JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 68, NO. 5, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.05.036

EDITORIAL COMMENT

High-Output Heart Failure Revisited*

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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 "under filling 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).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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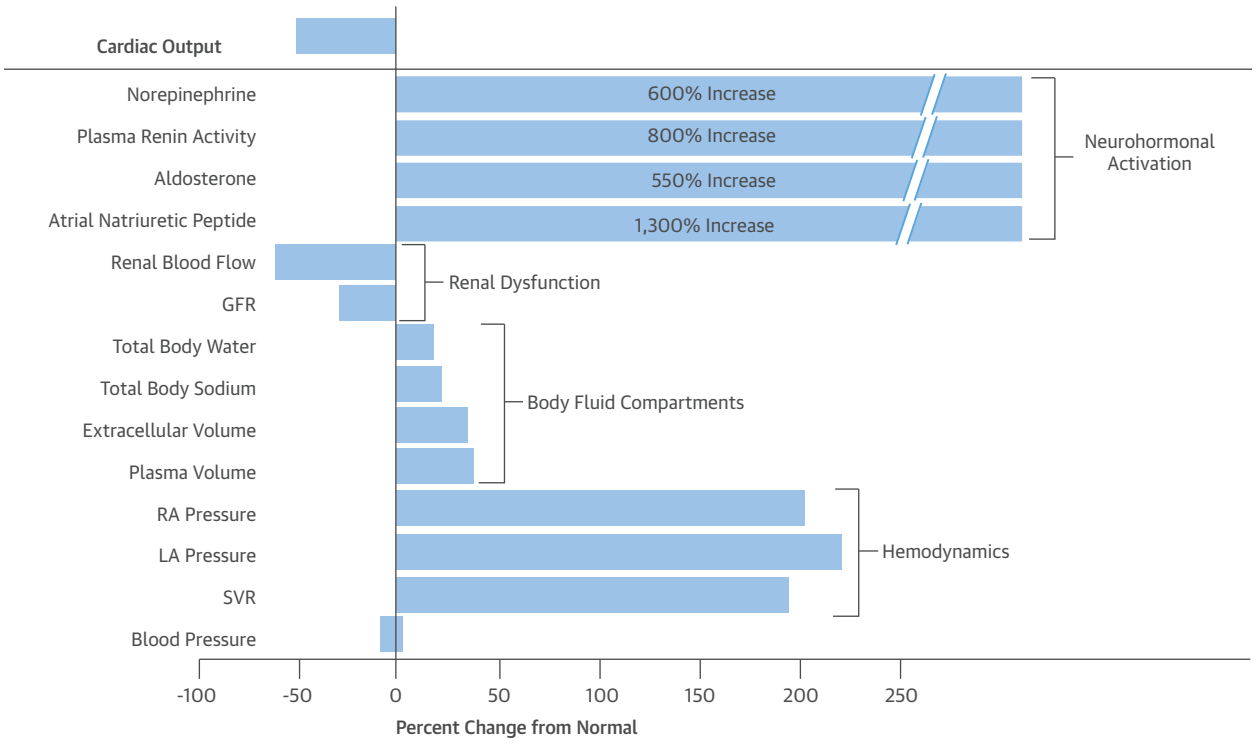
FIGURE 1 Pathophysiology of Fluid Retention in Low-Output Heart Failure



Bar graphs showing compensatory changes in a number of hemodynamic, neurohormonal renal function, plasma hormones, and body fluid compartment data, expressed as percent of normal in a group of patients with untreated congestive heart failure. GFR = glomerular filtration rate; LA = left atrial; RA = right atrial; SVR = systemic vascular resistance. Data from Anand et al. (3).

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.

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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 vasodilatation, 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