The syndrome of heart failure (HF) is characterized by exercise intolerance, limited by dyspnea and fatigue, and associated with neurohormonal activation and fluid retention. The primary stimulus that signals the kidney to retain salt and water is debated. In the late 1940s, Peters (1) developed the concept that in congestive HF, despite increased blood volume, there is “underfilling of the arterial tree” that modulates renal retention of sodium and water. He proposed a hypothetical effective arterial blood volume, a measure of fullness of the arterial tree, that he believed was reduced, even though the blood volume was increased. This concept has been popularized as a unifying hypothesis to explain salt and water retention in low and high cardiac output states, including cirrhosis, liver disease, kidney disease, and pregnancy (2). However, effective arterial blood volume is a poorly defined entity that cannot be measured, and for which there are no known receptors in the body. Because its validity cannot be tested, the concept of effective arterial blood volume has remained hypothetical for more than 65 years.

What then signals the kidney in HF to retain fluid? The possible sequence of events that lead to salt and water retention in patients with severe low-output HF can be constructed from Figure 1, which shows the average percent change from normal in measurements of a number of hemodynamic, neurohormonal, body fluid compartment, and renal function parameters in patients with severe untreated low-output HF (3). A severe decrease in left ventricular (LV) function causes a reduction in the cardiac output (CO) and threatens the arterial blood pressure. This leads to a baroreceptor-mediated activation of several neurohormones. The parasympathetic tone is inhibited and the sympathetic tone is enhanced, with subsequent activation of the renin-angiotensin-aldosterone system. The predominant effect of neurohormonal activation is one of severe vasoconstriction, with an increase in the systemic vascular resistance (SVR), which is more marked in the splanchnic bed. This results in a decrease in the renal blood flow (RBF), greater in proportion to the reduction in the CO. The glomerular filtration rate (GFR) is reduced, but to a lesser extent than the RBF, suggesting a greater efferent than afferent arteriolar vasoconstriction. These changes in renal hemodynamics set the stage for the kidneys to retain salt and water, expanding the body fluid compartments, elevating the right- and left-sided filling pressures, and causing the release of natriuretic peptides. The net effect of these pathophysiological effects is that the arterial blood pressure remains normal or is only mildly reduced in the untreated patient with low-output HF. Therefore, the compensatory mechanisms seen in low-output HF appear to be designed to preserve the arterial blood pressure (4–6), which is maintained partly by an increase in SVR, and partly by an expansion of the blood volume.

In all high-output HF states where the CO is increased, such as in chronic severe anemia (7), chronic obstructive pulmonary disease (8), and large arteriovenous fistula (9,10), the arterial blood pressure is also threatened or is reduced because of severe vasodilatation. The neurohormonal response observed in these high-output conditions is almost identical to that seen in low-output HF. Although the SVR is reduced in high-output HF, the renovascular resistance is increased, and the RBF and GFR are reduced because of neurohormonal activation. This results in a similar pattern of renal retention of salt and water as seen in low-output HF (3,11).
These studies on patients with low- and high-output HF, therefore, support the notion that preservation or maintenance of the arterial blood pressure is the main stimulus for the neurohormonal response seen in all forms of HF, and that a threat to or a fall in the arterial blood pressure, and not “underfilling of the arterial system” or decrease in effective arterial blood volume is the most likely primary signal for the kidney to retain sodium and water. Blood pressure falls or is threatened in low-output states because of a decrease in CO, and in high-output states because of a decrease in systemic vascular resistance.

In this issue of the Journal, Reddy et al. (12) provide a retrospective analysis of 120 patients with a diagnosis of high-output HF, selected from 16,462 consecutive patients referred to the Mayo Clinic catheterization laboratory for hemodynamic assessment between 2000 and 2014. The most common cause of high-output HF in their series was morbid obesity (31%), followed by liver disease (23%), arteriovenous shunts (23%), lung disease (16%), and myeloproliferative disorders (8%). Patients with high-output HF related to anemia and thyrotoxicosis were excluded. The common hemodynamic feature among all the patient groups was excessive vasodilation, although an increase in oxygen consumption suggestive of a hypermetabolic state was also observed, particularly in patients with myeloproliferative disorders.

High-output HF has traditionally been described in patients with chronic severe anemia, thyrotoxicosis, chronic obstructive pulmonary disease, some forms of severe hepatic or renal disorders, beriberi (thiamine deficiency), and with large arteriovenous fistula or multiple small arteriovenous shunts, as in Paget’s bone disease (9). The Mayo Clinic cohort is clearly a highly select population, referred to the cardiac catheterization laboratory for invasive assessment of the cause of HF. Hence, many of the classical etiologies of high-output HF, not requiring invasive assessment, would be under-represented. Nevertheless, this unique dataset of a sizable population of well-studied and invasively proven patients with high-output HF identified morbid obesity as an
important cause of high-output HF in the contemporary era that had not been recognized previously.

How does obesity cause high-output HF? In uncomplicated normotensive obese subjects, excess adipose accumulation is associated with increases in blood volume and CO, and a decrease in SVR that is proportional to the increase in body weight (13,14). The augmented venous return increases preload so that the right atrial, right ventricular, pulmonary artery, and LV end-diastolic pressures are frequently elevated (13,14). Although these hemodynamic alterations would favor the development of eccentric LV hypertrophy, the issue of LV geometry in obesity remains unresolved. Several recent studies have shown that although eccentric LV hypertrophy occurred more commonly, concentric LV remodeling or hypertrophy is often seen in obese subjects when obesity is associated with arterial hypertension (15). However, LV systolic dysfunction is uncommon, even in severe, class III obesity (BMI ≥40 kg/m²), in the absence of coexistent heart disease (16). In contrast, most echocardiographic and tissue Doppler studies have demonstrated that the diastolic filling is significantly impaired in obese subjects (17). Whether and to what extent these findings are confounded by the loading conditions of a hyperdynamic high-flow state is unclear. Thus, although alterations in cardiac hemodynamics, morphology, and ventricular function seen in uncomplicated obesity may predispose to the development of HF, the transition to HF has not been addressed in published reports, and few studies have compared the cardiac hemodynamics and morphology of obese patients with or without HF. Kasper et al. (18) showed that the cardiac index was depressed and the SVR index was increased in 43 class I (BMI 30.0 to 34.9 kg/m²) to II (BMI 35.0 to 39.9 kg/m²) obese patients to a similar extent, as compared with 409 lean patients with HF. The obese patients had dilated hearts (LV internal dimension in diastole 6.6 ± 0.9 cm) and low ejection fraction (EF) (25 ±14%). Alpert et al. (19), using echocardiography, found that as compared to severely obese patients without HF, those with HF had significantly larger LV internal dimensions, greater LV end-systolic wall stress, and significantly lower LV fractional shortening. Thus, the transition to clinical HF, termed obesity cardiomyopathy, appears to be associated with the development of significant systolic dysfunction. However, diastolic dysfunction may also contribute to obesity cardiomyopathy in some patients (14).

The Mayo Clinic obese patients did not have significant systolic or diastolic dysfunction to explain HF. The universal finding in most obese patients is vasodilation. The mechanism for vasodilation in obesity is not entirely clear. Some of the obese patients may have subclinical obstructive sleep apnea with carbon dioxide retention and consequent vasodilation (8), but increasing evidence suggests that the periadventitial adipose tissue plays an important vasoactive paracrine role in the regulation of vascular tone (20). Further research is required to understand whether regulation of vascular tone is abnormal in obese patients who develop high-output HF, and whether the mechanisms involved in fluid retention are similar to those in other high-output states described earlier in this editorial. Obesity has reached epidemic proportions in the United States and is an important risk factor for HF. In the Framingham Heart Study, after adjusting for traditional risk factors, the risk of HF increased by 5% in men and 7% in women for every unit increase in body mass index over a mean follow-up period of 14 years (21). However, physicians should be aware that in addition to the classical variety of HF with reduced EF, obese patients could present with high-output HF that may be erroneously diagnosed as HF with preserved EF (HFpEF). Clinically, distinguishing obesity related high output HF from HFpEF may be difficult because both conditions share several common features: normal ejection fraction, high filling pressures, and elevated natriuretic peptides. Moreover, adverse LV loading conditions are likely to contribute to LV diastolic filling abnormalities on echocardiographic assessment. However, patients with HFpEF, in general, are likely to have normal LV size, low or normal stroke volumes, and most importantly, tissue Doppler imaging of the mitral annulus should show a decrease in e’, the commonly used echocardiographic measure of reduced LV relaxation. In addition, because patients with HFpEF have reduced vasodilatation, especially with exercise, they are not likely to show evidence for hyperdynamic circulation that is characteristic of obesity-associated high-output HF. Of course, there would be many patients in whom all these features are not seen, especially in the elderly where e’ may be affected by age alone. The presentation of both HFpEF and obesity-associated cardiomyopathy may sometimes be subtle, have a mixed systolic/diastolic dysfunction on echo, and only modest abnormalities in natriuretic peptide levels and LV stiffness. These cases may need exercise testing with or without invasive evaluation to clarify the pathophysiology.
REFERENCES


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