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EDITORIAL COMMENT

"One Size Does Not Fit All"

How to Individualize Decongestive Therapy Strategies in Heart Failure*

Carsten Tschöpe, MD,[a,b,c] Burkert Pieske, MD[a,b,c,d]

Most admissions for acute heart failure (AHF) occur in patients with chronic heart failure (HF). Despite significant improvements in prognosis for patients with stable HF, there has been essentially no progress in the treatment of AHF. After admission for decompensation, data showed high short-term mortality rates of 11% to 15% (1). The prognosis does thus not differ between HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) (2). Most of these admissions are for clinical congestion, not hypotension nor shock, regardless of ejection fraction (1,2). Hypervolemia is a significant risk marker in HF and is linked to impaired prognosis (3). An important goal for decongestive treatment strategies is rapid attainment of stable euvolemic status. It is not clear to which extent values from euvolemic healthy persons are ideal for patients with HF (4). However, global and uncontrolled therapeutic interventions to reduce "increased" blood volume in decompensated HF can lead to excessive preload reduction, systemic hypoperfusion, and increased organ damage. Therefore, knowledge of a patient's actual volume status is important to monitor decongestive therapies.

In the clinical setting, it is often a challenge to assess true volume status and its distribution in the individual patient. Clinical markers such as elevated jugular venous distention, lower extremity edema, or S_3 remain inadequate. Parameters for hemoconcentration (e.g., increases in hemoglobin, hematocrit, or plasma albumin) are surrogates for changes in volume status, but they lack sensitivity and specificity (5,6). Thus, even in the absence of clinical signs of congestion, increased filling pressure often still persists ("hemodynamic" congestion) (7), and it may precede clinical congestion. Invasive measurement of elevated pulmonary capillary wedge pressure portends a higher risk for post-discharge mortality and repeat hospitalization (8). However, even invasive measurements of pulmonary capillary wedge pressure do not provide specific insights into complete volume status and its distribution between the intravascular and interstitial spaces. In addition, total blood volume (TBV), representing the intravascular volume load, is composed of the sum of plasma volume and red blood cell mass (RBCM), which cannot be evaluated by pulmonary capillary wedge pressure measurement.

This issue is important because both plasma volume and red blood cell mass can differ among patients with decompensated HFrEF. The reason is that volume overload is not a homogenous identity, and it depends on the interplay of multiple confounding factors (hemoglobin concentration, oncotic pressures, systemic hypotension, and intrinsic renal function) that influence fluid distribution with differential interstitial and intravascular volume expansion (9). The impact of these factors and the consequences on volume expansion in HFpEF remain matters of discussion. However, quantitative and qualitative differences in volume overload are important for treatment strategies and would require an improvement in diagnostic approaches.

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From the [a]Department of Cardiology, Charité Hospital, University of Medicine Berlin, Campus Virchow Clinic, Berlin, Germany; [b]German Center for Cardiovascular Research, Berlin, Germany; [c]Berlin-Brandenburg Center for Regenerative Therapies, Charité Hospital, University of Medicine Berlin, Campus Virchow Clinic, Berlin, Germany; and the [d]Department of Cardiology, German Heart Center Berlin, Berlin, Germany. Both authors have reported that they have no relationships relevant to this paper to disclose.

This use of differences in volume overload is shown by Miller and Mullan (10) in this issue of *JACC: Heart Failure*, in the setting of decompensated chronic HF. In this prospective pilot study, TBV was directly quantitated with a validated radionuclide technique in patients with decompensated HFrEF (n = 35) and HFpEF (n = 20). TBV was increased up to 27% to 37% higher than normal predicted values at hospital admission in nearly all

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55 patients, as expected. However, the heterogeneity in the magnitude of the intravascular volume overload was high in HFpEF and HFrEF (deviations from predicted normal TBV ranged from −5.2% to +77% in HFpEF and from 0% to 107% in HFrEF). This finding indicated that volume targeting treatment requires individualized management options and includes knowledge of the extent to which changes in plasma volume and RBCM contribute to intravascular hypervolemia. In this context, Miller and Mullan (10) demonstrate important qualitative differences in TBV between decompensated HFpEF and HFrEF. These investigators show that in HFrEF, intravascular volume expansion was triggered by increases in both plasma volume and RBCM expansion in most of their patients, thus indicating that polycythemia is an important feature of volume overload in HFrEF (5). Polycythemia reflects the consequences of neurohormonal activation and volume contraction of the splanchnic area during decompensation, and it leads to recruitment of red blood cells from the spleen or other sites within the splanchnic circulation (11,12). In addition, decompensation-induced ischemia activates oxygen sensors such as hypoxia-inducible factor-1-alpha, known to be increased in decompensated HFrEF, as well as a contributor to stimulation of erythropoiesis (13,14).

In contrast, TBV expansion in HFpEF was surprisingly characterized by an RBCM deficit, indicating that true anemia (hemoglobin ≤12 mg/day) and compensating plasma volume expansion reflect the qualitative changes of TBV in most patients with decompensated HFpEF. Anemia under these circumstances has several potential mechanisms. It could be the consequence of (functional) iron deficiency (15) and an impairment of erythropoietin stimulation (13). Responders and nonresponders to Erythropoietin in HFpEF have been identified, thereby further demonstrating that even the group with HFpEF has a heterogeneous syndrome (16). Impairment of renal function and hypoxia-inducible factor-1-alpha signaling are known to influence erythropoiesis, especially in diabetes and obesity (17). Miller and Mullan (10) found obesity significantly more often, and it was more severe in the HFpEF group. In addition, patients with decompensated HFpEF are known to be older, are more often female, and have a higher prevalence of arterial hypertension and atrial fibrillation and a lower prevalence of an ischemic cause, compared with patients with HFrEF (18). Thus, differences in comorbidities between HFrEF and HFpEF could contribute to the findings of Miller and Mullan (10). However, in both study groups, patients with a polycythemia- or anemia-like pattern were found, thus indicating that TBV expansion also underlies a quantitative and qualitative heterogeneity that must be taken into account for successful and safe decongestive therapy.

In most of the patients in this study with HFrEF, diuretic agents led to a reductions in TBV and in interstitial volume overload (85 ± 13%; range −2 to +18 l), as measured by changes in body weight minus changes in TBV. Although interstitial volume overload was significantly reduced (93 ± 6%; range −3 to +34 l) during diuretic therapy in HFpEF, TBV did not change. Thus, HFpEF volume overload seems to be more severely affected by interstitial transcapillary refill volume, as mobilized under diuretic conditions.

Several factors, including those discussed earlier, could contribute to the finding that the extravascular space is more prominently overloaded in decompensated HFpEF. Hemodynamically, increased left ventricular stiffness, a hallmark of HFpEF, leads to reduced preload reserve, including limitation of venous capacity compared with HFrEF (19,20). Endothelial dysfunctional, increased arterial stiffness, and impaired arterial-ventricular coupling may also contribute to the extraordinarily high interstitial volume level in HFpEF (20). Interstitial volume overload is linked to tissue ischemia-induced organ damage and leads to high mortality rates in AHF independent of ejection fraction (18). Furthermore, interstitial volume overload is not recognized by B-type natriuretic peptide plasma levels, as indicated by the finding that increased levels of this peptide were observed to be lower in HFpEF compared with levels in HFrEF. However, that does not necessarily mean that the degree of the decompensation-induced burden in HFpEF is lower because interstitial volume overload leads to a reduction in tissue oxygen supply, known to be involved in further organ damage. Other markers such as troponin, cystatin-C, and transaminases may be additionally necessary to guide

treatment of patients with especially decompensated HFpEF (18).

Most of the patients in this study with clinically recompensated HFrEF and HFpEF showed persistent hypervolemia at hospital discharge. This finding indicates that these patients were still at risk for early repeat hospitalization.

In conclusion, heterogeneity and differences in pathological features between HFrEF and HFpEF contribute to the problem that conventional therapies for decongestion have yielded uniformly poor results. A "one size fits all" therapy is not realistic under these circumstances. Decongestive therapy should remove large volumes of fluid quickly and safely and improve symptoms, particularly dyspnea, without aggravating renal dysfunction or causing neurohormonal activation. Loop diuretic agents and vasodilators are the mainstays of current therapy and are not ideal because although they produce immediate intravascular volume reduction and relief of symptoms, they activate neurohormonal forces that are deleterious to both the heart and the kidney (21). Ultrafiltration is an alternative to loop diuretic agents in AHF, but it has not proved advantageous in the setting of renal dysfunction, and if it is not carefully applied, it may also aggravate the neurohormonal imbalance. The establishment of quantitative volume analysis could be key to an individualized approach to monitor decongestive therapy strategies and to prevent or to limit these adverse effects. Such an approach could also be helpful by attempting to establish new volume targeting strategies including combinations of loop diuretic agents with aquaretic agents, glucose cotransporter-2 inhibitors, natriuretic peptide approaches (e.g., nesiritide, urodilatin, neprilysin inhibition together with renin-angiotensin-aldosterone blockade), and new vasodilators (e.g., serelaxin, cyclic guanosine monophosphate stimulators such as vericiguat and riociguat).

Whether the establishment of a quantitative volume analysis will lead to an improvement in mortality or morbidity in decompensated HF needs to be proved in further studies. However, the need for such measurements seems logical. Choice of the method used to integrate such measurements to guide decongestive therapy is still not established and must be practicable. The use of repeated measurements with a radiolabeled tracer would limit widespread application. Alternatives could include regional vascular volume measurements by lung thoracic impedance or implantable hemodynamic monitors such as the CardioMems HF system (St. Jude Medical, St. Paul, Minnesota). Implantable monitors would allow further control of HF in those patients after discharge (22–24). The benefit of such a system has already been reported in patients with HFrEF and HFpEF (24).

REPRINT REQUEST AND CORRESPONDENCE: Prof. Dr. Carsten Tschöpe, Department of Cardiology, Charité, Universitätsmedizin Berlin, Campus Virchow Clinic, Augustenburgerplatz 1, 13353 Berlin, Germany. E-mail: carsten.tschoepe@charite.de.

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