. It often occurs in patients with chronic severe anemia, hyperthyroidism, pregnancy, arterial-venous fistulas, and liver disease. However, the pathogenesis of obesity-related high output heart failure is not fully understood. The clinical management of obesity-related high output heart failure follows conventional heart failure regimens due to lack of specific clinical recommendations. This article reviews the possible pathophysiological mechanisms and causes that contribute to obesity-related high output heart failure. This review also focuses on the implications for clinical practice and future research involved with omics technologies to explore possible molecular pathways associated with obesity-related high output heart failure.

Keywords: Heart failure; Obesity; Etiology; Adipokines; Genomics

INTRODUCTION

Heart failure (HF) is a significant health problem that affects more than 6 millions of U.S. adults and is associated with a high annual total healthcare cost (>\$30 billion).¹ It is a complex clinical syndrome resulting from alteration and impairment of cardiac structure and/or function when the heart fails to meet the metabolic demands of the body. Typically, patients with HF experience dyspnea on exertion, fatigue and impaired tolerance with physical activity, that can significantly decrease their quality of life.^{2,3} The two major phenotypes of HF are heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).^{4,5} In both types of HF, cardiac output (CO) is reduced (<5 L/min) and fails to meet the metabolic requirements of the body. However, there are also patients who show signs and symptoms of HF even though their cardiac output is greater than 8 L/min. This type of HF is defined as high output HF.^{6,10} Multiple conditions are associated with high output HF, including obesity, chronic severe anemia, arterial-venous fistulas, hyperthyroidism, sepsis, chronic lung disease, and cirrhosis of the liver.⁹ Among these, morbid obesity is the leading cause for high output HF, accounting for 31% of all etiologies.⁸

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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Research has shown that approximately 50% of patients with HF are overweight or obese.¹¹⁾ An individual who has a body mass index (BMI) ≥ 35 kg/m² along with obesity-related health conditions such as HF is considered morbidly obese. There is considerable evidence that obesity is a significant independent risk factor for cardiovascular disease and a contributing factor for the development of HF.^{12,15)} The epidemic of obesity is concerning as the number of patients developing obesity-related HF is rising. The underlying mechanisms for the development of high output HF associated with obesity are not entirely clear. As a result, there is a lack of effective treatments specific for obesity-related high output HF and the current clinical practice guidelines fail to address any recommendations for obesity-related high output HF.¹⁶⁾ Patients with this type of HF are managed with conventional treatments that are often not effective.⁷⁾ Without a complete understanding of pathophysiologic mechanisms underlying obesity-related high output HF, it is challenging to appropriately treat these patients to improve their health outcomes. The purpose of this review article is to discuss the possible mechanisms contributing to obesity-related high output HF. The implication for clinical practice and directions for future research related to this syndrome will be examined.

PREVALENCE OF OBESITY

Obesity is becoming a significant public health problem with an alarming increased prevalence nationally and globally. In the U.S., the age-adjusted prevalence of obesity was 42.4% among adults in 2017–2018, as compared to 39.8% in 2015–2016.^{17,18)} There are increasing trends in obesity prevalence among adults that are ≥ 20 years of age.¹⁸⁾ Worldwide, adults that are overweight and obese (a BMI > 25 kg/m²) increased to 36.9% in men and 38% in women in 2013, as compared to 28.8% and 29.8% in 1980, respectively.¹⁹⁾ The increasing trends in overweight and obesity also occurred among children and adolescents globally.¹³⁾ Research has shown that the epidemic of obesity and substantial increase of obesity-related diseases can be attributed to urbanization, changes in food supply and diet, shifting of socioeconomic and demographic status, an increase in sedentary lifestyles and decreased physical activity.^{19,20)}

Despite increased prevalence of obesity, it is not always documented as a chronic disease in clinical practice even though it is associated with many chronic diseases that have formal diagnoses. In a 2017 study, Pantalone et al. examined electronic health records of 324,199 patients in a large U.S. integrated health system and found that 75% of patients were either overweight or obese based on BMI values; however, less than 50% of obese patients had a formal diagnosis.²¹⁾ This illustrates the need to recognize that obesity is a chronic disease that can negatively impact the wellbeing and health of patients due to its close association with many other diseases.

OBESITY ASSOCIATED COMORBIDITIES

Obesity is a significant independent risk factor for multiple cardiovascular diseases. Patients with obesity are likely to develop comorbidities such as hypertension, coronary artery disease, cardiomyopathy, HF, diabetes, dyslipidemia, and cerebrovascular disease.^{13,21)} For example, patients with obesity had a significantly higher prevalence of hypertension than lean individuals (42.5% vs. 15.3%, respectively).²²⁾ In addition, it has been reported that at least 75% of the incidence of hypertension is associated with obesity and often times these two conditions co-exist.^{23,24)} The lifetime risk for HF among patients with a BMI ≥ 30 kg/m² was double that of those with a BMI < 25 kg/m².²⁵⁾

The increasing trends in the prevalence of obesity across the globe and its close connection with other comorbidities, especially in the cardiovascular system has generated significant interest in understanding the role of obesity in the pathophysiologic mechanisms in these comorbidities.²⁶⁾ These included investigations of obesity in hypertension¹³⁾ and HF.¹⁴⁾¹⁵⁾²³⁾ It has been observed that obesity is associated with increased cardiac output without significant increase in ejection fraction during exercise.²⁷⁾ Unfortunately, despite obesity being a high prevalent chronic disease, its effects on high output HF are not well defined.

PREVALENCE OF OBESITY-RELATED HIGH OUTPUT HF

HF is a common cardiovascular disease that results from impaired cardiac function, structure, or both. The etiology of HF is multifactorial, including myocyte loss from myocardial infarction, sustained pressure overload (e.g., hypertension), volume overload (e.g., chronic kidney disease), and primary cardiomyopathy and so on.²⁸⁾ Currently, it is estimated that HF affected approximately 6.2 million adults in the U.S. and accounts for millions of office visits per year.²⁵⁾ It is projected that the prevalence of HF will increase 46% by 2030.²⁵⁾ In addition, HF is the most common diagnosis among patients who are hospitalized.⁹⁾ There are different types of HF, including HFrEF, HFpEF, and also high output HF. **Figure 1** illustrates distinguishing characteristics and common factors associated with high output HF and low output HF. Although high output HF is less common than HFrEF and HFpEF, there is lack of data on incidence and prevalence rates of high output HF in the existing literature. Often times, high output HF is secondary to other identifiable causes such as severe anemia, pregnancy, and atrioventricular fistula and it may not be identified appropriately. Furthermore, patients with high output HF are often misdiagnosed as HFpEF, unless right heart catheterization is performed.⁸⁾ This highlights the importance of needed research specific to high output HF, especially among those with obesity.

Nevertheless, it was reported that patients with obesity-related high output HF are usually younger than those with obesity-related HFpEF and share similar pathophysiologic mechanisms with obesity-related HFpEF at the onset. Research has shown that abnormalities of diastolic function (i.e., indices of left ventricular diastolic filling by pulse Doppler echocardiography) occur frequently in asymptomatic, morbidly obese patients as compared to non-obese

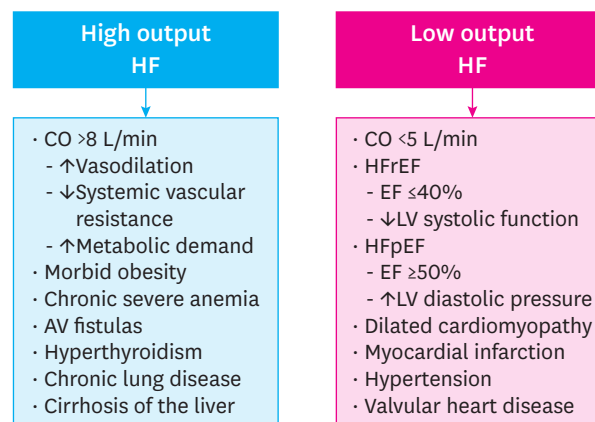


Figure 1. Distinguishing characteristics and factors that lead to high output vs. low output HF. AV = arterial venous; CO = cardiac output; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular.

control subjects.²⁹⁾ However, progressively high output failure eventually causes HF_{rEF} due to cardiomyopathy. Further research at the molecular and genomic level would further shed the light on the cardiomyopathic process to assist with differentiating HF_{pEF} and obesity-related high output HF. Compared to obesity-related HF_{pEF}, patients with obesity-related high output HF tend to have less comorbidities.⁸⁾³⁰⁾ Other reported phenotypic characteristics of obese patients with high-output HF included: 1) eccentric left ventricular remodeling³⁰⁾; 2) decreased levels of natriuretic peptides; 3) glomerular hyperfiltration⁸⁾; 4) increased aldosterone³¹⁾; 5) larger plasma volume; and 6) increased epicardial fat thickness.³⁰⁾ In addition, these patients had worse exercise capacity and elevated biventricular filling pressures with exercise.³⁰⁾ However, obesity-related high output HF had the lowest 5-year mortality at 19%, as compared to high output HF caused by other conditions.⁸⁾

PATHOPHYSIOLOGY IN OBESITY-RELATED HIGH OUTPUT HF

As its name of high output HF suggests, the heart fails to meet the metabolic demand of the body, despite a higher than normal cardiac output. This is contradictory to the typical low cardiac output observed in patients with HF. By definition, cardiac output is the amount of blood ejected by the left ventricle per minute. The average cardiac output for adults at rest is 5–6 L/min. In patients with high output HF, their cardiac output is greater than 8 L/min.⁹⁾ It has been reported that cardiac output as high as 10 L/min was observed in patients with severe obesity.³²⁾ The pathophysiologic mechanisms involved in obesity-related high output HF are not well defined in the existing literature.⁹⁾ In this review, we attempt to synthesize several possible mechanisms that obesity may contribute to the development of high output HF (**Figure 2**).

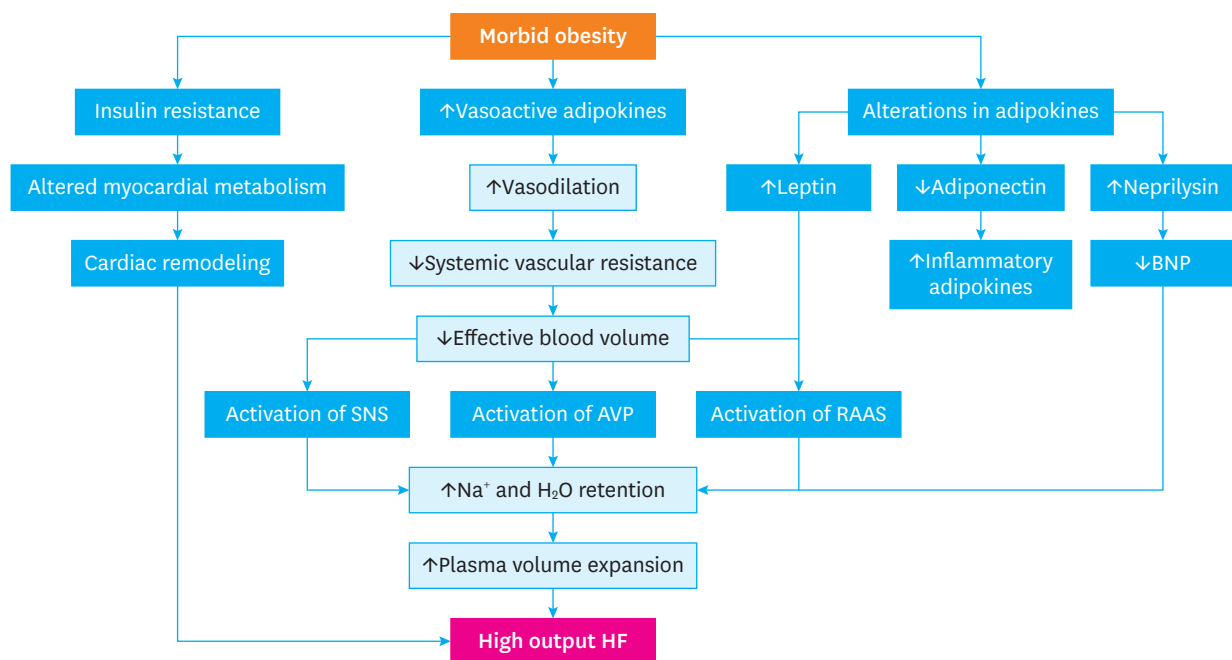


Figure 2. Possible pathophysiologic mechanisms underlying obesity-related high output HF. AVP = arginine-vasopressin; BNP = B-type natriuretic peptides; HF = heart failure; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

Vasoactive adipokines

Excessive vasodilation has been proposed as one of the important mechanisms that plays a role in obesity-related high output HF. The consequence of excessive vasodilation is reduced systemic vascular resistance that can lead to less effective tissue perfusion. In addition, decreased vascular resistance lowers the workload of the left ventricle, increasing stroke volume and subsequently cardiac output if preload and cardiac contractility remain the same.³³ The pathophysiological mechanisms responsible for vasodilation in obesity is not completely understood.¹⁰ It is known that adipose tissue functions as an vasoactive paracrine organ that can release various adipokines resulting in abnormal vascular tone, vasodilation and reduced vascular resistance.³⁴⁾³⁵ In addition, other proposed mechanisms are that patients with morbid obesity may have subclinical obstructive sleep apnea causing retention of carbon dioxide (a potent vasodilator) and subsequent vasodilation.³⁶ Without adequate vascular resistance, the same amount of blood volume becomes less effective in perfusing the tissue and providing optimal oxygen supply. The decreased arterial-venous oxygen gradient triggers the activation of neurohormonal reactions to compensate for the decreased oxygen and blood supply.

Activation of compensatory mechanisms

Effective blood volume is a measure of the fullness of the arterial vasculature.¹⁰⁾³⁷ When there is a decrease in effective blood volume, compensatory mechanisms including the renin-angiotensin-aldosterone system, sympathetic nervous system, and arginine-vasopressin axis become activated. In the short term, these compensatory mechanisms assist the myocardium to adapt to hemodynamic changes. However, long-term activation of these mechanisms can cause progressive deterioration in cardiac structure (e.g. hypertrophy, dilation) and function (e.g. systolic and diastolic dysfunction) from sodium and water retention, plasma volume expansion, and hypertension. This is often observed in the majority of patients with obesity.¹³ When the myocardium is no longer able to endure the increased workload and demand, HF develops, particularly among those with morbid obesity.⁸⁾¹³⁾³⁸

Altered myocardial metabolism and insulin resistance

It is also well known that obesity is a risk factor for insulin resistance, the underlying mechanism for type 2 diabetes. In general, carbohydrates and fatty acids are the primary myocardial energy substrates.³⁹ However, with increased insulin resistance, obesity can alter myocardial metabolism by increasing fatty acid oxidation in cardiac myocytes and decreasing myocardial efficiency by 50%.⁴⁰⁾⁴¹ This can impair left ventricular contractility, evidenced in both animal models and human studies.⁴⁰⁾⁴²

Altered cardiac metabolisms associated with obesity plays a major role in the development and progression of diastolic dysfunction often observed in patients with HF. Although the exact mechanisms are still unknown, obesity has a more predominant influence on diastolic dysfunction compared to hypertension. This was demonstrated in a study by Brandt et al. in which hypertension induced by a high salt diet had only a minor impact on E/e' ratio and there was no synergic effect between hypertension and obesity on diastolic dysfunction.²³ This could possibly explain why antihypertensive treatments are often ineffective in reducing mortality and morbidity in patients with HFpEF.⁴³ However, it is worth noting that development of HFpEF is multifactorial that may result from hypertension, obesity, diabetes, renal dysfunction, cardiorenal syndrome, and other contributing factors.

Cardiac remodeling and impaired cardiac diastolic function

Cardiac remodeling associated with obesity is characterized by left ventricular hypertrophy.¹³⁾⁴⁴⁾ Hemodynamic changes associated with obesity such as increased plasma volume and decreased systemic vascular resistance promote adaptive cardiac remodeling.⁴⁵⁾ Obesity is associated with a higher risk of diastolic dysfunction even in metabolically healthy patients.⁴⁶⁾ Obesity can negatively impact diastolic function even before developing any obesity-related metabolic abnormalities such as diabetes or dyslipidemia. In a recent retrospective study, Rozenbaum et al. reported that patients with higher BMIs had higher left atrial volume index, increased A wave, E/e' ratio, and systolic pulmonary artery pressure, that are indicators of diastolic dysfunction.⁴⁶⁾ In addition, patients with morbid obesity had increased risks for much larger left atrial volume index (>34 mL/m²) and greater E/e' (>14). A large left atrial volume index is an indicator of inadequate emptying of the left atrium that could be the result of increased left ventricular end-diastolic pressure and diastolic dysfunction in sinus rhythm.⁴⁶⁾ However, there is a lack of evidence supporting that obesity-related cardiomyopathy independently leads to significant systolic dysfunction.⁴⁵⁾

Epicardial adipose tissue and inflammatory adipokines

Epicardial adipose tissue has been proposed as an important mediator that obesity exerts its effects on myocardial tissue in relation to systemic inflammation.³⁸⁾ Under normal physiologic conditions, epicardial fat provides support and protection to myocardium, including serving as a mechanical cushion, producing heat, and releasing cardioprotective cytokines such as adiponectin.⁴⁷⁾ Adiponectin is beneficial and promotes adaptive physiological actions that reduce the risk of HF. These include inhibition of cardiac hypertrophy, inflammation, and fibrosis, promotion of natriuresis, and protection of the heart from pressure or volume overload.³¹⁾⁴⁸⁾ However, when excessive epicardial adipose tissue accumulates in obesity, some of these biological characteristics transform and functions similar to white adipose tissue.³⁸⁾ For example, synthesis of adipokines shifts from adiponectin to proinflammatory cytokines such as leptin, tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6.³⁸⁾⁴⁹⁾

Leptin is a key adipokine that balances energy demand and supply by regulating food intake and energy expenditure. It is mainly secreted by white adipose tissue and its level is positively related to the amount of body fat.⁵⁰⁾ Under physiological conditions, leptin sends signals to the hypothalamus to suppress appetite to decrease food intake. It can also increase the activity of the sympathetic nervous system to increase energy expenditure.⁵⁰⁾ Leptin also helps control neuroendocrine functions and metabolism. In patients with obesity, levels of leptin significantly increase; but selective leptin resistance develops, and leptin receptors become less sensitive to leptin stimulation in regulating appetite. However, leptin still activates the sympathetic nervous system and renin-angiotensin-aldosterone system and stimulates mineralocorticoid receptors. This most likely contributes to sodium and water retention in patients with HF.³¹⁾ Research also has shown that abnormalities of cardiac leptin signaling may contribute to obesity-related high output HF by promoting eccentric ventricular remodeling in which ejection fraction is preserved.⁵¹⁾⁵²⁾

Other proinflammatory adipokines such as IL-6, IL-1 β , TNF- α , and resistin may also contribute to the development of obesity-related high output HF by stimulating renal responses to neurohormonal overactivity corresponding with increased leptin.³¹⁾³⁸⁾ Additionally, increased levels of neprilysin are observed in obese patients with HF accelerating the degradation of B-type natriuretic peptides (BNP) and attenuating the cardioprotective effects of BNP related to inhibition of sodium reabsorption.³¹⁾

IMPLICATION FOR CLINICAL PRACTICE

Understanding the pathogenesis of obesity-related high output HF can be challenging, but there is accumulating evidence showing that weight reduction provides many beneficial effects on overall health and reducing risks for cardiovascular disease such as hypertension and HF.⁵³ Changes in lifestyle (e.g., increasing physical activity and decreasing sedentary time) are usually the first line of nonpharmacological intervention for weight loss. Dietary modification such as improving food quality and restriction in caloric intake can promote 5–10% weight loss.⁵⁴ Pharmacological interventions are considered when changes in lifestyle and dietary modification fail to induce weight loss.¹³ For patients with morbid obesity, bariatric surgery is effective in reducing significant weight, inhibiting the sympathetic nervous system, and decreasing leptin levels up to 12 months.⁵⁵ Early identification and recognition of obesity would promote healthcare providers to offer effective interventions to improve the health outcomes of patients with obesity.

Clinical management of patients with obesity-related high output HF is difficult. This is because the current clinical practice guidelines fail to make references to it.¹⁶ Patients with obesity-related high output HF are often misdiagnosed as HFpEF, as they share similar clinical characteristics including normal ejection fraction and elevated diastolic filling pressures.¹⁰ It is important that high output HF be considered as a differential diagnosis when patients present signs and symptoms of HF with a normal or near normal ejection fraction.⁸⁾⁵⁶ Since right heart catheterization is an invasive procedure and is not necessarily performed on all patients with HF, exercise testing may be considered to differentiate obesity-related high output HF as it is characterized with hyperdynamic circulation with exercise.¹⁰ Research has shown that cardiopulmonary exercise testing is a powerful and valuable clinical tool that can be used effectively in the evaluation (e.g., diagnostic and classification) and management (e.g., prognostic, risk stratification and treatment strategies) of patients with different types of HF.⁵⁷⁻⁶¹ During cardiopulmonary exercise testing, integrative multi-system responses to exercise (i.e., cardiovascular, pulmonary, neuropsychological, skeletal muscle etc.) provides a global assessment of cardiopulmonary functions. Parameters such as peak oxygen consumption (VO_2), minute ventilation/carbon dioxide production (VE/VCO_2) slope, peak partial pressure of end-tidal CO_2 (PETCO_2) and exercise oscillatory ventilation (EOV) are useful in determining exercise capacity and functional impairment.⁵⁹⁾⁶² Obesity is a significant contributing comorbidity affecting exercise testing among patients with HF. It is characterized by excessive VO_2 increase during cycle exercise at unloaded pedaling, near peak heart rate response at submaximal work rate, and reduced peak VO_2 .⁶³

Many patients with obesity-related high output HF are managed based on the conventional therapeutic regimens for HF (e.g., angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB]). Unfortunately, these pharmacological drugs can cause vasodilation, worsening the low systemic vascular resistance observed in patients with obesity-related high output HF. Therefore, such drugs should be cautiously used for these patients.⁷ Neprilysin inhibitors could potentially be useful in managing obesity-related high output HF. As discussed, increased levels of neprilysin in obese patients with HF cause degradation of natriuretic peptides, subsequently worsening sodium retention and plasma volume expansion.³¹ Inhibition of neprilysin increases bioavailability of natriuretic peptides, which have favorable cardiovascular benefits, including inhibiting secretion of aldosterone and counteracting its actions by promoting sodium excretion and decreasing

plasma volume.⁶⁴ Neprilysin inhibitors have been used in combination with angiotensin receptor blocker (e.g., sacubitril/valsartan) in treating patients with HFrEF effectively, but no beneficial effects were found for patients with HFpEF.⁶⁵ Alternatively, combination of neprilysin inhibitors with other inhibitors of aldosterone and sodium-glucose cotransporter-2 has been suggested as a mechanistic framework for therapeutic option among patients with obesity-related HFpEF.⁶⁴ However, the effects of this combination in patients with obesity-related high output HF are not clear and warrant future investigation.

IMPLICATIONS FOR RESEARCH

Pathophysiologic mechanisms contributing the pathogenesis of obesity-related high output HF are still not entirely clear. Limited evidence is available to guide and support the clinical management of patients with this condition. Research is needed to further explore the underlying mechanisms of this condition in order to develop interventions to alleviate the patient symptoms and improve patients' health outcomes.

Now with genomic testing, we can begin to examine and understand the various pathways and mechanism involved in obesity-related high output HF. The genomic approach can help provide system-level understanding of obesity-related molecular abnormalities contributing to pathogenesis of high output HF.⁶⁶ Currently, very limited data are available in the literature to understand why these patients have such high cardiac output. Although there have been studies that investigated genetic variants associated with obesity itself,^{67,68} no research has been found that examined genomics of obesity-related high output HF. After the completion of the human genome project and advancement in the next generation sequencing, genomic studies have become more accessible.^{69,74} In addition to genomics, other omics techniques such as transcriptomics, proteomics, and metabolomics could be used to understand the biological molecular pathways involved in the underlying mechanisms contributing to obesity-related high output HF.⁷² The insights gained from these omics studies would help identify targeted interventions to improve clinical outcomes of the patients.

Conducting omics studies in patients with obesity-related high output HF is not without challenges. Cardiac tissues are optimal to perform omics studies; however, the invasive biopsy procedure is high risk for patients with HF.⁷⁴ Instead, alternative samples such as body fluids or blood are used, which limit the direct investigation of myocardium.⁷² Development of animal models of obesity-related high output HF is needed and will be important to advance understanding of underlying mechanisms involved in obesity-related high output HF.

CONCLUSIONS

The pathophysiologic mechanisms involved in obesity-related high output HF is still not elucidated. A combination of multiple neurohormonal systems, metabolic factors, hemodynamic changes and various inflammatory mediators associated with obesity and HF contribute to the complexity of this challenge. Lack of adequate evidence supporting effective clinical management of this condition adds to the complexity. It is important to recognize obesity-related high output HF and differentiate it from HFpEF. Future research focusing on genomics is needed to understand the biological mechanisms contributing to high output HF associated with morbid obesity.

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