

Fluid overload contributing to heart failure

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Abstract

Background. In advanced heart failure, the compensatory responses to reduced cardiac output, in spite of fluid retention, lead to maladaptive consequences.

Methods. We performed a Medline survey for fluid overload and heart failure as well as reviewing textbook chapters.

Results. The increased sympathetic nervous system, renin–angiotensin–aldosterone system, and anti-diuretic hormone stimulation and release lead to a vicious cycle—augmenting pre-load, contractility and after-load, as well as increased fluid overload. The elevated work load on an already failed cardio-circulatory system results in further deterioration. Plasma volume is usually increased in untreated patients with increased extracellular fluid. However, it may range from reduced to increased in treated patients. Currently, diuretics remain the initial first line of therapy. In refractory cases, restoring plasma volume and osmolality, by adding albumin or hypertonic saline solutions, neurohormonal antagonists such as vasopressin receptors antagonists, aldosterone antagonists, or administration of nesiritide, may help in overcoming fluid overload.

Conclusion. Exact measurement of plasma volume in various forms of heart failure and adjusting the treatment accordingly, establishing favourable and detrimental effects of various therapies, and introducing additional and new therapeutic options require further investigation.

Keywords: fluid overload; heart failure; neurohormonal activation

Introduction

In normal subjects, extracellular volume (ECV), which comprises plasma (intravascular) and interstitial (extravascular) compartments, remains constant at wide ranges of sodium and water intake. The importance of homeostatic mechanisms had already been described by Claude Bernard in 1885 [1], and the pivotal role of the kidney in body fluid homeostasis by Ernest Starling in 1909 [2]. Sodium, the main extracellular ion, which makes up >90% of total solutes of extracellular fluid, largely determines the extracellular osmotic pressure. Therefore, sodium balance keeps the extracellular volume normal by sodium intake and its excretion by the kidney.

Modes of heart failure

In order to facilitate the evaluation of heart failure (HF) patients, several forms of HF have been suggested (Table 1). It should be emphasized that this subdivision of HF is an oversimplification. Actually, we seldom find a patient who has a single, pure form of HF. However, using this mode of classification improves our clinical, diagnostic and therapeutic approaches.

Plasma volume is expanded in patients who present with advanced HF. James Hope in 1832 [3] and Ernest Starling in 1896 [4] had described fluid retention in the syndrome of HF. James Hope proposed the backward failure hypothesis that when the ventricle fails to discharge its contents, blood accumulates

Table 1. Forms of heart failure

Forward	Backward
Right-sided	Left-sided
Wet	Dry
Acute	Chronic
Low-output	High-output
Systolic	Diastolic

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and pressure rises in the atrium and venous system emptying into it [3]. Mackenzie proposed the forward HF hypothesis, emphasizing the reduced cardiac output, which results in diminished organ and tissue perfusion, including the kidney [5].

Methods

We performed a Medline search using the search terms fluid overload and heart failure. Additionally, we reviewed chapters in cardiology, heart failure and internal medicine textbooks.

Results

Body fluid regulation

In patients with mild to moderate congestive heart failure (CHF), the kidneys are intrinsically normal, and when transplanted to a patient without HF they function normally [6]. The efferent mechanisms in the kidney operate to conserve sodium and water and are presumably abnormally active in CHF patients, despite ECV expansion. The renal afferent mechanisms also retain salt and water. A decrease in blood volume and cardiac output has been considered to trigger fluid retention [5]. However, plasma volume (PV) is actually increased in many patients, and cardiac output may be normal or even increased in subsets of HF patients with fluid retention, i.e. high-output or diastolic dysfunction.

Neurohormonal activation

In recent decades, the role of neurohormonal mechanisms in maintaining water and sodium balance in normal subjects, and neurohormonal activation in HF has been established. As a result of reduced cardiac output and hypoperfusion of vital organs, increased neurohormonal activity takes place, in order to restore circulatory homeostasis. However, this neurohormonal activation increases the workload of an already failing cardio-circulatory system. Consequently, cardiac function further deteriorates. The intensity of the neurohormonal activation and the neurohormonal plasma levels correlate with the severity of HF and survival, and the plasma levels, especially of brain natriuretic peptide (BNP), are currently useful as a diagnostic and prognostic tool.

The renin–angiotensin–aldosterone system (RAAS), which is activated in patients with HF, has a role in sodium and water retention. In normal subjects, pharmacological doses of aldosterone cause only limited sodium retention without oedema [7]. However, HF patients, do not ‘escape’ from the sodium-retaining effects of aldosterone, and they increase their water retention, presumably due also to the increased levels of angiotensin II [8–10].

Increased adrenergic activity acutely acts predominantly on the heart by augmenting contractility and

increasing after-load, but chronically enhances cardiac remodelling and myocyte apoptosis, resulting in reduced cardiac output. In addition, elevated sympathetic and other neurohormonal activity increase vascular permeability [11]. Catecholamines are also involved in the release of other neurohormones, such as renin, aldosterone and arginine vasopressin (AVP). The reduced arterial filling activates the baroreceptors, located in the carotid sinus, aortic arch and left ventricle. This baroreceptor activation stimulates the sympathetic nervous system, causing increased cardiac contractility and heart rate, and peripheral vasoconstriction, as well as additional neurohormonal activation [8].

AVP is very sensitive to osmotic changes. As little as a 1–2% change in extracellular fluid osmolality alters AVP release to maintain normal osmolality. HF patients frequently have sometimes quite severe hypo-osmolality [8,12]. Despite hyponatraemia in patients with HF, plasma levels are increased, due to non-osmolar release [13,14].

The natriuretic peptides—atrial natriuretic peptide (ANP) and BNP—cause vasodilatation and natriuresis and counteract the water-retaining effects of the adrenergic, RAAS and AVP systems. Their circulating levels are markedly elevated in HF patients with fluid retention. The haemodynamic and natriuretic responses to ANP infusion are attenuated in patients and animal with experimental HF [15]. ANP receptor antagonist administration in dogs with HF showed, that despite the attenuated effects, the natriuretic peptides exert a suppressive effect on renin, angiotensin II and norepinephrine levels and activity [16].

Endothelin, various growth factors and cytokines also have detrimental effects in the development of HF.

It should be emphasized that even normal levels of these hormones in HF are excessively high, considering PV expansion, that would actually suppress hormonal discharge in normal subjects (this suppression may occur only at early and mild stages of heart failure) [8].

Plasma volume

About 85% of PV is on the venous side of the circulation, and only ~15% is on the arterial side, which is <2% of total body fluid. It could be hypothesized that PV is expanded in cardiac failure, yet arterial underfilling could occur due to decreased cardiac output. However, salt and water retention by the kidney can also occur when cardiac output is increased, such as in pregnancy, cirrhosis and other high-output states. Schrier and Ecder [8] hypothesized that arterial underfilling can be caused by a decrease in either cardiac output or peripheral vascular resistance (vasodilatation). The neurohormonal, haemodynamic and renal responses are compensatory mechanisms to restore arterial circulatory integrity. Low-output HF causes an increase in peripheral vascular resistance, while reduced afterload usually increases cardiac output [8].

We found only a few studies measuring plasma volume and blood volume in HF patients [17–19]. Anand *et al.* [17] studied 11 control subjects and eight untreated HF patients with a cardiac index of 1.8 l/min/m^2 , a pulmonary wedge pressure of 30 mmHg and right atrial pressure of 15 mmHg. Their total body content, ECV, PV and blood volume (BV) were 16, 33 and 34% above control, respectively. Total exchangeable sodium was 37% above control, and renal plasma flow and glomerular filtration rate were reduced to -29% and 65% of those of control subjects. Feigenbaum and colleagues [18] studied 12 men with HF of ischaemic aetiology treated with diuretics and angiotensin-converting enzyme inhibitors and eight patients treated with β -blockers. They compared them with seven matched control subjects. In the HF patients, relative PV and BV were decreased to -23.4% and 17.4% , respectively. Androne and co-workers [19] measured the plasma volume in 37 patients with advanced heart failure, who also had anaemia. Seventeen patients (46%) had normal red blood cell (RBC) volume with 49% excess PV, resulting in haemodilution, while 20 true anaemia patients (54%) had a 23% deficit in RBC volume and 20% PV excess [19]. These paradoxical findings are probably the result of relatively small studies. In addition, while in the Anand *et al.* series the patients were untreated and had increased PV as well as ECV, in the other two studies the patients received medications, including diuretics. PV varied from excess to contraction, due to treatment differences, mainly the extent of the diuretic therapy.

Treatment

The options available to treat patients with advanced HF and fluid retention range from massive diuresis to biventricular pacing, haemofiltration, dialysis, left ventricular assist device and heart transplantation.

Generally, our initial goal in these patients is to bring them by diuresis towards the dry side. In our practice, we use loop diuretics in increasing dosages either in the form of tablets orally, or administration of either oral solution or intravenous furosemide. Concomitant administration of intravenous aminophyllin and furosemide may potentiate diuresis. Another effective approach is targeting various nephron sites to achieve synergistic effects [20]. Acetazolamide acts at the proximal convoluted tubule and is mainly used in glaucoma patients, or for correcting metabolic alkalosis, which sometimes accompanies excessive loop diuretic therapy. Adding thiazides, which act at the distal convoluted tubule, and/or potassium-sparing diuretics, which act at the collecting system, usually increases diuresis. The excessive diuretic therapy reduces PV, and may further impair renal function. In refractory cases, frequently elderly patients with advanced HF, lack of response to diuresis necessitates additional therapy. Reversal of arterial underfilling may increase water excretion, improve urinary dilution and significantly reduce

plasma neurohormones [14]. Infusion of hypertonic saline has been used for several decades in conditions with multiple organ underperfusion, such as haemorrhagic or septic shock [21]. The hyperosmolar sodium solution restores PV by mobilizing extravascular fluid into the intravascular space by the osmotic gradient, reduces tissue oedema, maintains cardiac output and subsequently causes peripheral arterial vasodilatation, increases renal blood flow, and may enhance renal response to diuretic therapy. Concomitant administration of albumin and furosemide may increase plasma osmolality and volume, enhance renal blood flow and increase diuretic response [22]. Licata *et al.* have recently described favourable effects of a high dose of furosemide (500–1000 mg) with a small volume (150 ml) of hypertonic saline (1.4–4.6%), depending on the patient's baseline serum sodium level measured, twice daily [23]. Drazner and Palmer remind us that this therapy is still unconventional, and the traditional approach to decompensated HF patients is still dietary salt restriction, water restriction and avoidance of intravenous sodium solutions [24]. However, they conclude that a hypertonic saline solution or more modest dietary salt restriction may change our practice, but requires further studies.

Neurohormonal modulation

Administration of selective V_2 or dual V_{1a}/V_2 antidiuretic receptor antagonists, tolvactan and conivactan, respectively, significantly increased free water excretion and plasma osmolality, corrected hyponatraemia and clinically improved patients with fluid overload due to HF [25].

Spironolactone, an aldosterone antagonist, when given in sufficient doses [6], causes marked natriuresis, especially in patients with marked fluid retention.

Recently, a recombinant human BNP, nesiritide, intravenously administered resulted in significant haemodynamic and clinical improvement in advanced decompensated HF patients, and currently has become an established treatment in patients with severe CHF [26,27].

Summary

In advanced HF, the compensatory responses to reduced cardiac output, arterial underfilling and organ and tissue hypoperfusion in spite of fluid retention lead to maladaptive consequences. The increased sympathetic nervous system, RAAS, and AVP stimulation and release leads to a vicious cycle, increasing preload, contractility and afterload, as well as increased fluid overload. The increased work load on an already failed cardio-circulatory system results in further deterioration. PV is usually increased in untreated patients with increased ECV. However, PV may range from reduced to increased values in treated patients. Currently, diuretics remain the initial first line of therapy. In refractory cases, restoring PV and osmolality, by adding albumin or a hypertonic

saline solution, neurohormonal antagonists such as vasopressin receptors antagonists, aldosterone antagonists, or administration of nesiritide may overcome fluid overload in HF patients.

Conclusion

Exact measurement of PV in various forms of HF and adjusting treatment accordingly, establishing favourable and detrimental effects of various therapies, and introducing additional and new therapeutic options require further investigation.

Conflict of interest statement. None declared.

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