

The Regulation and Measurement of Plasma Volume in Heart Failure

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Plasma volume, the intravascular portion of the extracellular fluid volume, can be measured using standard dilution techniques with radiolabeled tracer molecules. In healthy persons, plasma volume remains relatively constant as a result of tight regulation by the complex interaction between neurohormonal systems involved in sodium and water homeostasis. Although chronic heart failure (CHF) is characterized by activation of many of these neurohormonal systems, few studies have evaluated plasma volume in this condition under treatment. Untreated edematous decompensated heart failure (HF) is associated with a significant expansion of plasma volume. Patients with stable CHF, receiving conventional therapy, appear to have a contracted plasma volume, a concept that is in contrast to the widely held belief that CHF is associated with long-term hypervolemia. It is likely that significant changes in plasma volume occur during intensification of medical therapy or during transition from the edematous to the stable state. Clinical assessment of plasma volume may be of particular value during treatment in patients with decompensated HF, in whom the plasma volume is contracted despite an increase in total extracellular fluid volume. Under these circumstances, treatment with inotropes or renal vasodilators may be more appropriate than intravenous diuretics alone. Further studies evaluating plasma volume in HF may help to improve our understanding of the pathophysiologic mechanisms occurring in the development and progression of this complex condition. (J Am Coll Cardiol 2002;39:1901–8)
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It is estimated that around 60% of human tissue is made up of water, the majority being intracellular. The extracellular fluid volume (ECF) is composed of intravascular and extravascular compartments. The intravascular compartment is also known as the plasma volume (PV), whereas the extravascular compartment represents fluid within the interstitial space. It is possible to calculate the volumes of each of these compartments using standard dilution techniques with various tracer molecules. Within current clinical practice, PV measurements are used primarily in the investigation of hematologic disorders, particularly in the evaluation of an abnormal packed cell volume. Disproportionate fluctuations in PV may result in either hemoconcentration or hemodilution, thereby influencing the measured packed cell volume. For example, a reduction in PV will result in hemoconcentration, giving rise to an apparent polycythemia ("pseudopolycythemia"). Alterations in PV occur in a diverse array of clinical circumstances, including healthy subjects undertaking exercise (1), in pregnancy (2), and in pathologic conditions such as chronic anemia (3), chronic heart failure (CHF) (4) and cirrhosis (5). After an overview

of the normal physiology of sodium and water homeostasis, which is central to PV regulation, we will review the methods available for the measurement of PV. Alterations in PV that occur in patients with heart failure (HF) and their clinical importance will then be discussed.

REGULATION OF PLASMA VOLUME

The regulation of ECF, and hence PV, is achieved by a complicated interaction between afferent and efferent mechanisms (Fig. 1). Sodium is the major solute in the ECF, and as such is a prime determinant of osmotic pressure. Therefore, control of ECF is intimately related to sodium homeostasis. Because excretion of sodium and water occurs primarily via the kidney, this organ plays a pivotal role in PV regulation.

Afferent Mechanisms

Afferent sensing mechanisms and the subsequent neurohormonal responses are directed primarily toward the maintenance of circulatory homeostasis (5–7). Low-pressure volume receptors are located mainly in the cardiac atria (8). An increase in stretch of these receptors results in the secretion of atrial natriuretic peptide (ANP). Stimulation of atrial mechanoreceptors also leads to an alteration in neural signaling to the hypothalamus and medulla, thereby influencing vasopressin synthesis and release and sympathetic nervous system (SNS) discharge to the kidneys (9).

High-pressure receptors are located in the left ventricle, aortic arch and carotid sinus (6,10). A decrease in arterial pressure results in the inhibition of baroreceptor discharge and subsequent activation of the SNS and the renin-

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Abbreviations and Acronyms

ANP	= atrial natriuretic peptide
CHF	= chronic heart failure
cpm	= counts/min
ECF	= extracellular fluid
HF	= heart failure
¹²⁵ I-HSA	= human serum albumin labeled with radioactive iodine
PV	= plasma volume
SNS	= sympathetic nervous system

angiotensin-aldosterone systems and vagal withdrawal, together with the nonosmotic release of vasopressin.

Further receptors are located in the renal juxtaglomerular apparatus (11). A decrease in renal perfusion pressure or a reduction in tubular sodium load results in enhanced renin release. Both the SNS and ANP further modulate renin release (12,13).

Efferent Mechanisms

Sodium and water retention. RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM. In the kidney, angiotensin II is a powerful vasoconstrictor of efferent glomerular arterioles, helping to maintain the glomerular perfusion pressure (14). It also acts directly on renal tubular epithelial cells, increasing sodium reabsorption (15). By inducing constriction of mesangial cells, angiotensin II decreases the effective area for filtration, further conserving sodium and water (16). Angiotensin II also enhances the release of norepinephrine from nerve terminals and stimulates aldosterone production from the adrenal cortex (6,17). Aldosterone promotes the retention of sodium in cortical collecting tubules and activates the SNS (18). The absence of escape from the actions of aldosterone is an important feature in patients with CHF and depends, at least in part, on decreased sodium delivery to the collecting duct (6).

SYMPATHETIC NERVOUS SYSTEM. Stimulation by direct renal sympathetic innervation and circulating catecholamines result in an increase in renal sodium reabsorption. This is achieved by alterations in local hemodynamics and direct tubular effects similar to those described for angiotensin II (14). By direct stimulation of renin production and the subsequent activation of angiotensin II, the SNS further enhances sodium reabsorption (19).

VASOPRESSIN. Osmotic release of vasopressin occurs in response to an increase in extracellular osmolality sensed by cells in the anterior hypothalamus. Nonosmotic release results from disturbances in circulatory homeostasis detected by high-pressure mechanoreceptors (10). Vasopressin interacts with specific receptors found in the kidney, resulting in a net decrease in water clearance (20).

Natriuresis and diuresis. Atrial natriuretic peptide, originating in the atria, and brain natriuretic peptide, released from the ventricular myocardium in response to wall stress

(21), are structurally related peptides with important natriuretic and diuretic actions (20,22). An increase in the glomerular filtration rate arises from increased perfusion pressure caused by afferent arteriolar vasodilation and efferent arteriolar vasoconstriction (23). By relaxing mesangial cells, natriuretic peptides increase the effective area for filtration, an opposite effect to that of angiotensin II (24). Natriuretic peptides also inhibit sodium reabsorption in collecting duct cells in the inner medulla (25). Atrial natriuretic peptide appears to have a direct effect on vascular permeability because when infused into nephrectomized rats still results in a fall in PV (26). Patients with CHF demonstrate a degree of resistance to the effects of exogenous ANP (more so than BNP); a decrease in distal tubular sodium delivery seems to be implicated in this effect (6,20).

Vasodilatory prostaglandins, by counteracting neurohormonal-induced renal vasoconstriction, also contribute to sodium and water homeostasis (6). Their clinical importance is apparent when prostaglandin production is blocked by non-steroidal anti-inflammatory drugs, precipitating the retention of fluid in patients with CHF.

The mechanisms outlined so far go only partway in describing the complex interactions between neurohormonal pathways involved in salt and water balance. For example, angiotensin II facilitates the release of ANP (27). However, ANP is able to modulate the renal effects of angiotensin II (28). It is the crucial interaction between the systems described that enables normal subjects to maintain a relatively constant PV despite alterations in sodium and water intake (29). The importance of precise homeostasis in normal humans is exemplified when abnormalities are seen in diseased states such as congestive HF, where the potent sodium and water retaining actions of angiotensin II and aldosterone appear to overwhelm the opposing natriuretic peptide system.

MEASUREMENT OF PLASMA VOLUME

Several methods are available for determining PV, all of which involve the principles of dilutional analysis employed after the administration of tracer molecules. The International Committee for Standardization in Hematology has made recommendations based upon reliability, reproducibility and ease of operation in routine clinical use (30). Their recommended method is human serum albumin labeled with radioactive iodine (¹²⁵I-HSA).

¹²⁵I-HSA method. A known amount of ¹²⁵I-HSA is added to plasma prepared from the subject (30). A set volume is then injected peripherally into the subject while the remainder is retained to prepare a standard solution. Blood is drawn from a different vein (usually the opposite arm) after 10, 20 and 30 min. Radioactivity of the plasma samples and the standard are then determined in a scintillation counter. By extrapolation the radioactivity at time zero can be calculated. Using three samples reduces the effect of early loss of radionuclide from the circulation on

the derived measurement, when compared to a single 10-min sample (31). This will also allow time for adequate mixing within the circulation. The test can be performed at the bedside and takes just over 30 min, making it applicable to both stable and unstable patients. Having measured the radioactivity of the standard preparation, the PV can then be calculated by the following equation:

$$\frac{\text{Radioactivity of standard (cpm/ml)} \times \text{dilution of standard} \times \text{volume injected (ml)}}{\text{Radioactivity of postinjection sample (cpm/ml, adjusted to time zero)}}$$

The use of radioactive compounds (albeit at low dose) is not suitable for all subjects; therefore, alternative methods have been proposed, particularly for assessments made during pregnancy (2).

Evans blue dye dilution method. After intravenous administration, Evans blue dye binds to albumin, and its subsequent loss from the circulation is dependent on the rate of loss of albumin (32). The plasma concentration of Evans blue dye can be calculated spectrophotometrically by determining its absorbance at a specific wavelength. This method has limitations. For example, in turbid plasma, absorbance can be variable, and rapid escape from the intravascular space, leading to an overestimation of calculated PV, may occur (2,33). Despite these problems, this method remains useful in pregnancy and in other situations wherein the use of radiolabeled compounds is difficult or contraindicated.

Indocyanine green dilution method. After injection, indocyanine green is rapidly bound to plasma proteins before hepatic elimination (34). This method is safe in clinical practice (35); but the half-life of indocyanine green is short (36), and even minor inaccuracies in sampling time can lead to significant errors (34). Furthermore, the early sampling required by this method might not fully allow adequate mixing within the intravascular space, particularly in clinical scenarios associated with prolonged mixing time, such as CHF (37).

Other methods. High-molecular-weight dextran has a relatively long half-life and can be coupled to fluorescent compounds, thereby negating the need for radiolabels (38). Indeed, van Kreel et al. (39) found that the mean difference in PV when determined by both ¹²⁵I-HSA and dextran-70 techniques was only 6%. A potential limitation has been concern regarding allergic reactions (40).

It is possible to indirectly estimate percentage shifts in PV without knowledge of absolute values from serial concomitant hemoglobin and hematocrit concentrations using the following formula (41) (before = hemoglobin or hematocrit concentration at baseline, after = concentration after intervention):

$$\% \text{ Change in PV} = 100 \times \frac{\text{hemoglobin (before)}}{\text{hemoglobin (after)}} \times \frac{1 - \text{hematocrit (after)}}{1 - \text{hematocrit (before)}} - 100$$

Alternatively, PV can be measured at baseline using one

of the standard techniques and then subsequent changes may be followed indirectly with this method.

PLASMA VOLUME IN HF

To date, there have been few studies evaluating PV alterations in patients with HF. The majority of the available data refer to subjects already receiving conventional therapy such as diuretics and vasodilators, which may themselves influence PV. Anand et al. (4) performed a study comparing PV measurements in 6 patients presenting with untreated congestive HF and 11 healthy control subjects. These patients had significant fluid overload as evidenced by the presence of peripheral edema, elevated jugular venous pressure and ascites in three cases. Mean PV, determined by the ¹²⁵I-HSA method, was on average 34% higher in patients (57.9 ± 2.9 ml/kg) compared with control subjects (43.2 ± 3.0 ml/kg, *p* = 0.012). In patients with HF total body excess water averaged approximately 4 l per patient. This excess water was retained almost entirely within the extracellular space, with both extravascular and PV components increasing in approximately the same proportion (the total ECF rose by 33% and the PV rose by 34%). This was accompanied by the anticipated neurohormonal activation, with the patients with HF demonstrating significantly elevated plasma levels of norepinephrine, renin, aldosterone, ANP, growth hormone and cortisol. The authors concluded that in untreated edematous HF the natriuretic and vasodilatory influences of peptides such as ANP were overwhelmed by the opposing systems, leading to excess sodium and water retention. It therefore appears that in congestive HF underfilling of the arterial circulation occurs, despite an expanded plasma volume, and contributes to activation of the various neurohormonal responses. This further supports the theory that the neurohormonal response in CHF is an evolutionary mechanism aimed primarily at preserving arterial pressure (5,6).

In contrast, Feigenbaum et al. (42) determined PV, using the Evans blue dye technique, in 12 treated patients with clinically stable CHF (62.8 ± 8.2 years, New York Heart Association functional classification 2.5 ± 0.5, left ventricular ejection fraction 31.2 ± 9.7%, peak oxygen consumption 15.2 ± 3.3 ml/kg/min) and in 7 healthy control subjects (71.7 ± 5.3 years, peak oxygen consumption 26.0 ± 6.5 ml/kg/min). All patients were taking diuretics and angiotensin-converting-enzyme inhibitors, while eight were on beta-blockers. Plasma volume was actually contracted by approximately 23% in the treated patients with CHF when compared with controls (34 ± 12.9 ml/kg vs. 44.5 ± 9.0 ml/kg, *p* ≤ 0.05). Therefore, it appears that standard pharmacotherapy results in a contracted PV in stable CHF, a concept that is in contrast to the widely held belief that CHF is associated with long-term hypervolemia.

Although this study demonstrated the net effect of cardiovascular medications on PV in stable CHF, few data are available regarding the exact contributions of individual

drug classes. Diuretics are routinely prescribed for patients with CHF. The effect of diuretics on PV reduction has primarily been inferred from their acute influence on central hemodynamics (decrease in pulmonary capillary wedge pressure and cardiac output) (43) and subsequent neurohormonal response (increase in plasma renin and aldosterone, decrease in plasma ANP) (44,45), as well as their effect on body weight (46). Studies directly measuring PV shifts have produced conflicting results. Davidov et al. (47) demonstrated a 25% reduction in PV following administration of furosemide in CHF patients. In contrast, Schuster et al. (48) showed that intravenous furosemide actually expanded PV in critically ill patients with pulmonary edema. This was only seen in patients who did not have a significant diuretic response. There was no significant change in PV in the group who experienced a marked diuresis, suggesting that PV expands at a rate approximating to the volume removed by diuresis. The authors speculated that these results occurred secondary to furosemide-induced increases in venous capacitance and hence reduction in capillary hydrostatic pressure (although this effect could also result from a reduction in adrenergic activity associated with clinical improvement).

Whether PV is depressed in subjects receiving chronic diuretic therapy alone is not clear; the available evidence is conflicting and mainly relates to data obtained more than 25 years ago (49,50). In the study by Feigenbaum et al. (42), in which all patients were well diuresed, PV was contracted. These patients were, however, also receiving additional cardiovascular medications.

Less information is available regarding the effect on PV of other conventional therapies used in CHF. One might anticipate that angiotensin-converting enzyme inhibitors reduce PV via inhibition of the renin-angiotensin-aldosterone axis. Intravenous enalaprilat has been shown to reduce pulmonary artery wedge pressure and right atrial pressure without altering systemic vascular resistance, in keeping with PV reduction (51). Fouad et al. (52) evaluated the effect of captopril on PV, when added to optimized diuretic and digoxin therapy, in 19 patients with severe HF. Despite a reduction in body weight in the first week of treatment (presumed to be secondary to enhanced diuresis) the average PV increased significantly (from 100.83 ± 4.40 percent of normal to 105.37 ± 4.43 percent of normal, $p < 0.05$). The authors concluded that this was indicative of intravascular fluid shift. Plasma volume did, however, progressively decrease with longer follow-up (99.6 ± 3.88 percent of normal at one month and 92.3 ± 5.88 percent of normal at six months). In contrast, Herrlin et al. (53) were unable to demonstrate a change in PV after 12 weeks' treatment with enalapril, when added to diuretics and digoxin in eight subjects with moderate HF.

To our knowledge there have been no studies evaluating the direct effect of beta-blockers or digoxin on PV in HF. Studies have been performed following the introduction of beta-blockers in hypertensive patients. Propranolol had no

effect on PV in either the short term (three to six weeks) or long-term (five to six months) when used as monotherapy in the treatment of 14 hypertensive men (54).

A recent study examined the direct effect of infused low-dose ANP on PV and transcapillary escape of intravascular albumin in normal subjects (55). Initial PV was determined by the ^{125}I -HSA method. Subsequent change in PV was determined from alterations in hematocrit and hemoglobin measured at baseline and then after 1 h. The transcapillary escape of intravascular albumin was calculated from the percentage fall in ^{125}I -HSA occurring over 1 h. A reduction in PV and an enhanced transcapillary escape of intravascular albumin (after correction for volume change) was seen in response to ANP. The authors noted an increase in plasma albumin concentration and, therefore, concluded that the primary influence of ANP was on escape of intravascular fluid rather than albumin.

Assessment of PV has been performed in 15 patients with severe HF undergoing left ventricular assist device implantation, using the ^{125}I -HAS method (56). No control subjects were included in this study and PV measurements were merely compared to normal reference values. Although an improvement in cardiac function, together with reduction in circulating neurohormones, occurred following device implantation, this was not associated with a significant reduction in PV ($123 \pm 20\%$ of normal at baseline; $115 \pm 14\%$ eight weeks after device implantation, $p > 0.05$). The authors speculated that changes in PV might lag behind other physiologic and hemodynamic changes. Whether additional fluid volume within the device itself could influence the results remains uncertain.

In healthy people, PV does not remain static but instead demonstrates dynamic changes under certain conditions, such as exercise (1); PV decreases in a linear fashion when exercise intensity increases. This is primarily the result of fluid shift from the intravascular to the extravascular space. Acute exercise in stable patients with CHF also results in a reduction in PV, which is associated with an increase in hematocrit (57). In this study of 17 patients with CHF secondary to coronary artery disease, symptom-limited exercise resulted in an $11.10 \pm 1.22\%$ reduction in PV. The clinical relevance of this remains uncertain, but it has been suggested that an increase in hematocrit may be detrimental in patients with either ischemic heart disease or CHF by several mechanisms, including increased myocardial workload and a corresponding decrease in tissue oxygen delivery (58). Prolonged exposure to extreme altitude can also cause salt and water retention in normal subjects to a similar extent as that found in untreated congestive HF (59).

POTENTIAL APPLICATIONS FOR PLASMA VOLUME EVALUATION IN CHF

Many new therapies, directed toward neurohormonal systems integral to sodium and water regulation, are under evaluation for the treatment of CHF. It is important to

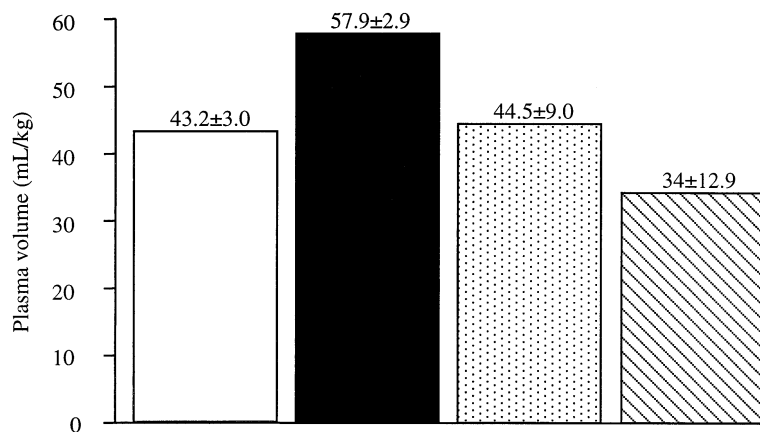


Figure 2. Amalgamated data on plasma volume measurements from the studies by Anand et al. (4) and Feigenbaum et al. (42), as assessed by human serum albumin labeled with radioactive iodine and Evans blue dye dilution method, respectively. Plasma volume was similar in both groups of control subjects. There is, however, a marked difference in plasma volume when comparing stable, well-treated patients with chronic heart failure (CHF) and untreated edematous patients in the two studies. This may reflect an increase in plasma volume in the order of 70% during an episode of decompensated heart failure. **White bar** = control subjects (4); **black bar** = edematous patients with CHF (4); **dotted bar** = control subjects (42); **diagonal bar** = treated patients with CHF (42).

establish what effect each therapeutic intervention has on PV. For example, many patients with CHF have impaired renal function, which could be further compromised by a decrease in perfusion associated with contraction of the PV. Hence, additional reduction in PV might not be desirable, and indeed may actually enhance activation of neurohormonal systems involved in sodium and water retention. With the associated vasoconstriction, this in turn may have adverse effects on left ventricular performance and long-term survival. Therefore, it may be desirable to perform an assessment of PV as part of the clinical assessment of the patient with CHF and combine this with neurohormonal and cytokine profiling (60) to determine the optimal combination of therapies.

Patients with decompensated HF in whom PV is contracted despite an increase in total ECF present a particular therapeutic challenge. In these circumstances monitoring PV may facilitate the tailoring of treatment, because inotropes or renal vasodilators may be more appropriate than intravenous diuretics alone.

No data are currently available regarding the alterations occurring in PV in response to intensified medication in patients with edematous CHF who have presented while already on treatment. It is likely that that significant reductions in PV occur in this setting. Anand et al. (4) confirmed that, when compared with healthy subjects, relative PV is expanded by 34% in patients with decompensated HF not receiving therapy. In contrast, Feigenbaum et al. (42) showed that relative PV is contracted by 23% in stable CHF patients when compared to controls. Although it is not possible to directly compare these studies because different methods were used for PV assessment (although the PVs in the control groups were very similar at 44.5 and 43.3 ml/kg), it seems reasonable to speculate that PV could decrease by as much as 40% following intensified treatment for decompensated CHF (Fig. 2). (Conversely, PV might

increase by as much as 70% during an episode of decompensated HF.) This is likely to have important implications when assessing alterations in plasma concentrations of molecules during this transition. For example, our group has previously demonstrated that elevated plasma levels of endotoxin (lipopolysaccharide) are seen in edematous CHF and levels decrease after an intensified diuresis associated with a reduction in weight of about 5 kg (61). This was taken as support for the hypothesis that translocation of endotoxin occurs across the edematous bowel wall and subsequently acts as a stimulus of the immune system (62). (In CHF immune activation is associated with an adverse prognosis [63] and it has been suggested that it may play a central role in the pathogenesis of this complicated syndrome [64].) This study (61) also confirmed that proinflammatory cytokines are elevated in CHF patients with peripheral edema. However, as with other studies (65), following restoration of the nonedematous state cytokine levels did not immediately return to baseline values found in stable CHF. Although this could result from long-term activation of monocytes or macrophages after exposure to endotoxin, it is also likely to be influenced by marked alterations in PV. Therefore, if as anticipated PV is reduced (perhaps by as much as 40% after intensified medical therapy and resultant diuresis), it is possible that the expansion of the intravascular compartment in the edematous state leads to an underappreciation of the burden of circulating cytokines. When considering a potentially toxic substance and following patients over time, one might speculate that the absolute circulating load is more relevant than the measured concentration. A comparison of circulating levels of cytokines (concentrations corrected for PV) would perhaps be more fitting when comparing the edematous and nonedematous states. We are currently undertaking studies in an attempt to clarify this important issue.

CONCLUSIONS

Regulation of sodium and water and hence PV is achieved by a complex series of neurohormonal interactions. Plasma volume determination, previously the concern of hematology departments, is now primarily performed in the nuclear medicine setting. This will enhance the access of this technique to cardiologists for both clinical and research perspectives. Although many methods are available to measure PV, the ¹²⁵I-HSA technique remains the standard. Limited data are available regarding PV measurement in patients with HF. The available data show that PV changes according to the clinical setting. Whereas PV appears to be expanded in edematous subjects before therapeutic intervention, it is contracted in patients with stable CHF treated with conventional therapy. Little is known, however, of how PV alterations relate to HF symptoms or how intensification of conventional treatment in CHF influences PV.

The measurement of PV may well be helpful in the clinical assessment of selected patients with CHF, thereby enabling the tailoring of increasingly complex combinations of therapies. Furthermore, it is important to evaluate how newer therapies for CHF patients affect PV. It is our contention that significant alterations of PV occur in subjects undergoing intensified treatment for decompensated CHF and that this might help to explain some of the paradoxes encountered when evaluating changes in plasma concentrations of various proinflammatory cytokines. More studies are required to clarify these important questions.

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