Fluid Volume Homeostasis in Heart Failure: A Tale of 2 Circulations

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ABSTRACT: Fluid volume homeostasis in health and heart failure (HF) requires a complex interaction of 2 systems, the intravascular and interstitial-lymphatic circulations. With the development of HF both the intravascular and interstitial compartments undergo variable degrees of volume remodeling which can include significant expansion. This reflects the impact of multiple pathophysiologic mechanisms on both fluid compartments which initially play a compensatory role to stabilize intravascular circulatory integrity but with progression in HF can evolve to produce the various manifestations of volume overload and clinical HF congestion. The intent of this review is to help enhance recognition of the pathophysiologic and clinical importance of the interlinked roles of these 2 circulatory systems in volume regulation and chronic HF. It would also be hoped that a better understanding of the interacting functions of the intravascular and interstitial-lymphatic fluid compartments can potentially aid development of novel management strategies particularly addressing the generally undertargeted interstitial-lymphatic system and help bring such approaches forward through a more integrated view of these 2 circulatory systems.

Key Words: fluid ■ interstitial-lymphatic ■ intravascular ■ review

The basis of this discussion most accurately and historically begins with William Harvey and the publication in 1628 of “Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus” (“An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings”). While his work was not accepted at the time without controversy by traditional medicine, the circulation of blood volume (BV) forms the core concept of cardiovascular physiology and fluid volume homeostasis—pump, pipes, and fluid hydraulics. However, the physiology of the circulatory system is recognized to be more complex than a simple pump and stiff pipes in that each of these components has unique dynamic properties in health and disease that impact the function and structure of the overall fluid system. Further, the extra-vascular interstitial compartment to include the lymphatic system (the second circulation) also has a central and often underappreciated role in volume homeostasis and the fundamental exchange functions supporting organ–tissue–cellular viability. The interdependence in function of these 2 circulatory systems has, however, made clinical study of their components difficult and as a result contributed to somewhat of a standstill in the investigation of the physiologic and pathophysiologic properties of fluid volume homeostasis in clinical heart failure (HF). Understanding their respective roles in maintaining a compensated state of volume homeostasis in health, as well as the dynamic responses in patients experiencing the hemodynamic, metabolic, and volume perturbations associated with HF remains central to advancements in clinical management. Therefore, it is necessary to widen our focus clinically to appreciate the significance of the 2 circulatory systems to better understand the pathophysiology driving dysfunctions in volume regulation and importantly in turn help develop innovative treatment strategies. While this review is not intended to be a comprehensive discussion of all aspects of this complex topic, it is hoped it will foster further interest among clinical and research colleagues in the importance of these 2 interlinked circulations. Further, help highlight the role of the interstitial-lymphatic circulation in HF particularly with a view to promote the development of novel therapeutic approaches.
INTEGRITY

BLOOD VOLUME AND CIRCULATORY INTEGRITY

Within the cardiovascular system, pressure gradients cannot exist without flow, and there is no flow without fluid volume (change in volume over time is flow). Pressure itself, however, does exist without flow in the circulatory system as reflected in mean circulatory pressure (≈7 to 15 mm Hg) measured under experimental conditions of cardiac standstill in animal models\(^2\) and cardiopulmonary bypass in humans. This pressure without flow reflects the basic relationship between fluid volume (blood volume) and the vascular capacity of the circulatory system. These 2 elements need to match like a proper fitting glove to the hand it contains to maintain the functional integrity of the circulation. This also relates to the concepts of “unstressed volume” and “stressed volume” and how BV is functionally (not anatomically) partitioned within the circulatory system.\(^3,4\) Unstressed volume relates to the quantity of BV needed to fill the vascular space without increasing pressure above zero—a common analogy is that of filling a balloon with water just to the point where it fills out the balloon but does not expand the balloon. More BV then contributes to stressed volume (about 20% to 30% of total BV and mainly residing within the arterial circulation) where pressure begins to increase above zero. Given that 60% to 70% of total BV resides in the venous system (at rest) and largely within the splanchnic venous capacitance vessels, most of the unstressed volume is contained within this reservoir. This reservoir is highly dynamic and is essential in maintaining circulatory homeostasis in health (eg, routine exercise) and trauma (eg, hemorrhage), but can also have a detrimental role in patients with impaired cardiac function.\(^5–9\) While data supporting the concept of BV redistribution are primarily preclinical\(^10,11\) and limited in clinical HF,\(^5,8,9\) the acute mobilization of BV with redistribution from this venous reservoir to the central circulation can contribute to elevations in cardiac filling pressures and potentially acute symptomatic pulmonary congestion and clinical decompensation. With an expansion of BV in chronic HF, there is an increase in venous capacitance over time enlarging the reservoir volume of particularly the abdominal splanchnic venous system.\(^6\) As a result promoters of sympathetic activation such as hypoxia (eg, as occurs with sleep apnea), acute myocardial ischemic events, systemic hypotension, medication non-compliance or changes in medications such as uptitration of vasodilators with associated systemic hypotension, and physical and emotional stress among other factors can trigger sympathetic-mediated splanchnic venoconstriction with associated decreases in venous capacitance and the mobilization of unstressed venous BV (estimated to be as much as 800 to 1000 mL) centrally with increase in venous return to the right heart.\(^6–9,11\) In the setting of systolic LV dysfunction, this volume can contribute to symptomatic congestion with rise in central venous pressure particularly when concomitant right ventricular systolic dysfunction is present. While more studies are needed to further elucidate the clinical contribution of this mechanism in HF, it can provide a basis for hemodynamic and symptomatic clinical congestion without a change in body weight or additional net fluid accumulation. In normal resting conditions the splanchnic vascular bed contains primarily unstressed volume and in chronic HF this splanchnic venous reservoir is expanded providing the capacity for large and potentially rapid fluid mobilization into the inferior vena cava increasing venous return to the right ventricle. Therefore, the components of total BV, central and splanchnic venous pressures, and venous vascular capacitance (and compliance) all play critical roles in the integrated pathophysiology of compensated and decompensated HF. As a result, the maintenance of fluid volume homeostasis is the work of maintaining an effective circulating BV without congestion to assure the fundamental imperative of organ perfusion despite the insults of HF.

INTERSTITIAL-LYMPHATIC FLUID HOMEOSTASIS

The transvascular distribution and redistribution of fluid depends upon factors such as elements of the conventional Starling forces (hydrostatic pressures at the capillary level, plasma oncotic pressure as affected primarily by serum albumin concentration, interstitial tissue pressure [turgor pressure], and interstitial oncotic pressure),\(^12,13\) However, it is important to recognize that more contemporary studies have advanced substantial revisions to the traditional Starling principle which support the concept that microvascular fluid exchange occurs across the whole capillary bed\(^14–15\) (these references provide a more detailed discussion which is beyond the scope of this review). Capillary membrane integrity with changes in permeability and the effectiveness of lymphatic drainage of the interstitial space are all physiologic elements that are altered in HF. Further, the pathophysiologic framework of interstitial sodium bound to glycosaminoglycan networks is disrupted in

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Description |
|--------------|-------------|
| BV           | blood volume |
| PV           | plasma volume |
| RBCM         | red blood cell mass |
HF secondary in part to increased dietary sodium intake and neurohormonal activation. This dysfunction alters the sodium buffering capacity of the interstitial compartment which in turn leads to increased interstitial fluid accumulation (edema), increased vascular permeability and impaired lymph vessel formation. Lymph formation which involves the transudation of fluid from the capillaries into the interstitial space and the drainage of this lymph fluid from the interstitial space is, therefore, based upon the net effect of many factors subject to impairment of function in HF. Figure 1 illustrates a conceptual framework of the volume changes that can occur in the intravascular and interstitial fluid compartments with the development of HF.

Under normal circumstances interstitial fluid is largely transported back to the venous system through the diffuse system of lymph nodes and to a more limited extent through the thoracic duct located at the junction of the left subclavian and jugular veins. A right lymphatic duct drains lymph fluid from a smaller region of the right side of the body. The importance of the lymphatic system is underscored in volume overload HF where lymphatic flow can be enhanced several-fold to compensate for the excess in fluid transudation into the interstitial space. This occurs until the lymphatic system becomes overwhelmed or compromised in functional integrity which then results in the accumulation of protein-rich tissue congestion manifested as peripheral tissue edema, pulmonary interstitial edema, and even pleural effusion and ascites. The increased tissue oncotic pressure attributable to the accumulation of filtered protein (principally albumin) and expansion of the interstitial compartment (often by several liters) promotes the typical clinical picture of congestion in decompensated HF. The function of the interstitial fluid compartment and its associated lymphatic circulation, therefore, plays a critical role to limit the development of “congestion” when fluid volume expansion occurs. Also fundamental to the flow of lymph is the impact of variations in systemic venous pressure which if elevated will impede the drainage of lymph through the thoracic duct and as a result increase the rate of fluid accumulation within tissues such as the lungs. The elevations in venous pressures (including central venous filling pressures) associated with HF can, therefore, impede the mechanism of fluid removal from the interstitial spaces resulting in the different distributions and presentations of edema—not all interstitial spaces are structurally the same or function uniformly with regard to fluid distribution, accumulation, and removal. With the development of clinical findings of tissue edema, the response is often the implementation of intravenous diuretic therapy to facilitate removal of excess interstitial fluid secondary in part to limited effectiveness of lymphatic drainage. Through diuretic-induced renal mechanisms of diuresis and natriuresis intravascular...
HEART FAILURE—A CARDIAC VIEW OF PHYSIOLOGIC RESPONSES

With the onset of myocardial injury and resulting impairment in cardiac function, a low cardiac output state initially develops causing relative arterial underfilling and a resulting compromised intravascular volume relative to the capacity of the circulatory system—a mismatch of stressed volume of the arterial circulation to the volume capacity of the arterial system. This can cause an initial inability to adequately perfuse vital organs with resulting clinical decompensation and its potential consequences. However, this is also where multiple compensatory mechanisms are activated to maintain, at least in the short-term, adequate cardiac output, organ perfusion, and the volume integrity of the circulatory system. One such mechanism is the transvascular refilling of the intravascular space secondary to a shift of fluid from the interstitial compartment which, however, is impacted by multiple factors influencing the refill rate and adequacy of fluid movement. Impaired cardiac output and arterial underfilling also stimulate baroreceptors with sympathetic activation as a first line of defense promoting arterial vasoconstriction to maintain an effective arterial blood pressure for vital organ perfusion. Additionally, vasoconstriction, primarily of the splanchnic venous circulation, can mobilize unstressed BV to the central circulation to help maintain preload and cardiac output (Frank-Starling relationship). A slower but also critical volume affecting mechanism is the renal activation of the renin-angiotensin-aldosterone systems in response to impaired cardiac output and glomerular filtration rate and the resulting decreased delivery of sodium to distal tubules which promotes by a tubule-glomerular feedback mechanism renal sodium and fluid retention contributing to intravascular and interstitial volume expansions. Thus, the fundamental goal of such compensatory mechanisms is to maintain an effective/adequate arterial perfusion pressure to sustain vital organ function and viability. However, compensation is not always maintained with often a narrow physiologic range separating a stable compensated state from decompensation. Figure 2 illustrates the multiple pathways that come into play in response to impaired cardiac function.

Many clinical studies have sought to describe the predictors of decompensation with the goal of limiting morbidity particularly HF-related hospitalizations. Often these studies have focused on physical exam findings, changes in symptoms, or measures of or changes in central hemodynamics to assess congestion. The assessments of intravascular and interstitial volumes are often not incorporated in the evaluations of clinical congestion partially because they have been elusive to clinical capture as qualitative indices or quantitative metrics. Fluid volume status and specifically the concept of an optimal BV (sometimes also described as “euvolemia”) are central to clinical compensation and its maintenance in chronic HF. However, “optimal” volume is likely to vary depending on the stage of HF as a compensated or decompensated state, renal function, and degree of dependence on diuretic intervention among other factors. Therefore, importantly, “optimal” BV may not always mean a “normal” BV in patients with HF, and BV expansion may be a needed compensatory mechanism.

BLOOD VOLUME HOMEOSTASIS IN HEART FAILURE

The importance of an effective BV to maintain the integrity of the circulatory system in health and disease is well recognized. The circulation will fail if intravascular volume is insufficient to fill the capacity of the vascular system. With the onset of HF and associated impaired cardiac output, relative arterial underfilling develops and, as a result, compensatory mechanisms as reviewed above are activated to adapt intravascular volume to critical perfusion pressure despite hemodynamic perturbations. Sympathetic-mediated arterial and venous constriction provide early responses to maintain organ perfusion, but necessary longer-term mechanisms also come into play which include an expansion in intravascular volume. The concept of BV expansion in patients with chronic HF is not new and has a background in earlier human physiology laboratory investigations demonstrating that both intravascular and interstitial compartment fluid volumes increase in HF, but also more recent studies showing that BV expansion and fluid volume distributions can be highly variable patient to patient. Persistence in intravascular volume expansion despite aggressive diuretic therapy and, importantly, significant variability in intravascular volume profiles (normal BV to marked expansion) despite similar clinical presentations and treatment has been demonstrated by quantitative...
volume analysis.\textsuperscript{32-36} Therefore, whether a stable BV expansion provides the optimal intravascular volume necessary to help maintain circulatory integrity in response to impaired cardiac output and altered vascular capacitance in chronic HF\textsuperscript{4,6,7,37,38} is a relevant clinical issue. Volume homeostasis may be impacted by the different phenotypes of HF particularly when defined as HF with preserved ejection fraction or with reduced ejection fraction.\textsuperscript{39} The extent of arterial underfilling and the potential role and appropriateness of compensatory BV expansion in HF with preserved ejection fraction require further study.

\textbf{CONCEPT OF OPTIMAL VOLUME IN HEART FAILURE}

This leads to the fundamental question of what is the “optimal” volume state in HF, and what constitutes the most favorable intravascular volume and interstitial volume profiles in the context of chronic HF and do these profiles impact clinical outcomes? We know that a “normal” BV in healthy state is going to differ from individual to individual by age, sex, body size, and body composition, and then also potentially by disease state. Basically, however, an optimal volume should refer to an effective circulating BV that supports appropriate oxygen carrying capacity and provides adequate tissue perfusion pressure to supply nutrients and remove metabolic waste and carbon dioxide and the most favorable clinical state possible. An effective circulation, therefore, requires the best fit of BV to the capacity of the vasculature where cardiac preload and cardiac output are appropriate to the hemodynamic and metabolic demands of the individual. Too little BV and pump function fails (mismatch of volume and capacity) too much and the heart fails from acute volume overload and congestion. So, what the intravascular circulatory system needs is the best ratio of BV to vascular capacity under the circumstances it is dealing with, such as the limits of cardiac output and arterial underfilling of HF. The relationship of BV to vascular capacity (arterial and venous) therefore establishes the hemodynamics (perfusion pressures) in relation to myocardial pump function to maintain integrity of the circulatory system and in turn help maintain survival. This also requires concert with an optimal interstitial volume to support
the intravascular space. Recently reported quantitative volume data indicated that a persistent expansion in BV (>25% of normal volume) in a cohort of patients with compensated chronic HF was independently associated with better survival and fewer HF rehospitalizations relative to patients who maintained a normal (nonexpanded) intravascular volume. These findings, while still formative, suggest that the concept of managing intravascular volume to a conventionally considered “normal BV” state in patients with chronic HF may have different and detrimental clinical ramifications pathophysiologically than permitting optimal BV expansion.

CONTRIBUTION OF RED BLOOD CELL MASS TO INTRAVASCULAR VOLUME HOMEOSTASIS IN CHRONIC HEART FAILURE

The contribution of the quantity of red blood cells (RBC), the red blood cell mass (RBCM), to intravascular volume in chronic HF often goes underrecognized or considered to be without immediate volume-related clinical relevance. Therefore, the distinction of the presence of true anemia (a deficit in RBCM), normal RBCM, or RBC polycythemia (an excess in RBCM) in relation to intravascular volume status and clinical outcomes has not been comprehensively evaluated. This in part was because of limitations in prior methodology to feasibly measure BV in common clinical encounters such as HF. Current clinically available and evolving methodology, however, now permit the quantitative assessment of intravascular volume and RBCM phenotypes with practical turnaround times for clinical management. We have previously reported that peripheral venous hemoglobin concentration can be a misleading index for actual RBCM and, therefore, overall intravascular volume status. While a low venous hemoglobin concentration may reflect a true anemia with associated RBCM deficit, it may also reflect a relative dilution-related “pseudo-anemia” where RBCM is normal but with pathologic plasma volume (PV) expansion results in a dilution of hemoglobin concentration and a misinterpretation of anemia. Therefore, the interpretation of the status of intravascular volume needs to consider RBCM phenotypes, as well as quantitative PV data. This would permit better identification of those patients with HF who should respond optimally to interventions such as RBC transfusion or iron replacement therapies from those individuals who have a normal RBC mass and without iron deficiency despite the measurement of a low peripheral venous hemoglobin concentration. The importance of distinguishing the different RBCM phenotypes in patients with chronic HF and the heterogeneity in these profiles is associated with significant differences in clinical outcomes. Therefore, the RBCM component of total BV should be considered when considering the approach to volume management, as well as its contribution to stratifying risk. Further and importantly, the finding in patients with chronic HF that RBC polycythemia (RBCM excess with compensatory PV expansion) is a significant contributor to intravascular volume expansion is common (41% in one patient cohort) and shown in multivariate analysis to be an independent predictor of better outcome relative to a normal RBCM. In contrast to RBC polycythemia and consistent with previous reports, true anemia is also common in patients with chronic HF and is an independent predictor, relative to normal RBCM, of increased risk of HF-related mortality and re-hospitalization. Dilutional pseudo-anemia which cannot be identified by hemoglobin concentration alone may also be present in a substantial number of patients with HF and potentially carry a different impact on clinical outcome relative to those with a normal RBCM and no PV expansion. Therefore, the importance of distinguishing dilutional pseudo-anemia from true anemia along with the presence or absence of iron deficiency can significantly impact the approach to patient management and help guide the most appropriate therapies. Also, important to note is that while a normal RBCM phenotype may be identified, the presence of iron deficiency even in the absence of true anemia still needs to be evaluated.

“CONGESTION”—THE FAILURE IN HEART FAILURE

The development of symptomatic clinical congestion, interpreted often as fluid volume overload, is the most common basis for hospitalization in patients with chronic HF. The relief of congestion, therefore, is a central goal of intervention, and diuretic therapy is often the mainstay to achieve that goal. In this context “congestion” most often refers to “clinical congestion” with signs and symptoms (dyspnea, jugular venous distension, pulmonary rales, and interstitial-alveolar edema, and peripheral edema, ascites) reflecting the patient’s decompensation from a previous stable state. Such findings do not necessarily reflect isolated pathophysiologic responses of hemodynamic, intravascular volume, or myocardial function therefore, making it important to recognize that “congestion” is not a single defining element of decompensation, but the result of multiple mechanisms producing different manifestations and degrees of volume exacerbation, some of which evolve to a symptomatic state while others do not. Thus, there can exist a full spectrum of volume expansion and fluid redistribution with hemodynamic congestion associated with elevation in central filling pressures without symptoms and then progress to a
state of symptomatic clinical congestion—therefore, not all “congestion” behaves the same. Further, congestion in HF is not solely attributable to central venous volume and hemodynamic changes as the interstitial-lymphatic system also has an integral role.

The effectiveness of treatment of congestion is commonly based on improvement in symptoms and objective clinical assessment. Change in body weight is a common metric used to assess adequacy of decongestive diuretic therapy. However, while weight loss can reflect clinical decongestion and symptomatic improvement, this metric is not consistently associated with improved survival or fewer hospitalizations. The findings of clinical studies linking diuresis-related weight loss to decongestion and outcomes such as HF-related mortality or re-hospitalizations are mixed. As observed clinically large volume diuresis (multiple liters) can occur promptly (within the first 24 hours) with intravenous diuretic therapy in volume overload patients with decompensated HF which helps recover clinical compensation and symptom improvement, but not necessarily prevent recurrence in follow-up evaluations. This may in part reflect the observation that fluid loss associated with diuresis-related weight decrease does not have a substantial net impact on intravascular volume, but rather is primarily a reflection of the transvascular transport pathways that function primarily to reduce interstitial compartment fluid excess. The decongestion of the interstitial compartment thus likely has a lesser impact on determining outcomes relative to the impact of intravascular volume status. Somewhat contrary to clinical expectations, this suggests that there is an importance in distinguishing fluid overload congestion of the interstitial compartment and the contribution of the lymphatic system from that of the intravascular space where volume expansion of the latter may have a separate compensatory role in chronic HF. Thus, discordance between weight loss associated with clinical decongestion and actual intravascular volume status may in part explain outcome disparities observed in clinical studies. Data supporting a greater degree of weight loss as a common metric of clinical decongestion do not necessarily translate into better HF-related outcomes. Such discordance, however, is not a consistently reported finding with some studies supporting while others failing to demonstrate an association among surrogate markers such as composite scores, signs and symptoms, hemodynamics, or biomarkers of decongestion with clinical outcomes. Further, observational data demonstrate that changes in diuresis-related weight loss do not bear a significant relationship to changes in intravascular volume. A basis for this observation is that the decrease in weight reflects the predominant draining of fluid from the interstitial compartment while the intravascular PV state is maintained with minimal change in volume. Also, patient-to-patient variability in intravascular volume profiles (greater or lesser expansion) appears to have a limited association to the extent of interstitial volume reduction in response to diuretic therapy. Therefore, diuresis-related changes in body weight reflect significant decreases in interstitial volume which are often observed clinically to be associated with rapid decongestion and symptom relief but not with significant admission to discharge changes in PV even if large PV expansion is present at hospital admission (Figure 3). A plausible hypothesis would be that the volume status of the intravascular compartment, particularly the integrity of the arterial circulation, is more a driver of clinical outcomes than even large changes in interstitial compartment volume.

CLINICAL TRANSLATION—CURRENT AND FUTURE APPROACHES TO VOLUME ASSESSMENT AND MANAGEMENT

Understanding volume physiology and pathophysiology can provide important insight into the clinical management and prognosis of patients with HF. Fluid volume homeostasis in health and HF requires the interaction of 2 circulatory systems, the intravascular- and interstitial-lymphatic circulations. In acute episodes of HF, intravascular volume redistribution to the central circulation with resulting hemodynamic congestion may be the main driver of symptomatic decompensation. Here adjunctive venous vasodilator therapy to recruit more splanchnic venous capacitance to back-distribute fluid volume is more appropriate than the initiation of diuretic therapy, which if overly aggressive, can compromise circulatory integrity. Splanchnic sympathetic nerve blockade is also being investigated as a method to inhibit venoconstriction and blunt inappropriate BV redistribution in acute and chronic HF. However, with volume overload and congestion particularly in chronic HF there is often expansion of both the intravascular and interstitial compartments with the latter being the primary site of fluid retention. This occurs in part secondary to limitations in lymphatic drainage and changes in capillary transudation properties resulting in the diverse clinical manifestations of congestion. Whether chronic inflammation is a culprit contributing to this dysfunction is yet to be clarified but if so, the question of how best to treat without exacerbating volume homeostasis will need to be addressed. The interstitial compartment responds to decongestive diuretic therapy intervention (the most common approach used clinically to manage fluid excess) with often large volume reductions (multiple liters) while intravascular volume remains relatively stable (often less than 10% to 15% reduction even with aggressive diuretic therapy). However, intravascular volume phenotypes are highly variable patient
to patient in terms of extent of BV expansion (normal nonexpanded BV to marked expansion) even in the presence of marked interstitial compartment fluid retention. Therefore, in the overall meaning of “congestion” it is important to distinguish intravascular from interstitial compartment responses to volume overload in HF and likewise the responses of these compartments to volume intervention therapies. The fundamental recognition that different volume phenotypes exist in patients with HF and that these phenotypes require different approaches to management, including interventions on the lymphatic system, is necessary to advance our thinking from a “one size fits all” approach.

While needing further study, the concept that a persistence in BV expansion may serve a compensatory role in maintaining circulatory integrity in chronic HF has physiologic merit. This, however, does contrast with the current generally followed clinical paradigm of maintaining or treating to what would be considered a “normal” intravascular volume in all patients with HF. An excess in RBC mass in addition to PV expansion and the development of RBC polycythemia would not be an unexpected physiologic compensatory response to maintain adequate oxygen carrying capacity to tissues in patients with HF. The concept of intravascular volume expansion as an element of compensation HF and a basis for better clinical outcomes has physiologic merit warranting further study to put understanding of volume homeostasis in HF in a necessary clinical context. Further, recognizing that biologic variability also exists in many systems, the physiologic variability in intravascular volume responses to HF should not be unexpected. Whether the identification of different volume phenotypes in HF can help guide more targeted and individualized patient management strategies is a next step for investigation. The methodology now clinically available to measure intravascular volume in the different stages of HF can help address this issue.

Additionally, and importantly, a better functional understanding of the contribution and limitations of the interstitial-lymphatic circulation and how this system relates to the maintenance of intravascular volume in HF is needed. Clinically feasible methods of intervening on the interstitial compartment and lymphatic system as adjunct approaches to optimize the management of clinical congestion are needed. Preclinical and clinical studies in the 1960s investigated thoracic duct cannulation and the construction of lymphovenous shunts to reduce venous pressure and improve volume overload congestion; however, while such studies provided valuable information these interventions have not advanced to the clinical arena. At this point there is not a clinically feasible technique to directly measure interstitial volume, but such methodology is evolving and will likely become a clinical tool allowing more complete evaluation of volume status in patients with HF. Current methodology, however, does permit direct quantitative measurement of intravascular volume by a clinically useful and time-efficient technique. More expansive
clinical implementation of such methods will help identify distinct volume phenotypes and potentially guide more effective and individualized fluid volume management strategies.

As suggested in this review, there are many clinical questions yet to be fully explored: Do differences in HF volume phenotypes impact outcomes and can intravascular volume status be manipulated to affect the most positive clinical outcomes? Can the lymphatic system be manipulated or remodeled by selective drug therapy or prolymphangiogenic factors to enhance interstitial fluid transport for steady state fluid management in chronic HF? Can thoracic duct drainage of fluid from the interstitial space be made more of a major channel through surgical or device (lymphovenous shunts) interventions in the present era of HF management? What are the body regional factors (local trauma) that compromise efficient lymph flow and how can they be identified and managed? Further, the roles of myocardial inflammation and the innate and adaptive immune systems are still being explored from pathogenesis and target for therapeutics perspectives in HF and in a similar way the contribution of inflammation of the lymphatic systems is an area that requires more study. Inflammation as a detrimental process of lymphatic and blood vascular systems carries significant pathophysiologic and clinical implications for patients with HF.

As readily appreciated, there are many issues yet to be studied (some still to be identified or better defined) to bring better clinical clarity to understanding the interrelations of the “two circulations” in HF. Further, how such data can be translated into more focused and precision patient care will be critical. The good part is that there are still more opportunities to explore and improve patient care and outcomes; the bad part is that we are not there yet.

ARTICLE INFORMATION

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Disclosures
None.

REFERENCES

1. https://www.biodiversitylibrary.org/page/5828191.
2. Rothe CF. Mean circulatory filling pressure: its meaning and measurement. J Appl Physiol. 1993;74:495–509. doi: 10.1152/jappl.1993.74.2.499
3. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology. 2008;108:735–748. doi: 10.1097/alan.Ob013e3181672067
4. Tyberg Jv. How changes in venous capacitance modulate cardiac output. Pflugers Arch. 2002;445:10–17. doi: 10.1007/s00424-002-0922-x
5. Greenway CV. Role of splanchic venous system in overall cardiovascular homeostasis. Fed Proc. 1983;42:1678–1684.
6. Gelman S, Mushlin PS. Catecholamine–induced changes in the splanchic circulation affecting systemic hemodynamics. Anesthesiology. 2004;100:434–439. doi: 10.1097/00000542-200402000-00036
7. Fallick C, Sobota PA, Dunlap ME. Sympathetically mediated changes in capacitance—redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail. 2011;4:669–675. doi: 10.1161/circheartfail.111.961789
8. Rapaport E, Weisbart MH, Levine M. The splanchic blood volume in congestive heart failure. Circulation. 1958;58:581–587. doi: 10.1161/01.cir.18.4.581
9. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. J Am Heart Assoc. 2017;6:e006817. doi: 10.1161/jaha.117.006817
10. Ogilvie RI, Zbrowski-Sluis D. Acute effect of rapid ventricular pacing and volume loading on total vascular capacitance. Can J Cardiol. 1992;8:1071–1078.
11. Barnes RI, Bower EA, Rink TJ. Haemodynamic responses to stimulation of the splanchic and cardiac sympathetic nerves in the anesthetized cat. J Physiol. 1986;378:417–436. doi: 10.1113/jphysiol.1986.sp016228
12. Taylor AE. Capillary fluid filtration. Starling forces and lymph flow. Circ Res. 1981;49:557–575. doi: 10.1161/01.res.49.3.557
13. Reed RK, Rubin K. Transcapillary exchange: role and importance of the interstitial fluid pressure and the extracellular matrix. Cardiovasc Res. 2010;87:211–217. doi: 10.1093/cvr/cvq143
14. Woodcock TE, Woodcock TM. Revised starling equation and the glycoprotein model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth. 2012;108:384–394. doi: 10.1093/bja/aer515
15. Levick JR, Michell CC. Microvascular fluid exchange and the revised starling principle. Cardiovasc Res. 2010;87:198–210. doi: 10.1093/cvr/cvq062
16. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WH-W, Mullens W. The pathophysiological role of interstitial sodium in heart failure. J Am Coll Cardiol. 2015;65:378–388. doi: 10.1016/j.jacc.2014.11.025
17. Aukland K, Reed RK. Intestinal–lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev. 1993;73:1–78. doi: 10.1152/physrev.1993.73.1.1
18. Laine GA, Allen SJ, Katz J, Gabel JC, Drake RE. Effect of systemic venous pressure elevation on lymph flow and lung edema formation. J Appl Physiol. 1986;61:1634–1638. doi: 10.1152/jappl.1986.61.5.1634
19. Warren JV, Merril AJ, Stead EA Jr. The role of the extracellular fluid in the maintenance of a normal plasma volume. J Clin Invest. 1943;22:635–641. doi: 10.1172/jci101435
20. Tarazi RC, Dustan HP, Frohlich ED. Relation of plasma to interstitial fluid volume in essential hypertension. Circulation. 1969;60:357–366. doi: 10.1161/01.cir.60.2.357
21. Fudim M, Salah HM, Sathananthan J, Bernier M, Pabon-Ramos W, Schwartz RS, Rodes-Cabau J, Côté F, Khalifa A, Virani SA, et al. Lymphatic dysregulation in patients with heart failure. J Am Coll Cardiol. 2021;78:66–76. doi: 10.1016/j.jacc.2021.04.090
22. Itkin M, Rockson SG, Burkhoff D. Pathophysiology of the lymphatic system in patients with heart failure. J Am Coll Cardiol. 2021;78:278–290. doi: 10.1016/j.jacc.2021.05.021
23. Eiskjaer H, Bagger JP, Danielsen H, Jensen JD, Thomsen St, Sorensen SS, Pedersen EB. Mechanisms of sodium retention in heart failure: relation to the renin-angiotensin-aldosterone system. Am J Physiol. 1991;260:F883–F889. doi: 10.1152/ajprenal.1991.260.6.f883
24. Mentez RJ, Stevens SR, DeVore AD, Laia A, Varder JM, AbouEzzeddine OF, Khozanie P, Redfield MM, Stevenson LW, O’Connor CM, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. JACC Heart Fail. 2015;3:97–107. doi: 10.1016/j.jchf.2014.09.003
25. Anand IS, Ferrari R, Kaira GS, Wahi P, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive heart failure. Circulation. 1989;80:299–305. doi: 10.1161/01.cir.80.2.299
26. Girerd N, Seronde MF, Coiro S, Chouhoud T, Bilbaut P, Braun F, Kenzou D, Malilier B, Nazezrallaie P, Roui G, et al. Integrative assessment of congestion in heart failure throughout the patient journey. JACC Heart Fail. 2018;6:273–285. doi: 10.1016/j.jchf.2017.09.023
27. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O’Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison BA, et al.
Prevalence, predictors, and clinical outcome of residual congestion in acute decompensated heart failure. Int J Cardiol. 2018;258:185–191. doi: 10.1016/j.ijcard.2018.01.067

28. Selvaraj S, Claggett A, Pozzi A, McMurray JJV, Jhund PS, Packer M, Desai AS, Lewis EF, Vaduganathan M, Lefkowitz MP, et al. Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced left ventricular function: PARADIGM-HF. Circulation. 2019;140:1569–1579. doi: 10.1161/circulationaha.119.039920

29. Gunton RW, Paul W. Blood volume in congestive heart failure. J Clin Invest. 1955;34:879–886. doi: 10.1172/jclint3144

30. Gibson JG, Evans WA Jr. Clinical studies of the blood volume. III. Changes in blood volume, venous pressure, and blood velocity rate in chronic congestive heart failure. J Clin Invest. 1937;16:851–858. doi: 10.1172/jclin31294

31. Seymour WB, Pritchard WH, Longley LP, Hayman JM Jr. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein, and kidney function during cardiac failure and after improvement. J Clin Invest. 1942;21:229–240. doi: 10.1073/jci101294

32. Warren JV, Stead EA Jr. Fluid dynamics in chronic congestive heart failure. Arch Intern Med. 1944;73:138–147. doi: 10.1073/jci101294

33. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007

34. Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamancia J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol. 2004;93:1254–1259. doi: 10.1016/j.amjcard.2004.01.070

35. Miller WL, Mullan BP. Volume overload profiles in patients with preserved (HFpEF) and reduced (HFrEF) ejection fraction chronic heart failure. Circulation. 2021;143:871–881. doi: 10.1161/CIR.0000052623.16194.80

36. Miller WL, Albers DP, Gansen DN, Mullan BP. Intravascular volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007

37. Miller WL, Albers DP, Gansen DN, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007

38. Miller WL, Albers DP, Gansen DN, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007

39. Miller WL, Albers DP, Gansen DN, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007

40. Miller WL, Albers DP, Gansen DN, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007

41. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. Circulation. 2015;131:2265–2273. doi: 10.1161/circulationaha.115.021424

42. Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low vs preserved left ventricular ejection fractions. Am J Cardiol. 2008;102:1069–1072. doi: 10.1016/j.amjcard.2008.05.058

43. Van PY, Rina GM, Cho SD, Underwood SJ, Hamilton GJ, Anderson R, Ham LB, Schreiber MA. Blood volume analysis can distinguish true anemia from hemodilution in critically ill patients. J Trauma. 2011;70:648–651. doi: 10.1097/TA.0b013e31820d5f48

44. Barbaro SV, Zanjani E, Jhund S, Maurer SD, Misir A, AbouEzzeddine OF, Groom JD, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805. doi: 10.1056/nejmoa1005419

45. Aronson D, Abbas Z, Allen E, Berger AJ. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. Eur J Heart Fail. 2013;15:637–643. doi: 10.1093/eurjhf/hft036

46. Guroje JD, Stevens SR, Mentz RJ, Cooper LB, Vader JM, AbouEzzeddine OF, Groom JD, et al. Diuretic strategies in patients with acute decompensated heart failure. Eur J Heart Fail. 2013;15:637–643. doi: 10.1093/eurjhf/hft036

47. Van der Meer P, Postmus D, Puninkowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol. 2012;61:1973–1981. doi: 10.1016/j.jacc.2012.12.052

48. Ezekowitz JA, McAllister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes. Circulation. 2003;107:223–225. doi: 10.1161/01.cir.0000052622.51963.fc

49. Horwich TB, Foranov GC, Hamilton MA, MacLei8n WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol. 2002;39:1780–1786. doi: 10.1016/s0735-1073(02)01854-5

50. Anand IS, Gupta P. Anemia and iron deficiency in heart failure. Circulation. 2018;138:80–98. doi: 10.1161/circulationaha.118.030099

51. Gheorghiae M, Follath F, Puninkowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Foranov GC, Jaarsma T, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12:423–433. doi: 10.1002/ehjhf.hft045

52. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Routleau JL, Olli EO, et al. Diuretic strategies in patients with compensated heart failure. N Engl J Med. 2011;364:797–805. doi: 10.1056/nejmoa1005419

53. Aronson D, Abbas Z, Allen E, Berger AJ. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. Eur J Heart Fail. 2013;15:637–643. doi: 10.1093/eurjhf/hft036

54. Guroje JD, Stevens SR, Mentz RJ, Cooper LB, Vader JM, AbouEzzeddine OF, Groom JD, et al. Diuretic strategies in patients with acute decompensated heart failure. Eur J Heart Fail. 2013;15:637–643. doi: 10.1093/eurjhf/hft036
65. Miller WL. Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. *Circ Heart Fail.* 2016;9:e002922. doi: 10.1161/CIRCHEARTFAILURE.115.002922

66. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. *Nat Rev Cardiol.* 2020;17:269–285. doi: 10.1038/s41569-019-0315-x

67. Joris J, Cuenaoud HF, Doern GV, Underwood JM, Manjo G. Capillary leakage in inflammation—a study by vascular labeling. *Am J Pathol.* 1990;137:1353–1363.

68. Russell PS, Hong J, Windsor JA, Itkin M, Philips ARJ. Renal lymphatics: anatomy, physiology, and clinical implications. *Front Physiol.* 2019;10:1–18. doi: 10.3389/fphys.2019.00251