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Review Article

Underlying Causes of High Output Heart Failure

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ABSTRACT

In the U.S., each year, there are more than 500,000 new cases of all types of heart failure. With high output cardiac failure, there is an elevated cardiac output associated with several conditions and diseases, including obesity, chronic anemia, systemic arterio-venous fistula, hypercapnia, mitochondrial dysfunction, and hyperthyroidism. The underlying pathophysiologic mechanisms relate to a reduction in systemic vascular resistance from arterio-venous shunting or peripheral vasodilation. Often there is a decrease in systemic arterial blood pressure and neurohormonal activation leading to heart failure symptoms of dyspnea and fatigue. In a persistent high output state, patients may experience tachycardia, valvular abnormalities, and ventricular dilatation and/or hypertrophy. In this article, there is a review of high output heart failure, including the prevalence, pathophysiology, and common clinical causes of this disease.

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Introduction

Most clinicians are familiar with patients that have heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) with normal or low cardiac output accompanied by increased systemic vascular resistance [1]. With the growing rate of obesity in the U.S., clinicians are caring for an increased number of patients with high output heart failure associated with decreased systemic vascular resistance [2]. High output heart failure occurs when there is an elevation in cardiac output to meet the metabolic demands of the body [3]. There are a variety of conditions and diseases such as obesity, anemia, cirrhosis, and hyperthyroidism resulting in high output heart failure [4, 5].

Patients with high output heart failure present with similar symptoms such as fatigue and dyspnea as patients with other types of heart failure. These patients have a high cardiac output > 8 L/min or a cardiac index > 3.9 L/min/m². With a persistent high output state, the patients develop ventricular dilatation and/or hypertrophy, tachycardia, and valvular abnormalities [5, 6]. Obesity is the most common etiology for high output heart failure and these patients have increased demand for tissue

perfusion and plasma volume with extreme vasodilation [7]. The exact pathophysiologic mechanisms for this tremendous vasodilation in obese patients need further investigation. In this article, we reviewed the etiology and pathophysiology of high output heart failure. In addition, there is a description of the various causes for patients who develop this type of heart failure.

Prevalence

Although heart failure is common, with 500,000 new cases reported annually, the incidence and prevalence of high output failure are much lower [8]. This has been attributed to conditions resulting in a high output state, including an increased metabolism with an associated demand for blood and a bypass of the arterioles and capillary bed, leading to increased oxygen consumption with a low systemic resistance [9, 10]. In western countries, there is an increasing prevalence of high output heart failure with high morbidity. One possible reason for this rise in this type of heart failure is the increase in obesity, especially those with a body mass index > 35 kg/m². The survival of obese patients with high output heart failure is lower compared to patients with other types of heart failure because of the dramatic vasodilation that occurs [5].

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Pathophysiology

High output heart failure is both unique and complex, with multiple elements contributing to the decline [11]. Factors that play a role in the development of high output heart failure include low systemic vascular resistance, reduced arterial-venous oxygen gradient, and an elevated cardiac output. In high output heart failure, the metabolic demand exceeds the body's metabolic supply [12]. The renin-angiotensin-aldosterone system is activated together with the adrenergic nervous system and an increased serum vasopressin (antidiuretic hormone) concentration. The myocardium undergoes excessive vascular dilatation to increase oxygen consumption to maintain contractility. Over time, this hypermetabolic state retains excessive blood resulting in extreme vasodilation. Patients with obesity have excess adipose tissue that often increases blood volume and cardiac output with a decrease in systemic vascular resistance. The expanded venous return increases the preload that often leads to elevations in pressures within the right atria, pulmonary artery, and right and left ventricles [7]. Obesity is now recognized as a more potent risk factor than others, and more recently, there appears to be an obese-HFpEF phenotype. Whereas this relationship is not understood, obesity appears to be an important risk factor for HFpEF [13].

Causes

There are multiple causes associated with high output heart failure. The most common causes include obesity, arteriovenous fistula, liver disease, hyperthyroidism, and severe anemia. It has also been reported that mitochondrial diseases contribute to the development of high output heart failure.

I Obesity

Obesity is the leading cause of high output heart failure. In a retrospective study, Reddy *et al.* reported that obesity accounted for 31% of 120 cases of high output heart failure [5]. Although the underlying mechanisms of obesity-related high output heart failure are still not fully characterized, it has been proposed that increased vasodilation and decreased systemic vascular resistance associated with obesity possibly contribute to the pathogenesis [6, 14]. In obesity, multiple adipokines (e.g., leptin, IL-1 β , IL-6, TNF- α), activation of compensatory mechanisms, altered metabolism, and cardiac remodeling are triggering factors for the development of high output heart failure [15-18].

II Arteriovenous Fistula

Arteriovenous fistula is the second most common cause of high output heart failure (23%) [5]. In the circulatory system, blood ejected from the left ventricle normally travels to the aorta, peripheral arteries, arterioles, then into capillaries and venules. The arterioles provide the greatest vascular resistance, serving as a regulator for blood pressure [19]. In arteriovenous fistula, blood is shunted from an artery directly into a vein due to either congenitally abnormal or acquired connection between the artery and vein. Without the regulation of arterioles, there is a decrease in vascular resistance, leading to increased blood flow into the venous system. Consequently, there is an augmented venous return that causes increased preload, leading to an elevated stroke volume and increased cardiac output [20]. There have been reports that high output heart failure

presents as the initial clinical manifestation in patients with arteriovenous fistula [21].

III Liver Disease

Similar to the arteriovenous fistula, chronic liver disease accounts for 23% of high output heart failure cases [5]. As a vital organ, the liver plays important roles in anabolism and metabolism, including the production of amino acids, gluconeogenesis, and breakdown of waste products and drugs. The complex cardiohepatic interactions play important roles in the pathogenesis of heart failure when there is a significant liver disease [22]. Chronic liver disease such as cirrhosis causes significant disruption of hepatic architecture, inducing arteriovenous shunts and decreased systemic vascular resistance [23]. In addition, impaired liver function in clearing vasoactive cytokines leads to excessive vasodilation that further lowers systemic vascular resistance [24]. As a result, there is an increased stroke volume and cardiac output. The hyperdynamic circulatory state in the cirrhotic liver contributes to the pathogenesis of high output heart failure.

IV Hyperthyroidism

Hyperthyroidism is a common thyroid disease that affects 1.3% of adults in the United States [25]. Physiologically, thyroid hormones, including triiodothyronine and thyroxine, are mainly responsible for metabolism. Excessive circulating thyroid hormones cause an increase in metabolic rates and metabolic demands [26]. Patients with hyperthyroidism experience increased heart rates, feeling anxious, excessive sweating, disturbed sleeping and having heat intolerance [27]. In order to meet the increased metabolic demands, the heart responds by increasing the heart rate, thus causing an elevation in the overall cardiac output. However, in the long term, uncontrolled hyperthyroidism can lead to persistent increased myocardial workload and cardiac remodeling to compensate for the changes that leads to the development of high output heart failure [28, 29].

V Severe Anemia

Anemia is the most common red blood cell disorder, affecting 5.6% of Americans [30]. It is caused by decreased haemoglobin, whose primary role is to carry and transport oxygen. Significantly reduced oxygen-carrying capacity in severe anemia contributes to the compensatory increased blood flow rate in order to meet the metabolic demands by increasing heart rate and cardiac output. The accelerated hemodynamics increases the cardiac workload, eventually leading to hypertrophy and high output heart failure [31].

VI Mitochondrial Disease

Mitochondrial disease is also reported in the literature as one of the other causes for high output heart failure [32, 33]. The mitochondrion is the powerhouse of cells that is responsible for generating adenosine triphosphate (ATP) through oxidative phosphorylation [34]. Either deficiency in mitochondria or mitochondrial dysfunction lowers the capacity to produce sufficient ATP that is critical for cell functions and survival. Research has shown that mitochondrial dysfunction contributes to the pathogenesis of heart failure involving multiple mechanisms (e.g., oxidative stress, inflammatory responses, disturbed mitochondrial Ca²⁺ homeostasis etc.) [35, 36]. Mitochondrial disease is associated with

lactic acidosis that can cause reduced systemic vascular resistance. Mitochondrial disease can also lead to cardiomyopathy and subsequently, high output heart failure. This was reported in a case study where the patient with primary mitochondrial disease developed refractory high output heart failure [33]. Although it is rare in mitochondrial disease, high output heart failure should be considered when patients present signs and symptoms of heart failure.

Conclusion

There are many pathophysiologic states that are related to high output heart failure and they are often curable conditions. This type of heart failure is related to excessive vasodilation and is most frequently caused by obesity, liver dysfunction, and arteriovenous shunts [37]. These patients have similar symptoms of fatigue and dyspnea as patients with normal to low cardiac output heart failure. Further research is particularly needed in patients with obesity to better understand whether regulation of vascular tone and fluid retention are similar to those with other types of heart failure.

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Conflicts of Interest

None.

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