

EDITORIAL COMMENT

## In Search of Euvolemia in Heart Failure\*

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In preparation for the writing of this editorial, I consulted my copy of the *Stedman's Medical Dictionary* (23rd Edition, copyright 1976) and was surprised to find that the word "euvolemia" was nowhere to be found. A subsequent search in PubMed (search terms "euvolemia" or "euvolemic" in any field) revealed that the first published article with these terms appeared in a 1979 study of renal physiology in rats. The word euvolemia appears in the heart failure consensus guideline statements from the American College of Cardiology/American Heart Association, Heart Failure Society of America, and European Society of Cardiology. In each of the guideline documents, euvolemia is not strictly defined, but is used in context to describe the "ideal volume status" for the patient (also referred to as the "dry weight"), and is proposed as an appropriate goal for titration of diuretic therapy in heart failure patients. This usage is based on the Greek origins of the prefix "eu," most often translated as "good" or "well."

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In this issue of the *JACC: Heart Failure*, Miller and Mullan (1) present novel findings that invite the reappraisal of the clinical application of the term euvolemia in hospitalized patients with heart failure. In this prospective cohort study, intravascular blood volume was directly measured with a validated radionuclide technique in 26 hospitalized heart failure patients shortly after hospital admission and after clinical stabilization at the time of discharge (in 17 of the 26 patients). Intravascular blood volume was increased above normal predicted values at hospital admission in 24 of the 26 subjects. Although this finding might be expected in the presence of signs and symptoms of congestion at the time of the hospital admission in the majority of the patients, the direct intravascular blood volume measurement

demonstrated surprising heterogeneity in the magnitude of the intravascular volume overload (deviations from predicted normal total blood volume ranged from +9.5% to +107%), and further demonstrated that increased intravascular blood volume could be attributable to increases in the red cell volume (deviations from predicted normal red cell volume ranged from -24 to +65%) and/or increases in the plasma volume (deviations from predicted normal plasma volume ranged from +13 to +128%). The most provocative finding was that despite an average weight loss of 6.9 kg in response to diuretic therapy and improvement in symptoms of congestion at hospital discharge, intravascular blood volume changed little during the hospital stay (net decrease 0.7 ± 1.1 liters) and remained well above normal predicted values at hospital discharge (deviations from predicted normal total blood volume ranged from +9 to +51%).

The DOSE (Diuretic Optimization Strategies Evaluation) trial demonstrated a high rate of adverse outcomes at 60 days after hospital discharge (42% risk of death, repeat hospital stay, or emergency department visit) despite diuretic treatment titrated to clinical euvolemia by expert heart failure clinicians (2). The current investigators demonstrate that clinical euvolemia at the time of hospital discharge is frequently associated with quantitative evidence of a persistent pathological increase in intravascular volume. These findings are concordant with the previous publication by Androne et al. (3) that demonstrated that increased intravascular blood volume in nonedematous ambulatory heart failure patients was common and was associated with an increased risk of adverse outcomes compared with heart failure patients with measured blood volume in the predicted normal range. The finding of a persistent increase in intravascular blood volume despite clinical euvolemia suggests the hypothesis that high rates of post-discharge adverse clinical outcomes in hospitalized patients with heart failure may be partly attributable to incomplete decongestion at hospital discharge.

Evaluation for hemoconcentration during heart failure hospitalization has been proposed as an alternate means to assess euvolemia, because hemoglobin values would be expected to increase only when the intravascular plasma volume had been reduced to normal levels in response to diuretic therapy (4,5). The direct measurement of red blood cell volume in the current study indicates that serial assessment of hemoglobin levels may be confounded by dynamic changes in red cell mass associated with heart failure decompensation. In contrast to the previous study of intravascular volume overload in ambulatory heart failure patients by Androne et al. (3), 65% of the acutely decompensated patients in the current investigation had evidence of increased red blood cell volume at hospital admission. Red blood cell volume decreased by an average of 200 ml during hospitalization, accounting for 29% of the decrease in total intravascular blood volume observed in response to treatment. Increased hematocrit has been previously reported in canine models of acute heart failure, and has been shown to

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be dependent on splenic contraction as the source of increased red cell mass (6,7). Splenic contraction in response to adrenergic activation also occurs in humans (8), and is known to be associated with increased hematocrit during exercise in normal humans and in ambulatory heart failure patients (9–11). The findings of the current investigation suggest that neurohormonal activation during acute heart failure decompensation may recruit red blood cells from the spleen or other sites within the splanchnic circulation, with subsequent re-sequestration after stabilization in response to treatment (12). These dynamic changes in circulating red cell mass and other confounding factors, including loss of red blood cells due to laboratory phlebotomy, and changes in intravascular plasma volume related to posture at the time of blood sampling, limit the potential clinical utility of serial hemoglobin levels as a clinical marker of euvolemia in heart failure.

The current findings clearly demonstrate the discrepancy between clinical euvolemia and measured normovolemia (defined here as a measured intravascular blood volume in the normal predicted range), but do not provide insight into the clinical utility of the intravascular blood volume measurement for therapeutic optimization in heart failure patients. The clinical interpretation of the blood volume measurement is potentially limited by several considerations. First, the direct blood volume measurement provides assessment of the total blood volume, but does not provide information on regional distribution of blood volume. Dynamic changes in compliance of the splanchnic venous circulation in response to neurohormonal activation can transfer blood to the thoracic circulation and increase left ventricular end-diastolic pressure in acute heart failure without change in total blood volume (6,7). Second, the normal predicted values for blood volume used in the current study are based on data derived from a population of healthy individuals across a wide range of body habitus (13). Increased venous capacitance in response to nitroglycerin and other vasodilators is known to be associated with increased intravascular venous blood volume (14,15). Normalization of blood volume data based on healthy individuals may therefore underestimate the “normal” intravascular volume in heart failure patients treated with vasodilators. Therapeutic interventions to reduce “increased” blood volume in this setting might lead to excessive pre-load reduction and systemic hypoperfusion.

In conclusion, the data presented by Miller and Mullan (1) support a proposal for revision of the current use of the term euvolemia. Alternative descriptive terms could be adopted for resolution of congestive signs and symptoms (e.g., “decongested”), and euvolemia could be re-defined to represent the “good volume” that is associated with the best clinical outcomes in heart failure populations. Future studies that combine measures of total intravascular volume, regional vascular volume (thoracic impedance), cardiac filling pressures (implantable hemodynamic monitors), measures of adequate organ perfusion, and clinical outcomes are

needed to characterize this newly defined euvolemic state. Meanwhile, clinicians must recognize the limitations of physical assessment for the diagnosis of volume overload in heart failure patients, and should consider use of direct measurements of intravascular volume and/or intravascular pressures for better estimation of euvolemia as part of a therapeutic strategy to reduce the risk of adverse outcomes.

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**Key Words:** decompensated chronic heart failure ■ diuretic therapy ■ total blood volume quantitation ■ volume overload.