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CRITICAL CARE

REVIEW

Supporting hemodynamics: what should we target? What treatments should we use?

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Abstract

Assessment and monitoring of hemodynamics is a cornerstone in critically ill patients as hemodynamic alteration may become life-threatening in a few minutes. Defining normal values in critically ill patients is not easy, because 'normality' is usually referred to healthy subjects at rest. Defining 'adequate' hemodynamics is easier, which embeds whatever pressure and flow set is sufficient to maintain the aerobic metabolism. We will refer to the unifying hypothesis proposed by Schrier several years ago. Accordingly, the alteration of three independent variables – heart (contractility and rate), vascular tone and intravascular volume – may lead to underfilling of the arterial tree, associated with reduced (as during myocardial infarction or hemorrhage) or expanded (sepsis or cirrhosis) plasma volume. The underfilling is sensed by the arterial baroreceptors, which activate primarily the sympathetic nervous system and renin–angiotensin–aldosterone system, as well as vasopressin, to restore the arterial filling by increasing the vascular tone and retaining sodium and water. Under 'normal' conditions, therefore, the homeostatic system is not activated and water/sodium excretion, heart rate and oxygen extraction are in the range found in normal subjects. When arterial underfilling occurs, the mechanisms are activated (sodium and water retention) – associated with low central venous oxygen saturation ($ScvO_2$) if underfilling is caused by low flow/hypovolemia, or with normal/high $ScvO_2$ if associated with high flow/hypervolemia. Although the correction of hemodynamics should be towards the correction of the independent determinants, the usual therapy performed is volume infusion. An accepted target is $ScvO_2$ >70%, although this ignores the arterial underfilling associated with volume expansion/high flow. For large-volume resuscitation the worst solution is normal saline solution (chloride load, strong ion difference = 0, acidosis). To avoid changes in acid–base equilibrium the strong ion difference of the infused solution should be equal to the baseline bicarbonate concentration.

Introduction

Hemodynamic assessment is one of the cornerstones of critical care medicine, as hemodynamic alterations may become life-threatening in minutes. Assuring normal hemodynamic values is therefore mandatory to allow one to buy time for patient healing. The problem arises when we have to define normal hemodynamics in critically ill patients. If we are able to define normal hemodynamics, the target values for therapy will follow. In this brief opinion paper we will limit ourselves to the macrohemodynamics and we will discuss the determinants of hemodynamic impairment, the limits of normal, impaired and failing hemodynamics, and the volume therapy to be applied.

Determinants of hemodynamic impairment

We believe the best approach to this issue is the one proposed by Schrier [1], who – based on a series of studies [2,3] – finally introduced a unifying hypothesis to explain the hemodynamic impairment associated with different diseases or syndromes. His approach, slightly modified, is presented in Figure 1, which summarizes the hemodynamic determinants, the neuro-endocrinal signaling and the body response. In this framework we may first consider which variables are independent. These variables belong to three categories: the heart (contractility and heart rate), the vascular tone and, finally, the intravascular volume. In a given disease or syndrome one or more of these variables may be affected. As an example, acute myocardial infarction is paradigmatic of the problems relative to heart contractility and/or rate. A primary alteration of the vascular tone is typical of

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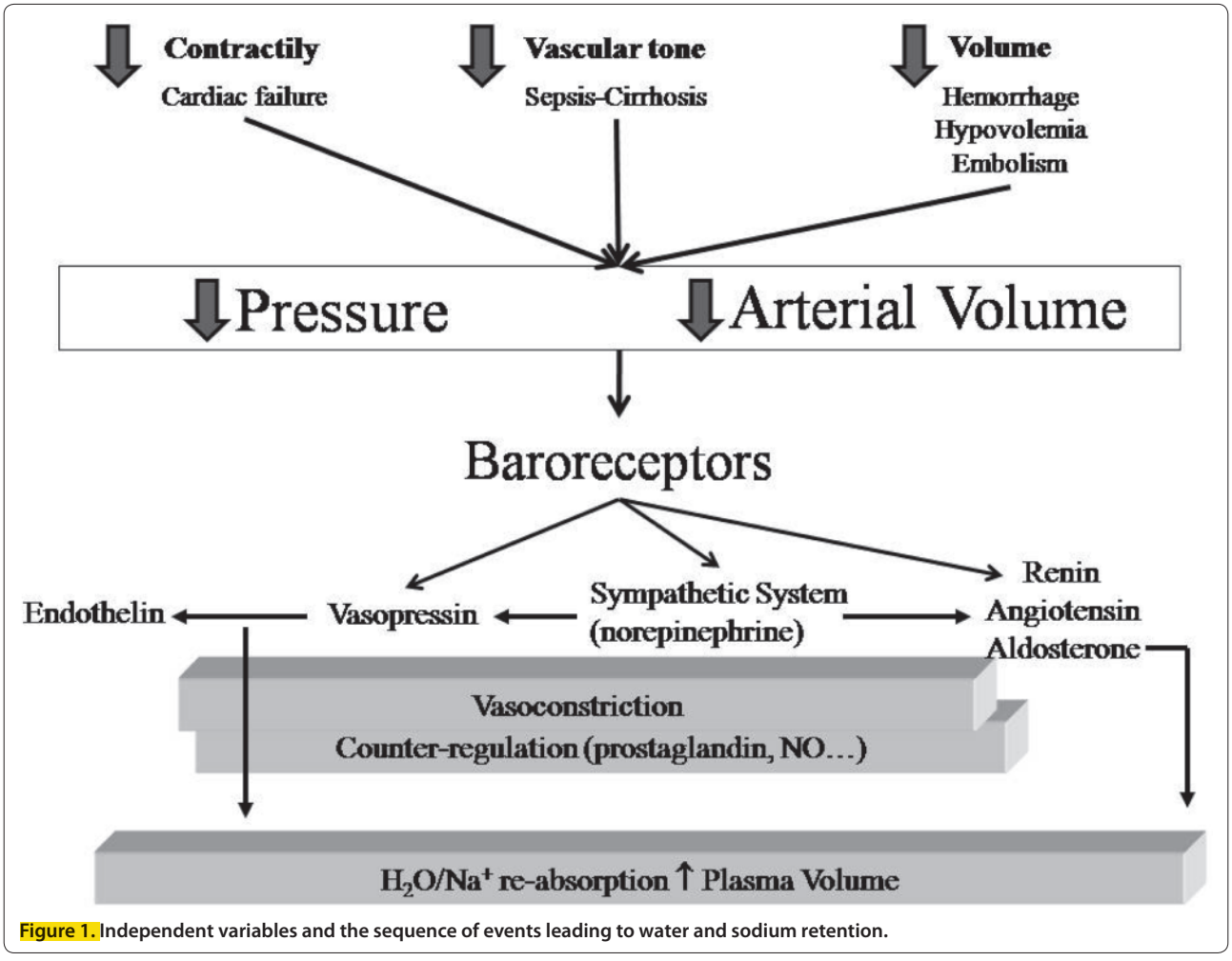

Figure 1. Independent variables and the sequence of events leading to water and sodium retention.

cirrhosis and septic syndrome. A decreased intravascular volume is typical of hemorrhage. In critically ill patients more than one variable may be altered at the same time, as in sepsis where the impairment of heart contractility and the decrease of intravascular volume due to capillary leakage may be associated with the decrease of the primary artery vessel tone.

We believe that physicians approaching the hemodynamic status of a given patient should first consider which independent determinants are more probably altered. Of interest to note, however, is that, among the primary determinants, the heart rate is the only one always assessed in clinical practice. The contractility measured by echocardiography is occasionally assessed while the vascular tone and the intravascular volume are not measured. One must note that the variables usually evaluated to assess hemodynamics and volemia, such as pressures and flows, are dependent variables that, when altered, may recognize different causes. The identification of or, at least, the estimate of which of the independent hemodynamic determinants is altered makes the therapy a logical consequence. Unfortunately, independent of the altered variable, the first intervention is usually volume replacement. A typical example is represented by hypotension following the induction of anesthesia. In this case the primary cause of hemodynamic impairment is the pharmacologically-induced decrease of the vessel tone but the correction is usually performed by volume infusion.

The baroreceptors, located in the carotid and aortic arch [4], sense the underfilling of the arterial tree (which in a normal situation contains 15% of the intravascular blood volume). This underfilling may be caused either by a decreased intrathoracic volume or cardiac output, as typically occurs during hemorrhage or heart failure, or by arterial vasodilation, as may occur in cirrhosis or sepsis. Interestingly, one must bear in mind that the concept of arterial tree underfilling, which, in some way, recalls the concept of effective circulating blood volume [5,6], may co-exist either with hypovolemia or with hypervolemia, as most of the expanded blood volume may be confined in the venous tract, which acts as a capacitive reservoir.

Whatever the cause of the arterial tree underfilling, the body response is similar and primarily consists of activation, via baroreceptors, of the renin–angiotensin–aldosterone system and the nonosmotic release of vasopressin [7]. As shown in Figure 1 other factors may be activated, and a counter-regulation may occur. It is important, however, to realize that the primary body response is directed towards the integrity of the arterial circulation, by maximizing, through the kidneys, the reabsorption of salt and water, while increasing the arterial pressure. There are several elements in favor of this unifying hypothesis, as recently reviewed [7]. Here it is sufficient to say that different diseases or syndromes in which underfilling may occur, with or without plasma expansion, present increased renin, angiotensin and aldosterone levels as well as an increase of vasopressin (anti-diuretic hormone) despite a frequently associated hypo-osmolarity. In general, we believe that the hemodynamic problem and, possibly, the therapeutic interventions may be better understood if considered in this framework.

Normal hemodynamic, hemodynamic impairment and hemodynamic failure

The concept of normal hemodynamics is not easy to define in critically ill patients. In general, we believe that hemodynamics is adequate when the oxygen delivery to the tissues is sufficient to maintain an aerobic metabolism. This may occur in critically ill patients at hemodynamic values greater than or lower than the values considered normal in healthy subjects at rest. As an example, in cases of decreased hemoglobin content and/or its oxygen saturation, a frequent finding in the ICU, or if hypermetabolism is present, the cardiac output must be greater than normal to provide adequate oxygen transport. In contrast, when the metabolic requirements are reduced, as may occur in critically ill patients during deep sedation or paralysis, the aerobic metabolism may be satisfied with a hemodynamic set of values lower than those considered normal in healthy subjects. In other words, the normality of hemodynamics should not be judged considering the hemodynamic values *per se*, but instead the body response. When the body senses its hemodynamic set as adequate, the baroreceptors may be activated or not activated. If the easily measured variables such as heart rate, urinary output and sodium concentration in the urine remain in the range found in normal subjects, we may assume that the hemodynamics is normal and, obviously, adequate.

In the presence of abnormal hemodynamic values, either greater or lower than normal, the hemodynamics may be still adequate if it guarantees an aerobic metabolism. This metabolism is obtained by activating all of the homeostatic mechanisms described above. The hemodynamics then becomes inadequate (hemodynamic failure) only when signs of anaerobic metabolism appear, despite the full activation of the mechanisms normally operating to maintain homeostasis. The most recognizable and easy measurable output of such mechanisms are water and sodium retention [1] as judged at least 6 hours after withdrawal of diuretic therapy (too often misused in intensive care). This response, at least in the early phase, should not be confused with kidney failure. On the contrary, the response may be a sign of the maximal response of a normal kidney activated by the sympathetic system and subjected to vasopressin. What is not usually realized is the speed of the change in sodium urine concentration when the system is activated [8]. Figure 2, as an example, presents the electrolyte changes during controlled hemorrhage. As shown, the kidney reacts to the blood volume decrease by retaining sodium earlier than significant changes in mean arterial pressure may be detected.

If the underfilling is caused by decreased blood volume or cardiac output, the water and sodium retention is generally associated with an increased tissue oxygen extraction, as indicated by a decrease in central venous oxygen saturation ($ScvO_2$). This is, in our opinion, a reasonable surrogate of the mixed venous saturation [9,10]. We may express $ScvO_2$ as a function of its determinants according to the following formula:

$$ScvO_2 = SaO_2 - (VO_2/Q)\times 1/Hb$$

As shown, central venous saturation depends on the arterial oxygenation (SaO_2), on the appropriate match between oxygen consumption/metabolic requirement (VO_2) and on cardiac output (Q), as well as on the oxygen carrier (Hb). All determinants of oxygen transport, as well as the metabolic rate, may influence the central venous saturation, which is an extremely sensitive, although not specific, indicator of changes in respiratory function (SaO_2), metabolism (VO_2), cardiac output (Q) and oxygen carrier (Hb). The physiological meaning of $ScvO_2$ may also be expressed as:

$$ScvO_2 = 1 - VO_2/DO_2$$

This equation indicates that oxygen venous saturation reflects the residual amount of oxygen in the venous side after consumption (VO_2) of part of the oxygen delivered (DO_2). In normal conditions, at rest, the amount of oxygen extracted from the oxygen delivered is about 25% (VO_2/DO_2). The $ScvO_2$ is therefore around 75%. The arbitrary recommended threshold of $ScvO_2$ used in several studies and in guidelines for sepsis treatment is 70% [11-14]. One must note, however, that $ScvO_2$ lower than the threshold is not necessarily associated with anaerobic metabolism.

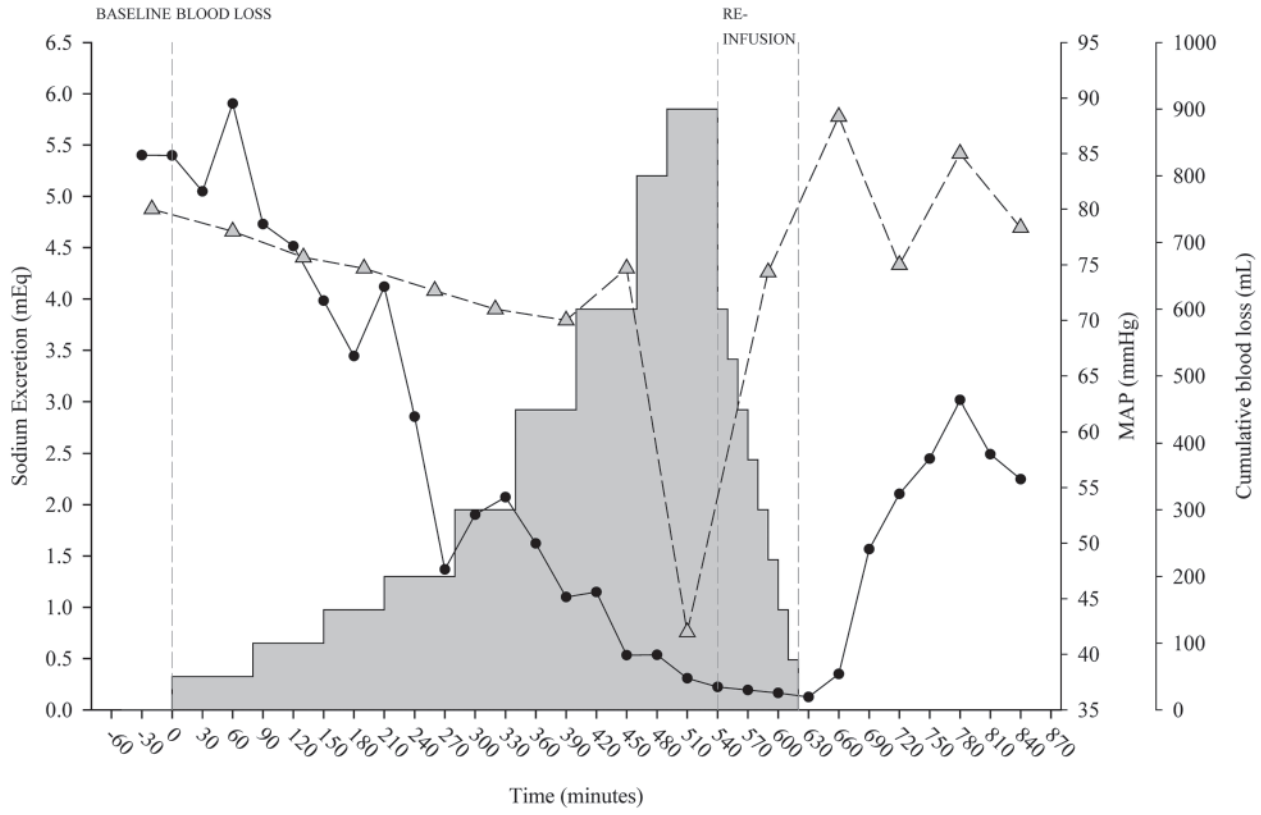

Figure 2. Sodium excretion and mean arterial pressure during controlled hemorrhage and reinfusion. The amount of sodium excreted (computed as the product of sodium concentration and urine amount) in 30 minutes (black circles) and the mean arterial pressure (MAP; grey triangles) during controlled hemorrhage and reinfusion (grey area plot) in an experimental swine model. Vertical grey dashed lines indicate the end of baseline/beginning of hemorrhage, end of hemorrhage/beginning of reinfusion and end of reinfusion. As shown, the kidney reacts to the blood volume decrease by retaining sodium and reducing urine volume earlier than significant changes in MAP may be detected. Courtesy of Dr A Protti.

As an example in healthy subjects during physical exercise, $ScvO_2$ may decrease to 40% while maintaining aerobiosis, because in this condition cardiac output remarkably increases. The most frequent reason for a decrease in $ScvO_2$ in the ICU is cardiac failure. In the framework of the unifying arterial tree underfilling hypothesis, the association between sodium/water retention and low $ScvO_2$ is a strong indicator of underfilling due to low flow and/or hypovolemia, as typically observed during heart failure, hemorrhage and dehydration. In contrast, when the underfilling is due to the arterial vasodilatation associated with volume expansion or elevated cardiac output, as in cirrhosis or in some phases of sepsis, $ScvO_2$ may be higher than 70 to 75%. Therefore, it is important to realize that even normal or higher than normal $ScvO_2$ may be associated with abnormalities of hemodynamics, as assessed by activation of the renin–angiotensin–aldosterone system and vasopressin release. Considering water/sodium retention and hypo-$ScvO_2$ or hyper-$ScvO_2$ together may therefore indicate whether the arterial tree underfilling is primarily due to low heart contractility/hypovolemia or vasodilatation, respectively. Obviously this is an oversimplification of the problem, but we believe that this approach may provide a reasonable framework when considering the hemodynamic set in a given patient.

When all of the compensatory mechanisms are overcome, the hemodynamic failure is overt and its marker is the appearance of metabolic acidosis associated with increased plasma lactate concentration. We believe that the best approach to understand the relationship between metabolic acidosis and lactate in tissue hypoxia has been provided by Hochachka and Mommsen [15], who elegantly showed how lactate production and ATP hydrolysis are coupled and must be considered together. Here it is enough to say that the appearance of acidosis indicates the energy failure of a group of cells that, in the absence of correction, may result in cellular death after a few hours.

Figure 3 reports the impressive relationship between metabolic acidosis and mortality in a general population of critically ill patients. In contrast, elevated metabolic alkalosis, usually caused by diuretic therapy, is not associated with increased mortality. Beyond pH, several

approaches have been proposed to assess the hemodynamic failure [16,17], such as base excess, lactate, decreased strong ion difference (SID), increased anion gap, increased venous to arterial difference in partial pressure of carbon dioxide (PCO_2) and its ratio to the arterial–venous oxygen content. All these variables, however, are just different facets of the same reality; that is, the perturbation of the acid–base equilibrium due to nonvolatile acid load, originating from suffering cells (lactate) or dead cells (intracellular strong acid content is higher than plasma content). In mammalians, when metabolic acidosis starts due to the hemodynamic failure, the time for correction is limited before irreversible mitochondrial damages and cell death occurs.

Treatment target

The ultimate goal of the intervention on hemodynamics is to guarantee the maintenance of full aerobic metabolism. The hemodynamic correction may therefore be considered a symptomatic treatment allowing buying time for the cure of the underlying disease. According to Figure 1, the most rational therapy to correct the hemodynamic alterations should be addressed to the correction of the pathogenetic mechanisms; that is, heart contractility/rate, vascular tone or intravascular volume. In clinical practice, independent of the variable primarily altered, the first intervention is usually the volume replacement, according to the following sequence: first, volume; second, cardioactive drugs; and third, blood.

The most popular hemodynamic target, at least in sepsis, is to reach or maintain $ScvO_2$ >70% [13,14]. This has been popularized by Rivers and colleagues' study [12], in which the septic patients at entry had baseline $ScvO_2$ <50%. Targeting $ScvO_2$ of 70%, Rivers and colleagues obtained a significant improvement of the survival rate. In contrast, in a previous study, we could not find any difference in outcome in the same kind of patients with a similar target [11]. The baseline SvO_2 of these patients, however, was 68% – remarkably different from that in Rivers and colleagues' study. We also found that targeting SvO_2 of 70% was analogous to target a cardiac index of 2.5 l/minute/m^2. The most plausible explanation for the discrepancy between these studies is the time of intervention: earlier in Rivers and colleagues' study, in the emergency room; and later in our study, after admission to the ICU. However, one should note that all these studies focused on problems associated with a low SvO_2 state, ignoring the possible hemodynamic derangements occurring in high SvO_2 states.

Volume replacement

Fluid challenge

Volume replacement treatment requires assessment of the patient's intravascular volume status (cardiac preload)

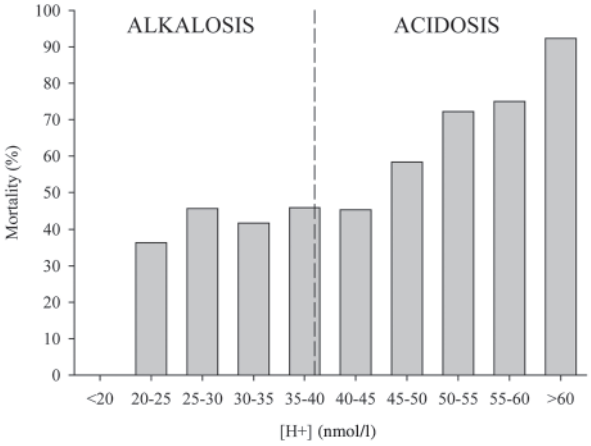

Figure 3. Relationship between acidosis/alkalosis and mortality in critically ill patients. Relationship between acidosis/alkalosis (expressed as hydrogen ion concentration) and mortality in a general population of 754 critically ill patients (data recorded at entry to the ICU).

and the likelihood of responsiveness (that is, increase the stroke volume) to a fluid challenge test. In fact, data suggest that about 50% of the critically ill patients positively respond to challenge tests [18-20]. Multiple tools have been suggested as indicators for fluid administration, most of them as predictors of response and as targets [21]. Clinical signs, such as thirst, skin turgor, blood pressure, urine output, and so forth, are unreliable indexes of intravascular volume status. Similarly, cardiac filling pressures (central venous pressure (CVP) and pulmonary artery occlusion pressure) that have been traditionally used to guide fluid management are poor predictors [22]. CVP has been used for over 40 years to guide fluid management, as an indicator of intravascular volume (values <8 cmH_2O indicate hemodynamic impairment), even though this relationship has not been proven. Other techniques, based on echocardiography, such as left ventricular end-diastolic area, or based on thermodilution, such as global end-diastolic volume index, gave unsatisfying results [18].

CVP has been used for decades as an indirect measure of left ventricle preload as it well approximates the right atrial pressure, the major determinant of right ventricle filling [23,24]. Moreover, changes in CVP in response to fluid challenge tests have been used to predict volume responsiveness (target 8 to 12 cmH_2O) [13]. However, there is increasing evidence that – due to a series of variables, such as venous tone, intrathoracic pressures, ventricular compliances and geometry variations, occurring in critically ill patients – the relationship between CVP and right ventricular end-diastolic volume is poor and that CVP (absolute or changes) does not correlate with volume responsiveness [19]. Similar problems were

encountered when referring to the pulmonary artery occlusion pressure [25,26].

During the past decades a number of dynamic tests have been used to dynamically monitor the changes in stroke volume after a maneuver that modifies venous return. These methods have been found more reliable and less invasive than static ones [24].

Heart–lung interaction during mechanical ventilation has been used to evaluate the variations in stroke volume, systolic pressure and pulse pressure. Pulse pressure variation estimated from the arterial waveform and stroke volume variations from pulse contour analysis and pulse oximeter plethysmographic waveform variations have been found to be reliable predictors of a positive response to challenge tests [20]. These hemodynamic effects are due to the cyclic increase/decrease of intrathoracic pressures during mechanical ventilation, affecting right and left ventricular preloads and afterloads. During insufflation, the increased intrathoracic pressures reduce right ventricular stroke volume and increase left ventricular stroke volume. After the blood pulmonary artery transit time (nearly two or three heart beats) even the left ventricular preload decreases with a consequent stroke volume decrease, which is at its minimum value during end expiration. A ventilation-induced change in left ventricle stroke volume of 12 to 13% has been reported highly predictive of volume responsiveness [20]. These methods, however, have some limitations, including the use of tidal volume normalized on ideal body weight >8 ml/kg and the absence of either spontaneous respiratory activity or arrhythmias [27].

Other dynamic tests have been proposed as reliable methods to assess volume replacement responsiveness. These include Doppler echocardiography to assess changes in aortic flow velocity and stroke volume [28,29] and changes in venocaval diameter during positive pressure ventilation estimated by echocardiography [30-33]. The end-expiratory occlusion test consists of the interruption of mechanical ventilation for 15 seconds to suppress the cyclic decrease of cardiac preload during insufflations. The procedure should increase cardiac preload, and an increase of 5% in cardiac output and arterial pulse pressure should predict fluid responsiveness [34]. Finally, passive leg raising has been proposed as an autotransfusion method independent of mechanical ventilation [35]. In conclusion, there is no gold standard clinically available to assess the volume status of the patient. However, the combined use of different methods may provide, in our opinion, an excellent assessment of the hemodynamic status.

Which fluid?

Three kinds of fluids are available: crystalloids, artificial colloids and albumin. Although a definitive indication of the superiority of one fluid compared with the others is still not available, the data obtained in the last few years have provided, to different extents, some indications. In our opinion, however, discussion of the benefits/risks of the different solutions only applies when large volumes are infused in a relatively short time. Modest infusion, such as 1 to 1.5 l over 24 hours, is likely to be clinically irrelevant. We may roughly divide the effects of the infusion into two main arms: effects due to the volume of the infusion, independent of composition of the solution; and effects due to the quality of the infusion, dependent on the kind of and quantity of solutes present in the fluid replacement.

In critically ill patients, the most general indication for large-volume resuscitation is the refilling of the blood vessels (note that the volume infused is not necessarily proportionally distributed between the arterial and venous trees). Traditionally, we thought that to achieve the same intravascular volume the amount of crystalloids compared with colloids should be in a ratio of 3:1 [13,36]. The most recent large trials comparing colloids and crystalloids, however, indicate that this figure must be corrected – the ratio between crystalloids and colloids, to obtain the same effect, being around 1.5:1 [37-39].

The primary effect of volume is to alter the acid–base status of the blood. This effect becomes clinically relevant when the extracellular fluid dilution is in the order of 10% [40]. We investigated the genesis of acidosis induced by crystalloids in theory [41], *in vitro* [41,42]and *in vivo* [43]. In line with previous results [44-46], we found that dilutional acidosis occurs only when the three determinants of the acid–base status [47,48] – SID, PCO_2 and total protein content – are unevenly diluted. If these determinants are equally diluted, as during *in vitro* experiments, whatever the composition of the solution used to dilute the plasma (from distilled water to normal saline), the pH does not change if the system is closed because the relative proportions between the pH determinants, equally diluted, are unmodified. If the system *in vitro* is open (by tonometry) to restore the PCO_2 to that before the dilution, acidosis occurs because the carbon dioxide (volatile acid load) content increases back to the predilution value while the SID and total protein content values remain diluted [41].

Finally, *in vivo*, the SID of the infused solution becomes a determinant to affect the acid–base status [43]. When the SID is lower than the baseline plasma bicarbonate concentration, such as during normal saline infusion, and PCO_2 is maintained constant, the pH decreases. If the SID of the infused solution is equal to the baseline plasma bicarbonate, acidosis does not develop. On the contrary, if the SID of the infused solution is greater than the baseline plasma bicarbonate concentration, the pH tends to increase [42,43]. The main risks of large crystalloid

infusion are therefore edema diffused to the various organs [49] and disturbances of the acid–base equilibrium [40,50,51], depending on the electrolyte composition. With this background, normal saline is the worst approach for large-volume resuscitation; in fact, with the SID of the solution being equal to 0, acidosis is unavoidable. Moreover, the chloride load and the relatively high osmolarity may increase the burden of the kidney with chloride-dependent constriction of the afferent arterioles [52,53].

Abbreviations

CVP, central venous pressure; PCO_2, partial pressure of carbon dioxide; SID, strong ion difference; $ScvO_2$, central venous oxygen saturation.

Competing interests

The authors declare that they have no competing interests.

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Declarations

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Conferences and Reviews

Paradoxes of Body Fluid Volume Regulation in Health and Disease

A Unifying Hypothesis

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The body's normal homeostasis is maintained by the integrity of the excretory capacity of the kidneys. In advanced cardiac failure, however, the avidity of the renal sodium and water retention contributes to the occurrence of pulmonary congestion and peripheral edema. In patients with advanced cirrhosis, the kidneys again fail to excrete the amounts of sodium and water ingested, thus leading to ascites and peripheral edema. The signals for this renal retention of sodium and water in a patient with cirrhosis must be extrarenal because when the same kidneys are transplanted into persons with normal liver function, renal sodium and water retention no longer occurs; rather, the kidneys maintain normal fluid and electrolyte balance. Excessive sodium and water retention by the kidneys also occurs during pregnancy despite a 30% to 50% increase in plasma volume, cardiac output, and glomerular filtration rate. What are the afferent and efferent signals whereby normal kidneys retain sodium and water so that total extracellular, interstitial, and intravascular volumes expand far beyond those limits observed in normal subjects? These dilemmas are the subject of this review, in which a "unifying hypothesis of body fluid volume regulation" is presented.

(Schrier RW, Niederberger M: Paradoxes of body fluid volume regulation in health and disease—A unifying hypothesis. West J Med 1994; 161:393-408)

The regulation of body fluid volume is important in almost every area of medicine and has been the focus of myriad investigations during this century. When most of life was in a saltwater environment and the species' integument was freely permeable to solutes and water, the compositions of the milieu *intérieur* and *extérieur* were comparable. But when the species moved to land, there was the necessity for a sensitive regulatory system for body fluid volume and composition. The importance of this system was perhaps best emphasized by Claude Bernard when he wrote that "the constancy of the milieu *intérieur* is the condition of free and independent existence."[1]

Various studies in this century examining the regulation and composition of body fluid volume have led to many paradoxical observations, some of which we will summarize here. With the loss of gastrointestinal fluid or hemorrhage, a decrease in extracellular fluid, plasma, and blood volume occurs, and the kidneys respond in what would be viewed as an appropriate manner by retaining sodium and water. But in circumstances such as pregnancy, cirrhosis, and heart failure, extracellular fluid volume, plasma volume, and blood volume are all expanded, and yet the kidneys also retain sodium and water.

Cardiac output has also been examined as the primary regulatory determinant of body fluid volume and renal sodium and water excretion. Cardiac output is decreased with volume depletion associated with diarrhea or hemorrhage, but it is increased in high-output cardiac failure, cirrhosis, and pregnancy; yet, the kidneys retain sodium and water in these three circumstances.

The glomerular filtration rate (GFR) has been proposed as the primary determinant of sodium and water regulation in the body. Thus, with volume depletion, the GFR decreases, and water and sodium retention occurs. The GFR, however, can be increased by 30% to 50% in pregnancy, and yet sodium and water retention occurs and leads to a 30% to 50% expansion of blood volume and extracellular fluid volume.[2] The sensitive regulation of vasopressin (antidiuretic hormone) was shown whereby a 1% to 2% change in extracellular fluid osmolality alters vasopressin release[3]; yet, one of the hallmarks of the edematous disorders is overt hypo-osmolality.[4] Thus, factors other than vasopressin and extracellular

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ABBREVIATIONS USED IN TEXT

ANP = atrial natriuretic peptide
cyclic GMP = cyclic guanosine monophosphate
GFR = glomerular filtration rate

fluid osmolality must be involved in regulating renal water excretion, or perhaps there is a "resetting" of the vasopressin osmostat.

The discovery of aldosterone seemed to be a key to renal sodium excretion and thus to extracellular fluid volume regulation.[5] Yet, when excessive amounts of aldosterone are administered to normal persons, only limited sodium retention occurs, and no edema appears—that is, "aldosterone or mineralocorticoid escape" occurs On the other hand, when exogenous aldosterone is administered to patients with cirrhosis or cardiac failure, they do not escape from the sodium-retaining effect of aldosterone, and thus ascites and pulmonary edema, respectively, worsen. The hormone, atrial natriuretic peptide (ANP), was then discovered,[6] and it was thought that sodium retention in heart failure and cirrhosis might be due to a deficiency of this hormone. When the ANP level was measured, however, the plasma concentrations were increased, not decreased, in both heart failure and cirrhosis.[7] Moreover, although exogenous ANP administration causes an increase in urinary flow and sodium excretion in normal subjects, when it is administered to patients with heart failure and cirrhosis, there is a renal resistance to the hormone.[8-10] These examples are just a few of the apparent paradoxes that must be addressed when attempting to understand how body fluid volume and composition are regulated. In this presentation, we propose a unifying hypothesis of volume regulation that addresses these paradoxes. The validity of this hypothesis will be examined in the circumstances of low- and high-output cardiac failure, cirrhosis, and pregnancy.

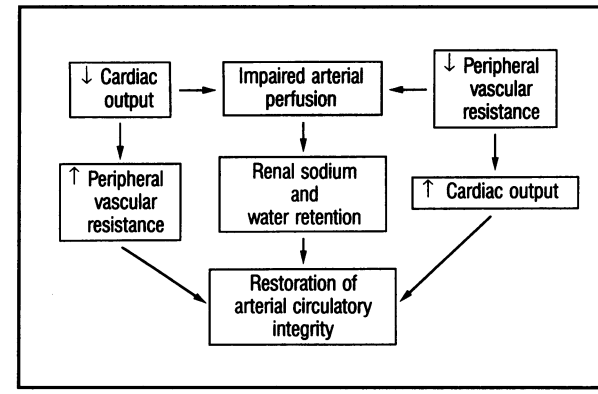

Figure 1.—A decrease in cardiac output or peripheral arterial resistance initiates sodium and water retention in disorders involving edema (from Schrier[18] with permission).

Low-Output Cardiac Failure

At the turn of the century, Starling in Great Britain proposed the backward theory of heart failure.[11] He proposed that in heart failure an increase in venous pressure with fluid transudation from the capillaries into the interstitium leads to a contraction of blood volume, thus triggering renal sodium and water retention. Administering albumin was therefore proposed as a means to treat heart failure. In contrast, it was later proposed that cardiac failure causes primary sodium and water retention that actually leads to an expansion of blood and plasma volumes.[12] This volume expansion then increases venous pressure with subsequent transudation of fluid from capillaries into the interstitium and edema formation. It was therefore proposed that vene-

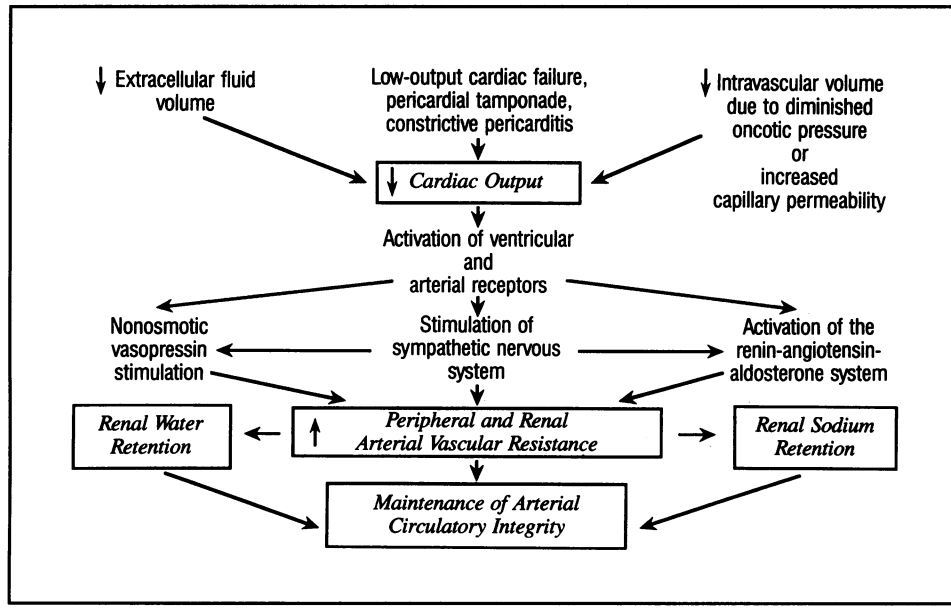

Figure 2.—The sequence of events is shown in which a decrease in cardiac output initiates renal sodium and water retention (from Schrier[15] with permission).

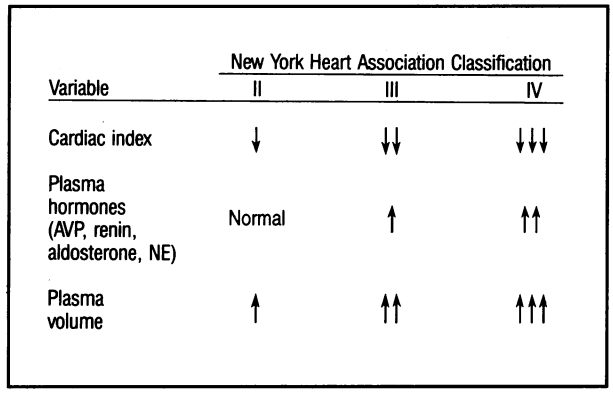

Figure 3.—Neurohumoral and plasma volume responses to progressive cardiac failure are classified according to the New York Heart Association (from Schrier[16] with permission). AVP = arginine vasopressin, NE = norepinephrine

section be considered the treatment of choice for cardiac failure.

Now that most of the body fluid volume compartments can be measured, blood and plasma volumes are known to expand in heart failure. About 85% of the plasma volume is located on the venous side of the circulation and 15% on the arterial side. There is, however, no readily sensitive technique to measure arterial blood volume, which constitutes only 2% of total body fluid. Nevertheless, with this background it is possible to hypothesize that the total plasma volume could be expanded in heart failure if it were mostly on the venous side of the circulation, but underfilling of the arterial circulation could occur due to a decrease in cardiac output. On the other hand, as discussed, cardiac output can be increased in certain circumstances in which sodium and water retention occurs, namely pregnancy, cirrhosis, and high-output heart failure.

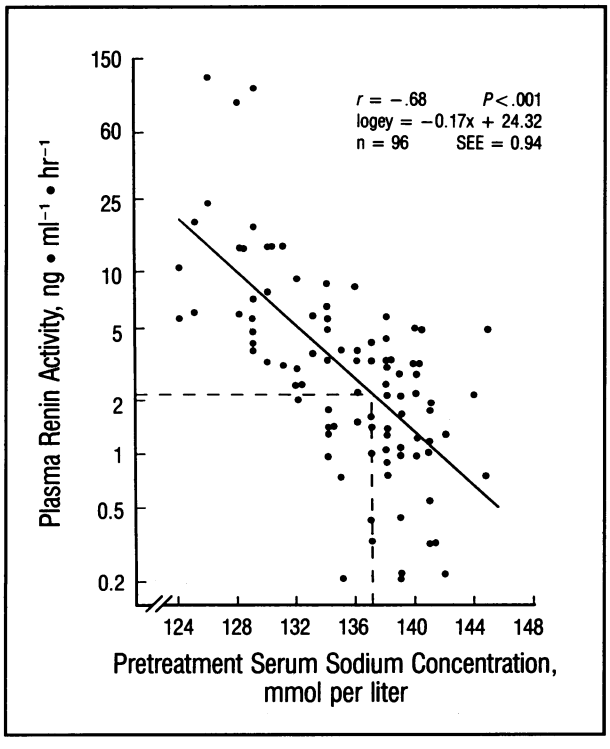

Figure 4.—The relationship is shown between serum sodium concentration and plasma renin activity before vasodilator therapy in 96 patients with severe chronic heart failure (from Lee and Packer[19] with permission). SEE = standard error of the estimate

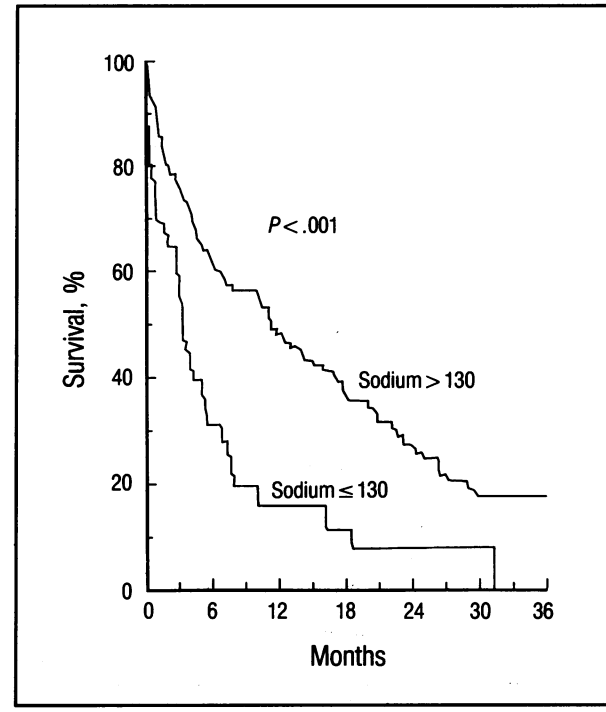

Figure 5.—Kaplan-Meier analysis shows cumulative rates of survival in patients with heart failure stratified into 2 groups based on pretreatment serum sodium concentration—>130 mmol per liter (n=163) versus ≤130 mmol per liter (n=40). Patients with severe hyponatremia had a highly unfavorable long-term prognosis (*P*<.001, Wilcoxon-Breslow) (from Lee and Packer[19] with permission).

If the arterial circulation is the dominant compartment in body fluid volume regulation, there must be a second determinant of arterial underfilling in addition to a diminished cardiac output. This second determinant is proposed to be an increased holding capacity of the arterial circulation as determined by capacitance and arterial vascular resistance. Thus, we propose a unifying hypothesis of body fluid volume regulation that indicates that either a decrease in cardiac output or peripheral arterial vasodilation causes arterial underfilling, and all the subsequent events occur in an attempt to restore arterial circulatory integrity (Figure 1).[13-18] In low cardiac output failure, there would be a secondary increase in peripheral vascular resistance, whereas with arterial vasodilation there is a secondary increase in cardiac output. In both circumstances, renal sodium and water retention occurs in an attempt to restore arterial circulatory integrity.

Virtually all circumstances of sodium and water retention in which the kidneys are normal can be incorpo-

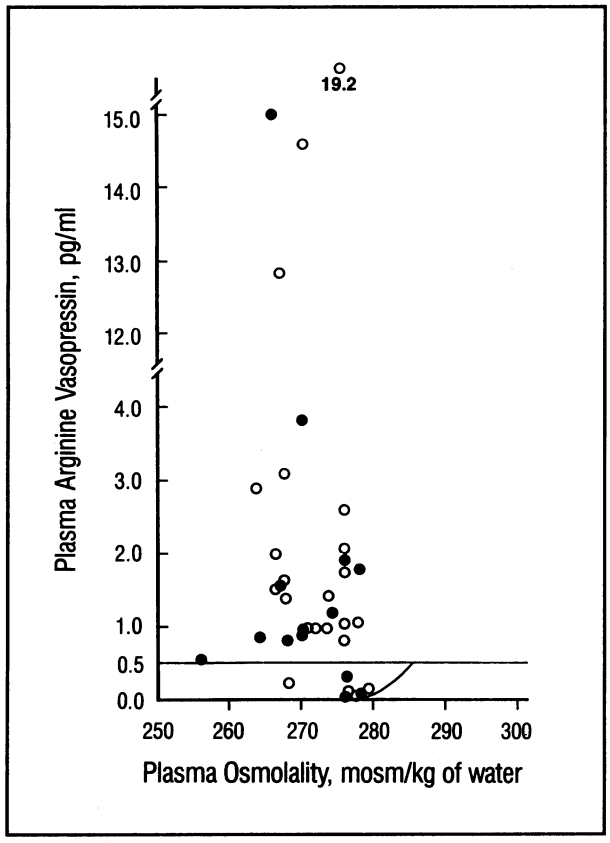

Figure 6.—Plasma arginine vasopressin (AVP) levels are shown in 37 hyponatremic patients with congestive heart failure. ● = patients who never received diuretics before the measurement of AVP levels (n=14); ○ = those patients who received diuretics within 24 hours of blood sampling for AVP measurement (n=23) (from Szatalowicz et al[23] with permission).

rated into this unifying hypothesis. A decrease in cardiac output leading to arterial underfilling may occur with diarrhea, low-output heart failure, pericardial tamponade, constrictive pericarditis, a loss of oncotic pressure due to a protein-losing dermopathy or enteropathy, or with a hypersensitivity reaction causing the loss of colloid from capillaries to the interstitium (Figure 2).[15] The resultant arterial underfilling is sensed by receptors in the ventricle, baroreceptors in the carotid artery and the aortic arch, and renal afferent arterioles. The resultant increased renal sympathetic tone is known to stimulate the renin-angiotensin-aldosterone system and the nonosmotic release of vasopressin. Although less sensitive, the nonosmotic stimulation of vasopressin with arterial underfilling overrides the osmotic regulation of vasopressin release.

As will be discussed, angiotensin and increased adrenergic tone contribute to the impaired escape from the sodium-retaining action of aldosterone, and the nonosmotic release of vasopressin contributes to the water retention. All these responses to arterial underfilling are directed toward the restoration of arterial circulatory integrity.

As cardiac output progressively decreases in a patient with heart failure, a progressive increase in the compensatory neurohumoral profile as assessed by measuring plasma vasopressin, renin, aldosterone, and norepinephrine levels would be expected (Figure 3).[16] Thus, those patients with heart failure with the highest plasma renin activity have the lowest pretreatment plasma sodium concentrations secondary to the stimulation of thirst and the nonosmotic release of vasopressin.[19] Moreover, high plasma renin activity and aldosterone and norepinephrine levels before treatment with diuretics indicate a poor prognosis.[20,21] Patients with this condition have arterial underfilling due to low cardiac indices; the resultant sodium and water retention causes the plasma volume to expand, mostly on the venous side of the circulation.

As shown in Figure 4, pretreatment plasma sodium concentrations in patients with heart failure correlate with plasma renin activities.[19] Moreover, the worst prognosis in a patient with heart failure before treatment occurs with low plasma sodium concentrations.[19] As shown in Figure 5, a pretreatment serum sodium concentration below 130 mmol per liter (130 mEq per liter) in patients with heart failure predicts a worse prognosis than for

TABLE 1.—*Water Excretion and Hemodynamic and Biochemical Characteristics of 2 Groups* of Patients with Heart Failure Classified Along Values of Plasma Vasopressin†*

Clinical Characteristic	*Group I (n=17)*	*Group II (n=8)*	P
Water excretion, %	31.4 ± 3.2	57.1 ± 7.3	<.005
Minimal urinary osmolality, mosm/kg of water	371 ± 36	162 ± 29	<.001
Maximum free water clearance, ml/min	−0.04 ± 0.28	2.03 ± 0.65	<.01
Osmolar clearance, ml/min	1.75 ± 0.2	1.61 ± 0.22	NS
Creatine clearance, ml • min^{-1} • 1.73 m^{-2}	55.4 ± 4.9	53.7 ± 10.4	NS
Cardiac index, liters • min^{-1} • m^{-2}	1.9 ± 0.1	2.47 ± 0.2	<.05
Pulmonary wedge pressure, mm of mercury	30.2 ± 1.4	21.7 ± 1.5	<.02
Right atrial pressure, mm of mercury	13.2 ± 1.2	10.2 ± 1.3	NS
Mean arterial blood pressure, mm of mercury	85.8 ± 2.7	90.8 ± 4.0	NS
Pulse, beats/min	81 ± 3	82 ± 5	NS
Plasma renin activity, ng • ml^{-1} • hr^{-1}	4.4 ± 0.7	1.99 ± 0.4	<.01
Plasma aldosterone, ng/dl	74.1 ± 11.6	10.2 ± 2.1	<.001
Arterial Po_2, mm of mercury	80.3 ± 2.7	80.8 ± 5.9	NS

NS = not significant

*Group I patients had high plasma vasopressin levels (mean, 3 pg/ml); group II patients had undetectable plasma vasopressin levels (<0.5 pg/ml)

† From Bichet et al with permission.[28]

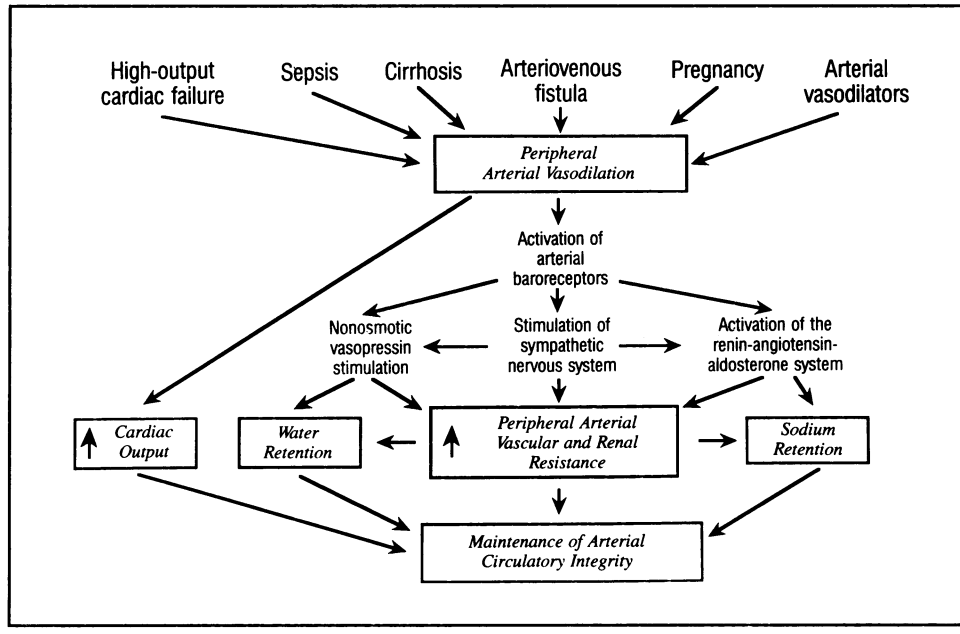

Figure 7.—The sequence of events is shown in which peripheral arterial vasodilation initiates renal sodium and water retention (from Schrier[15] with permission).

those patients with serum sodium concentrations above 130 mmol per liter.

Evidence exists that the increased plasma norepinephrine concentrations in heart failure are a reasonable index of sympathetic activity. Measurements of tritiated secretion rates of norepinephrine in patients with heart failure demonstrated substantially higher secretion rates than in normal persons, whereas the norepinephrine clearance rates were comparable.[22] Thus, increased plasma norepinephrine concentrations in patients with heart failure are primarily due to increased sympathetic activity. As for the role of the sympathetic nervous system in the nonosmotic release of vasopressin, pathways from arterial baroreceptors in the carotid artery and aortic arch travel through the glossopharyngeal and vagus nerves to the nucleus tractus solitarius in the midbrain and then to the hypothalamus, where vasopressin is synthesized in the paraventricular and supraoptic nuclei. With immunohistochemical staining, vasopressin neurons in the paraventricular and supraoptic nuclei can be shown to be interspersed with catecholamine nerve endings. The axons of the vasopressin-synthesizing cell bodies terminate in the posterior pituitary where the hormone is stored and released. This reflex terminates in the nonosmotic release of vasopressin, which is less sensitive but more potent than the osmotic regulation of vasopressin.

Using the vasopressin bioassay, vasopressin was not incriminated in the hyponatremia of heart failure. The bioassay, however, could only detect plasma vasopressin concentrations above 10 pg per ml. When a sensitive radioimmunoassay for vasopressin was developed, it was clear that normal urine concentration and dilution occur in response to plasma vasopressin levels between 0.5 and 4 pg per ml, values that were not detectable with the bioassay. As shown in Figure 6, 30 of 37 patients with heart failure did not have suppressed plasma concentrations of vasopressin, even though they had hypo-osmolarity and hyponatremia; thus, a nonosmotic release of vasopressin occurred in these patients.[23]

TABLE 2.—*Hemodynamics in Rats With High Output Heart Failure**

Hemodynamics	*Control Rats*	*Aorto-caval Fistulae*	P
Mean arterial pressure, mm of mercury	116 ± 9	102 ± 8	<.001
Cardiac output, ml • min^{-1} • 100 grams $^{-1}$ of body weight	39.6 ± 6.7	50.0 ± 9.0	<.001
Peripheral vascular resistance, mm of mercury • min^{-1} • 100 $grams^{-1}$ of body weight	3.11 ± 0.71	1.98 ± 0.37	<.002
Heart weight, grams	1.15 ± 0.13	1.89 ± 0.28	<.001

* Riegger et al with permission.[29]

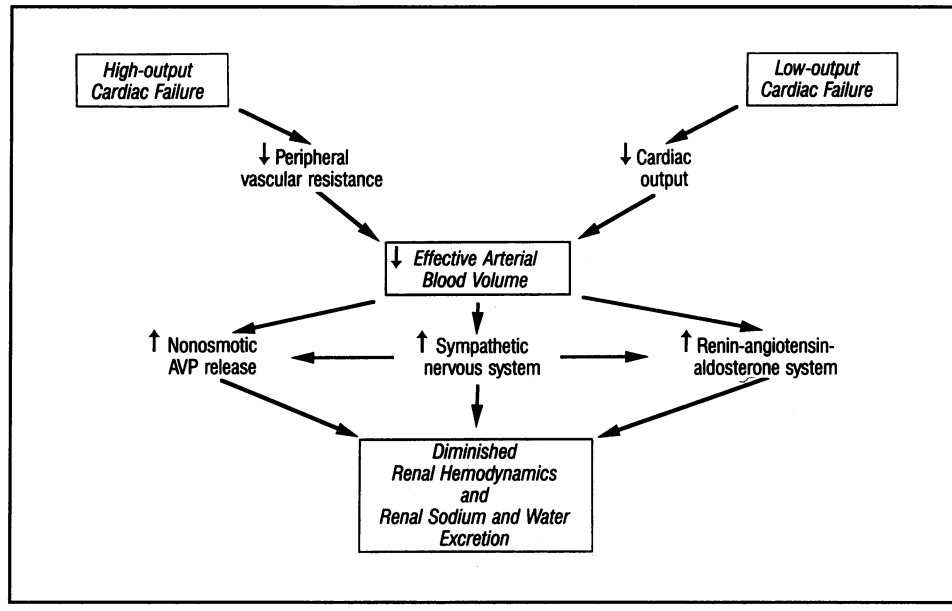

Figure 8.—The mechanisms of high- and low-output cardiac failure are shown. Although the initiating "underfill" event differs in high- and low-output failure, the subsequent pathways leading to renal sodium and water retention are similar (from Schrier[13] with permission). AVP = arginine vasopressin

When complementary DNA probes are used for the preprohormone of vasopressin in the hypothalamus, experimental cardiac failure in animals exhibits increased messenger RNA for vasopressin compared with that in control animals.[24] Thus, both increased nonosmotic vasopressin gene expression and vasopressin release are associated with heart failure.

The V_2 receptor is the antidiuretic receptor for vasopressin, whereas the V_1 receptor is the vascular receptor. In experimental low-output heart failure, impaired diluting ability as demonstrated with an acute water load can be corrected with a V_2 vasopressin antagonist.[25] Thus, in this experimental model of acute heart failure, the nonosmotic release of vasopressin appears to account completely for the impaired water excretion. Orally active nonpeptidic vasopressin antagonists have now been developed in Japan.[26,27]

Patients with hyponatremia in heart failure and with detectable plasma vasopressin concentrations (mean, 3 pg per ml) should have more evidence of arterial underfilling—stimulation of the neurohumoral profile—than patients with heart failure with undetectable

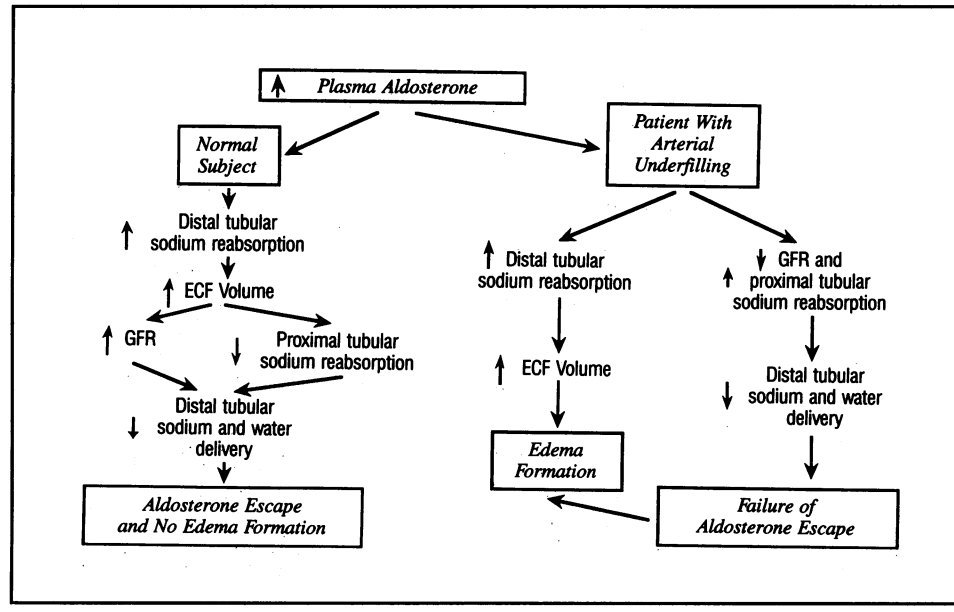

Figure 9.—Events involved in normal (left) and impaired (right) aldosterone escape are shown (from Schrier[15] with permission). ECF = extracellular fluid, GFR = glomerular filtration rate

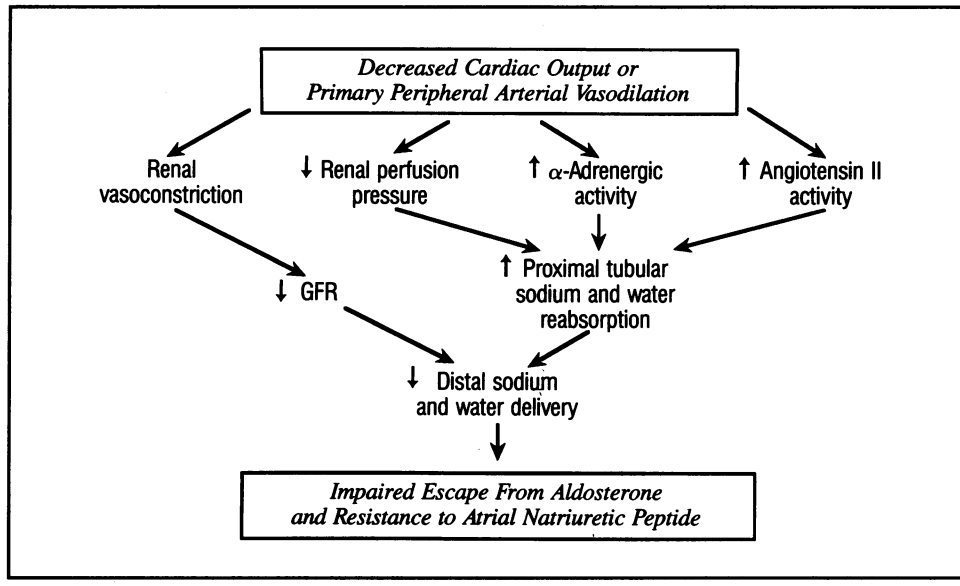

Figure 10.—A decrease in cardiac output or peripheral arterial vasodilation can initiate events that diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to atrial natriuretic peptide (from Schrier and Bettor[30] with permission). GFR = glomerular filtration rate

vasopressin levels (<0.5 pg per ml). As shown in Table 1, those patients with evidence of nonosmotic vasopressin release showed significantly lower cardiac indexes, higher pulmonary wedge pressures, and higher plasma renin and aldosterone concentrations.[28] Moreover, when these patients with detectable plasma concentrations of vasopressin were treated with agents to decrease the cardiac afterload, the resultant increase in the cardiac index was associated with improved water excretion and the suppression of plasma and platelet vasopressin.[28]

High-Output Cardiac Failure

In the context of this unifying hypothesis of body fluid volume regulation, the second initiator of arterial underfilling is peripheral arterial vasodilation. Thus, systemic arterial vasodilation should account for the remainder of the circumstances in which sodium and water retention occurs despite normal kidney function. As shown in Figure 7, these clinical states include high-output cardiac failure, sepsis, cirrhosis, large arteriovenous fistulae, pregnancy, and large doses of arterial vasodilators such as minoxidil and hydralazine. The neurohumoral compensatory responses of arterial underfilling due to arterial vasodilation are the same as occurs with arterial underfilling due to a decrease in cardiac output.

In Table 2 are results obtained in an experimental model of high-output cardiac failure.[29] The diminished systemic vascular resistance is associated with an increased cardiac output, cardiac hypertrophy, and activation of the neurohumoral profile of arterial underfilling, namely increased plasma renin activity, aldosterone, norepinephrine, and vasopressin. Thus, one of the paradoxes of body fluid volume regulation can now be ad-

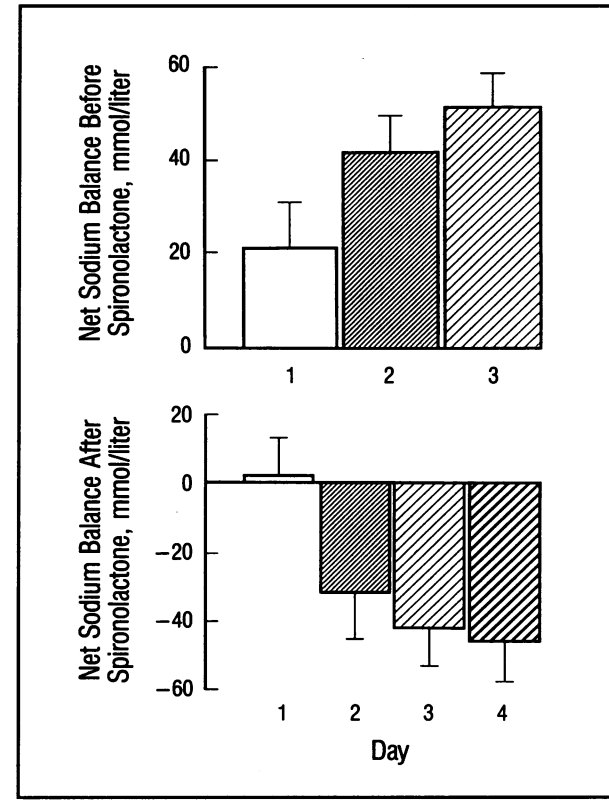

Figure 11.—A reversal of sodium retention by aldosterone antagonism occurs in patients with congestive heart failure. Net positive cumulative sodium balance is seen for the periods before spironolactone is given (**top panel**), and net negative cumulative sodium balance is seen after the initiation of spironolactone therapy (400 mg per day; **bottom panel**). The increase in sodium excretion with spironolactone therapy was significant ($P < .01$) (from Hensen et al[34] with permission).

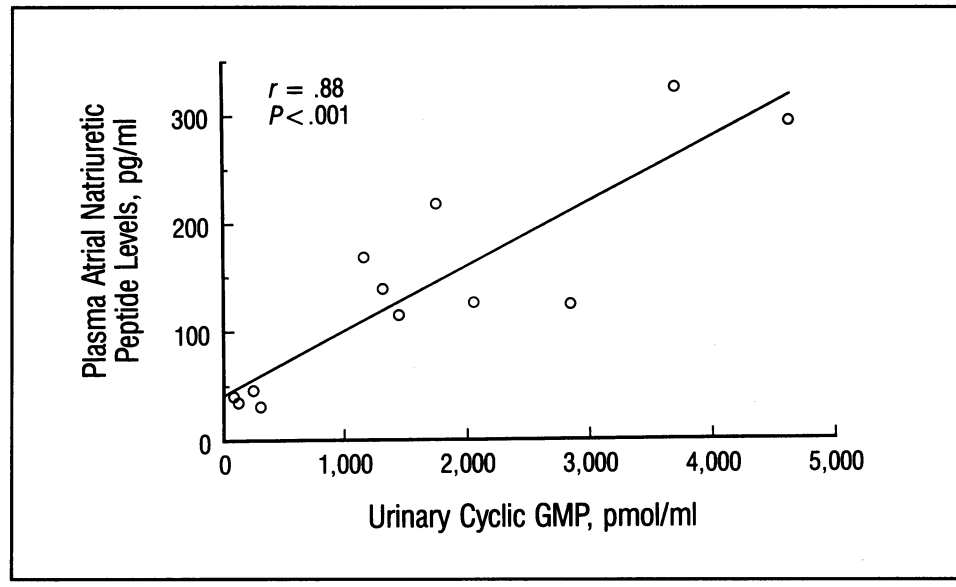

Figure 12.—Plasma atrial natriuretic peptide levels correlate with urinary cyclic guanosine monophosphate (cyclic GMP) levels in patients with heart failure (from Abraham et al[37] with permission).

dressed whereby sodium and water retention can occur in patients in whom cardiac output is low, as with low-output cardiac failure, or high, as with thyrotoxicosis and beriberi. Thus, although the causes of arterial underfilling are different in low- and high-output cardiac failure, the secondary responses to arterial underfilling are comparable (Figure 8).[13]

Aldosterone Escape and Atrial Natriuretic Peptide Resistance in Cardiac Failure

The renal site of action of vasopressin, aldosterone, and ANP is the collecting duct in the terminal portion of the nephron. Either a decrease in the GFR or an increase in proximal tubular reabsorption, or both, can diminish distal sodium and water delivery to the site of action of these hormones in the collecting duct. Because escape from the sodium-retaining effect of aldosterone is dependent on an increased rate of delivery of sodium to the distal nephron, the responses to arterial underfilling may diminish sodium delivery to the collecting duct, thereby explaining the impaired aldosterone escape that is characteristic of arterial underfilling (Figure 9).[15]

In circumstances of arterial underfilling due to either a decrease in cardiac output or primary peripheral arterial vasodilation, a number of factors would lead to a decreased sodium and water delivery to the collecting duct (Figure 10).[30] Advanced heart failure is associated with renal vasoconstriction and a decrease in renal perfusion

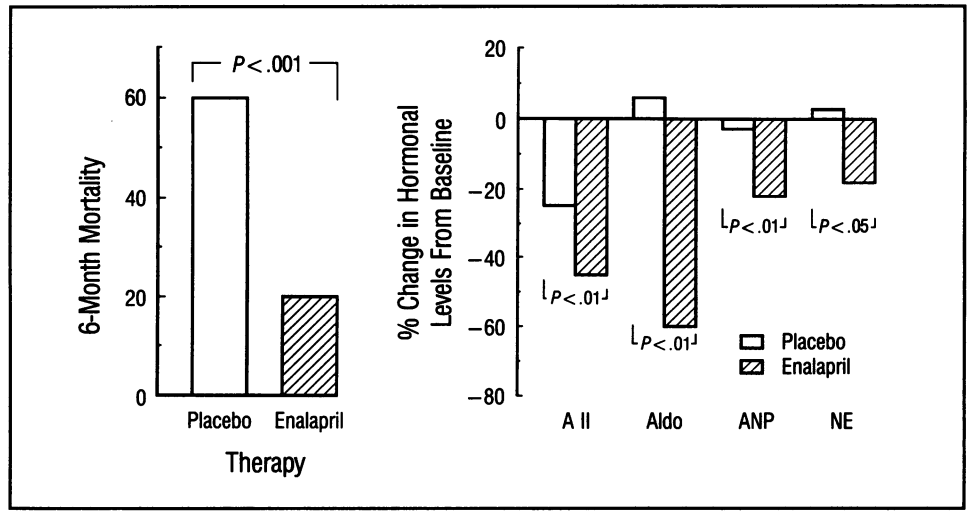

Figure 13.—Enalapril therapy reduces 6-month mortality and hormonal levels in patients with severe congestive heart failure (from Swedberg et al[40] with permission). A II = angiotensin II, Aldo = aldosterone, ANP = atrial natriuretic peptide, NE = norepinephrine

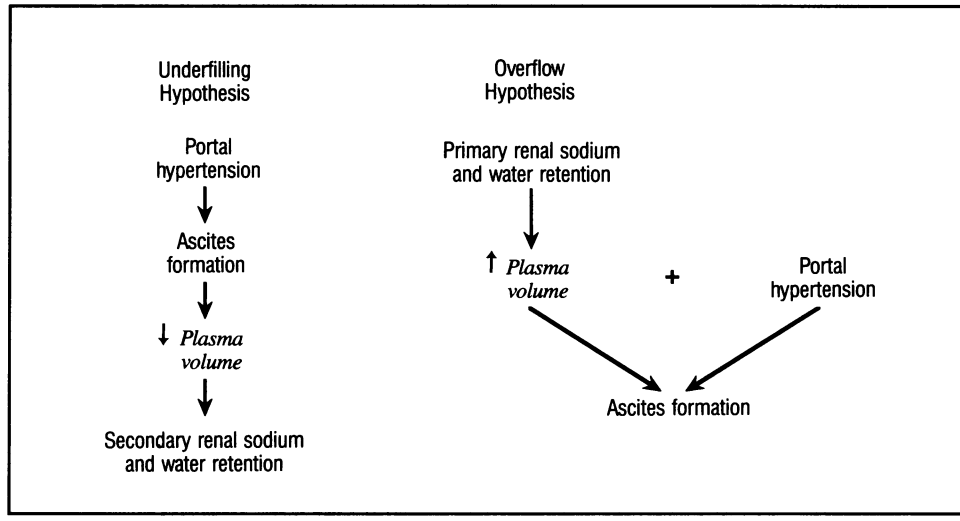

Figure 14.—The characteristics of underfilling (left) and overflow (right) hypotheses of renal sodium and water retention in cirrhosis are shown (from Schrier[17] with permission).

that decrease distal tubular sodium and water delivery. Moreover, direct effects of adrenergic stimulation[31] and angiotensin[32,33] increase proximal tubular sodium and water reabsorption. Thus, impaired aldosterone escape secondary to the consequences of arterial underfilling suggest that aldosterone-mediated sodium retention is important in heart failure. Support for this conclusion derives from the demonstration that large doses of spironolactone (400 mg per day) reverse sodium retention in patients with heart failure (Figure 11).[34]

A resistance to the normal diuretic and natriuretic response to exogenous ANP is another hallmark of heart failure both in experimental models[35,36] and in humans.[8,9] There are several explanations for this ANP resistance: inhibition of renal ANP receptors; immunoreactive plasma ANP that is biologically inactive; or increased neutral endopeptidase activity in the proximal tubule that degrades ANP, thus limiting the hormone delivery to the distal collecting-duct sites of action. These three possibilities for ANP resistance should be associated with decreased activation of the secondary messenger for ANP, namely cyclic guanosine monophosphate (cyclic GMP). When cyclic GMP levels are measured in the urine of patients with heart failure, levels are increased and are correlated with plasma ANP concentrations. When this correlation between plasma ANP and urinary cyclic GMP was studied in patients with heart failure, a linear relationship was found (Figure 12).[37] This last finding supports the concept that diminished renal distal tubular sodium and water delivery is the mechanism of ANP resistance in heart failure, rather than the aforementioned other possibilities.

Because increased renal adrenergic tone is known to increase proximal tubular sodium reabsorption, renal denervation in animals with experimental heart failure might be expected to reverse the ANP resistance. Recent studies have indeed shown that renal denervation reverses the resistance to ANP in experimental heart failure.[38] The first detectable hormonal increase in heart failure is the plasma ANP level, thus raising the possibility that the early onset of sodium retention in cardiac decompensation is delayed by ANP. The following study provides some experimental evidence to support this possibility in early heart failure, even though ANP resistance characterizes advanced heart failure.[39] A comparable decrease in mean arterial pressure was produced in dogs by ventricular tachycardia and thoracic vena caval constriction. Whereas plasma ANP levels rose only with ventricular tachycardia, a decrease in sodium excretion occurred only with caval constriction. The role of the increased ANP concentration with ventricular tachycardia to delay sodium retention was supported by the finding that caval constriction no longer caused sodium retention if exogenous ANP was simultaneously infused to produce a plasma ANP concentration comparable to that observed with ventricular tachycardia.

Variable	Compensated Cirrhosis (no ascites)	Decompensated Cirrhosis (ascites)	Hepatorenal Syndrome
Peripheral arterial vasodilation	↑	↑↑	↑↑↑
Plasma hormones—AVP, renin, aldosterone, NE	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Figure 15.—The "peripheral arterial vasodilation hypothesis" is shown. Normal plasma hormone concentrations indicate relative stimulation in the presence of plasma volume expansion. Hypoalbuminemia may attenuate plasma volume expansion (from Schrier[44] with permission). AVP = arginine vasopressin, NE = norepinephrine

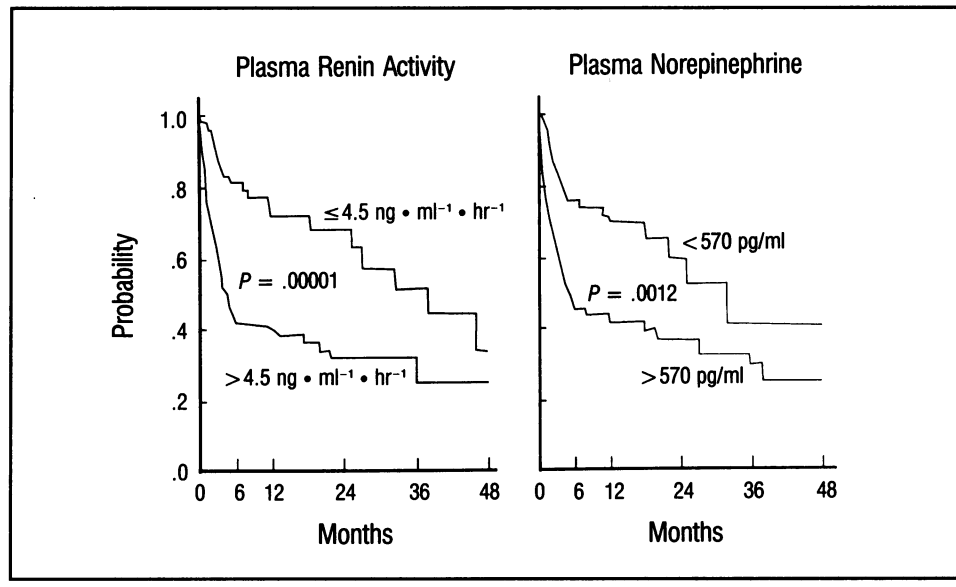

Figure 16.—The plasma renin and norepinephrine concentrations are prognostic indicators in patients with cirrhosis (from Llach[45] with permission).

To summarize, with heart failure, arterial underfilling may occur due to a decrease in cardiac output with myocardial disease or peripheral arterial vasodilation with thyrotoxicosis and beriberi. In the latter circumstance, however, cardiac dysfunction may also accompany the arterial vasodilation. With advanced myocardial disease, the compensatory neurohumoral responses in cardiac failure may become maladaptive. For example, the sodium and water retention may cause pulmonary congestion, whereas the rise in peripheral vascular resistance increases cardiac afterload and myocardial metabolic demand. Results of the CONSENSUS study demonstrate that treatment with angiotensin-converting enzyme inhibitor decreases six-month mortality in association with a decrease in plasma levels of angiotensin, aldosterone, norepinephrine, and ANP (Figure 13).[40]

Cirrhosis

In Figure 14 are shown the two primary hypotheses that have been proposed to explain the sodium and water retention and ascites formation with cirrhosis.[17] With the classic "underfilling hypothesis," portal hypertension causes ascites with an associated decrease in plasma volume that causes secondary renal sodium and water retention.[41] When the plasma volume was found

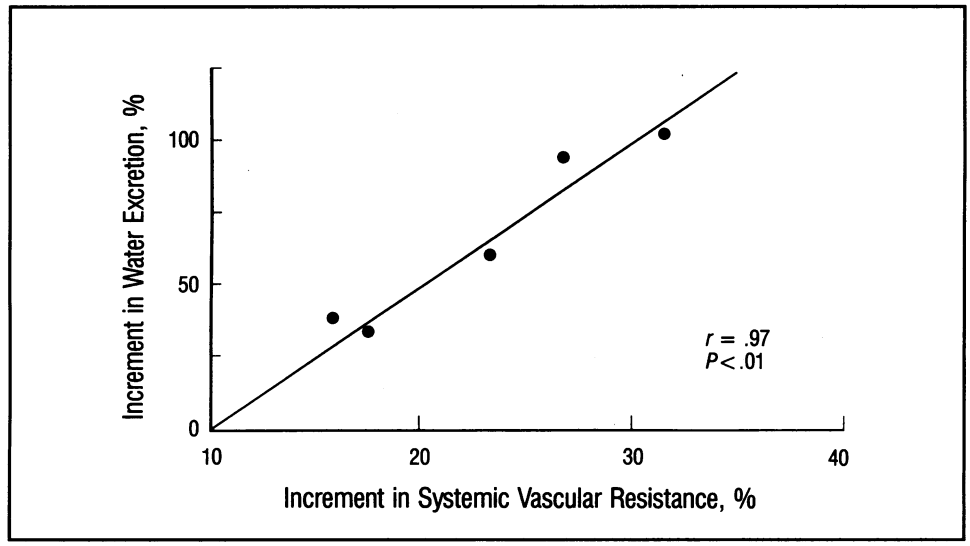

Figure 17.—A correlation is seen between the increase in systemic vascular resistance and the increase in water load excretion from immersion alone to immersion with norepinephrine infusion (from Shapiro et al[52] with permission).

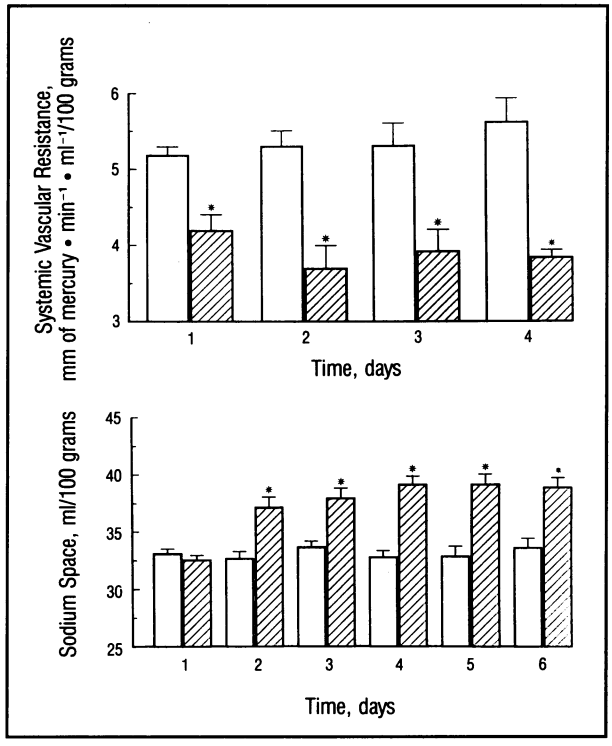

Figure 18.—A temporal relationship is shown between decreased peripheral vascular resistance (**top panel**) and increased sodium space (**bottom panel**) in rats with prehepatic portal hypertension (**shaded bars**) versus sham-operated rats (**white bars**) (from Albillos et al[54] with permission). * = $P < .05$

to be expanded in cirrhosis and this volume expansion antedated the ascites formation, this underfilling hypothesis was no longer tenable. Thus, the "overflow hypothesis" was proposed.[42] This hypothesis proposes that a diseased liver, or some consequence such as an increase in intrahepatic pressure, causes primary sodium and water retention with the expansion of the plasma volume. Ascites then occurs because of the overflow of the plasma volume expansion into the abdominal cavity due to portal hypertension. This overflow hypothesis, however, cannot account for the clinical spectrum of cirrhosis from compensated to decompensated to the hepatorenal syndrome states. This is because the expansion of the plasma volume, on both the venous and arterial sides of the circulation, cannot explain the progressive activation of the neurohumoral profile that characterizes both progressive cirrhosis and arterial underfilling.

The "peripheral arterial vasodilation hypothesis" was therefore proposed.[43] As shown in Figure 15, this hypothesis explains the rise in cardiac output, the fall in mean arterial pressure, and stimulation of the neurohumoral profile of arterial underfilling over the entire clinical spectrum of liver disease.[44] With this hypothesis, patients with cirrhosis with pretreatment hyponatremia and the highest plasma renin, aldosterone, norepinephrine, and vasopressin levels should have the worst prognosis. That is indeed the case. As shown in Figure 16, those patients with cirrhosis with the highest plasma renin and norepinephrine activities have the poorest survival rates.[43]

Using a complementary DNA probe for the prepro-hormone, levels of the hypothalamic messenger RNA for vasopressin were shown to be increased in experimental cirrhosis.[44] Thus, in cirrhosis, there is not only an increased release of vasopressin from the pituitary, but also an enhanced hypothalamic biosynthesis occurs, as is also characteristic of heart failure.

It is clear that patients with cirrhosis differ in their degree of arterial underfilling and may be separated by their capacity to excrete a water load of 20 ml per kg of body weight. Those patients with cirrhosis who have impaired water excretion demonstrate more evidence of arterial underfilling than patients with cirrhosis who normally excrete the same 20-ml-per-kg water load.[47] Nonexcreting patients have lower plasma sodium concentrations, higher urinary osmolalities, and higher plasma renin, aldosterone, norepinephrine, and vasopressin concentrations than patients who excrete a water load normally.[47] In 26 patients with cirrhosis, there was a significant correlation between plasma norepinephrine, as an index of sympathetic activity, and plasma vasopressin and renin activity. The administration of a V_2 vasopressin antagonist has been shown to improve water excreting and diluting ability in experimental cirrhosis,[48] thus incriminating the nonosmotic release of vasopressin in water retention. There is also a role of the V_1 vasopressin receptor in maintaining blood pressures in patients with cirrhosis.[49] In experimental cirrhosis, the V_1 vasopressin vascular antagonist causes a fall in blood pressure, indicating that vasopressin, as well as angiotensin and the sympathetic nervous system, is an important factor in maintaining arterial circulatory integrity in cirrhosis.

In these same 26 patients with cirrhosis studied on a constant sodium intake, there was a significant positive correlation between plasma renin activity and plasma norepinephrine levels and a negative correlation between urinary sodium excretion and plasma norepinephrine levels.[47] These results are consonant with a role of angiotensin and adrenergic stimulation in decreasing sodium delivery to the distal nephron in cirrhosis, as occurs in heart failure. The sodium and water retention in cirrhosis clearly is also due to extrarenal events, as the kidneys of patients with the hepatorenal syndrome have been shown to be no longer retaining sodium when transplanted to recipients with normal livers,[50] or when normal livers are transplanted into these patients with the hepatorenal syndrome.[51]

On this background, a combined maneuver of head-out water immersion and administering exogenous norepinephrine to reverse arterial vasodilation was studied in hyponatremic, ascitic patients with cirrhosis in an effort to reverse the sodium and water retention.[52] The results demonstrated that this maneuver returned sodium and water excretion to normal in these patients with ad-

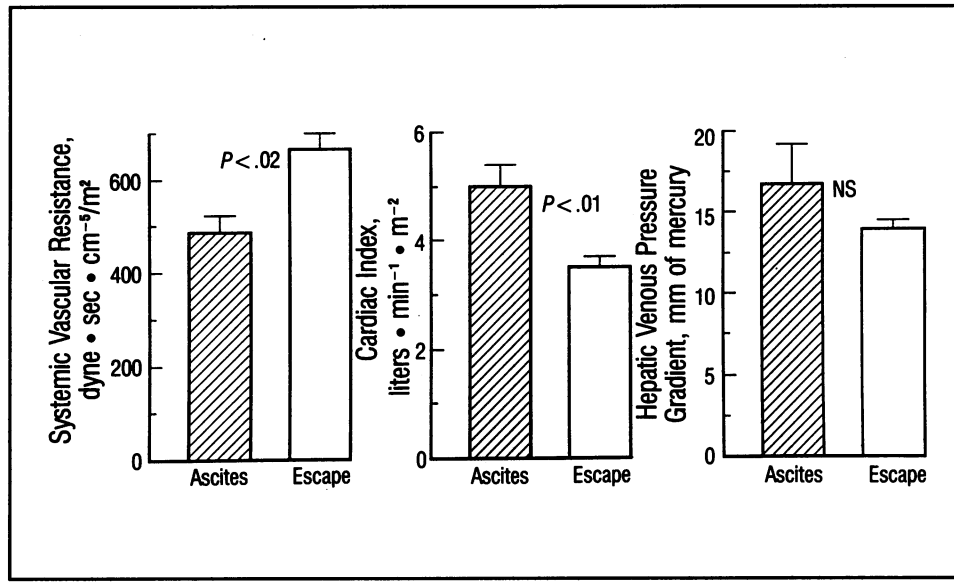

Figure 19.—Baseline systemic hemodynamic measurements and hepatic venous pressure gradient are shown, as an index of portal pressure, in a group of 19 cirrhotic patients without a history of sodium retention treated with mineralocorticoids (from La Villa et al[55] with permission). Escape (n = 15): patients who showed a mineralocorticoid escape phenomenon and did not develop ascites; Ascites (n = 4): patients in whom persistent sodium retention and ascites developed during mineralocorticoid administration; NS = not significant

vanced cirrhosis, thus supporting the concept that arterial underfilling due to arterial vasodilation in the splanchnic and other vascular beds is the cause of sodium and water retention. Further support from these results for the peripheral arterial vasodilation hypothesis was the finding of a strong correlation between the increment in water excretion and that in systemic vascular resistance (Figure 17). As in heart failure, there is evidence for an important role of aldosterone in the sodium retention that occurs in cirrhosis. Investigators showed that 16 of 21 patients with cirrhosis treated over three to four weeks with large doses of the competitive aldosterone antagonist spironolactone had resolution of their ascites, in contrast to only 4 of 22 matched, untreated patients with cirrhosis.[53]

Studies in rats with portal hypertension due to portal vein constriction provide information about the temporal relationship between portal hypertension, splanchnic vasodilation, and sodium retention.[54] As shown in Figure 18, a fall in systemic vascular resistance

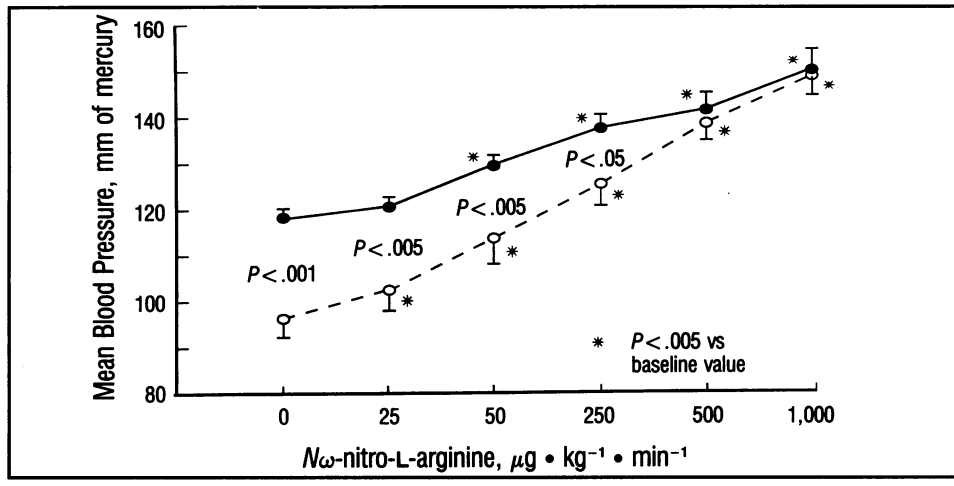

Figure 20.—Mean blood pressures are shown under basal conditions and after the administration of sustained, increasing doses of Nω-nitro-L-arginine in cirrhotic (-o-) and control (-•-) rats. Data are given as mean ± standard error of the mean. *P* values given in the figure are those obtained when comparing cirrhotic and control rats (from Clària et al[56] with permission). * = *P*<.005 versus baseline values

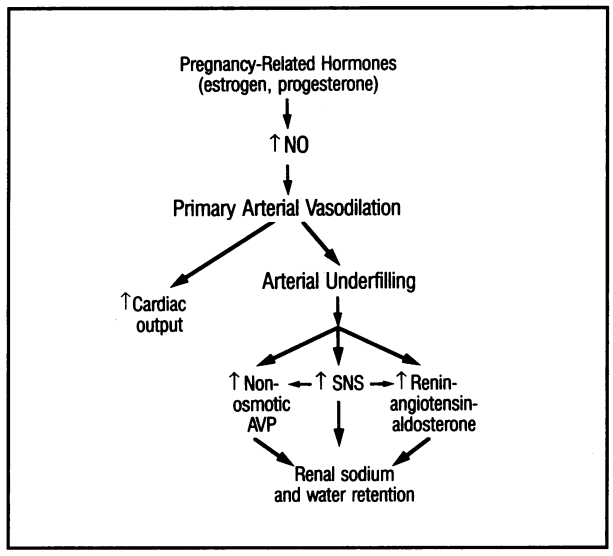

Figure 21.—The peripheral arterial vasodilation hypothesis in pregnancy is illustrated. AVP = arginine vasopressin, NO = nitric oxide, SNS = sympathetic nervous system

occurs within 24 hours after the onset of acute portal hypertension, whereas a rise in total body sodium first occurs within 48 hours after the onset of portal hypertension. These results are compatible with arterial underfilling due to arterial vasodilation initiating sodium retention in association with portal hypertension.

Studies in patients with compensated cirrhosis without ascites provide further important information about the mechanisms of sodium retention and ascites formation. These studies examined the capacity to escape from the sodium-retaining effect of mineralocorticoid hormone. In support of the peripheral arterial vasodilation hypothesis, ascites developed in those patients who did not have mineralocorticoid escape, and they had lower systemic vascular resistances and higher cardiac outputs than those patients who had mineralocorticoid escape (Figure 19).[55] No difference occurred in the hepatic venous pressure gradient, as an index of portal hypertension and intrahepatic pressure, between these two groups of cirrhotic patients. In vasodilated patients, plasma renin activity was also not suppressed, and their plasma ANP levels were not increased during mineralocorticoid administration.

What causes the systemic vasodilation in cirrhosis? There is now substantial evidence suggesting that at least one factor in the vasodilation associated with cirrhosis is the induction of nitric oxide synthase in either vascular smooth muscle, endothelial cells, or both. Administering L-arginine analogues, which block nitric oxide synthase, has been shown to increase the mean arterial pressure in a dose-response manner so that with maximal doses there is no difference in arterial pressures between control and cirrhotic animals (Figure 20).[56] Because plasma endotoxin concentrations have been shown to be increased in cirrhosis[57] and endotoxin may induce nitric oxide synthase in vascular smooth muscle,[58,59] these results support a role of nitric oxide—that is, endothelium-derived relaxing factor—in the vasodilation associated with cirrhosis. Other vasodilators, however, as well as portosystemic shunting, may also be involved in the later stages of cirrhosis.[60-69]

A resistance in ANP has also been shown to occur in cirrhosis in a manner similar to that in cardiac failure. There also does not seem to be any defect in the biologic activity of ANP receptor activation because exogenous ANP has been shown to increase urinary cyclic GMP levels even in those cirrhotic patients whose urinary flow or sodium excretion rates did not increase in response to increasing doses of exogenous ANP.[70,71] Evidence for diminished distal sodium and water delivery due to the consequences of arterial vasodilation (Figure 10) as a cause for the ANP resistance is the finding that this phenomenon can be reversed by renal denervation in experimental cirrhosis in rats.[72]

Local effects of arterial vasodilation also contribute to sodium and water retention in cirrhosis and other vasodilated states. Specifically, albumin distribution space and interstitial compliance have been shown to be increased in both cirrhotic rats[73] and normal rats treated with the arterial vasodilator minoxidil.[74] Thus, a relative increase in interstitial oncotic pressure and a decrease in interstitial hydrostatic pressure with the dilation of precapillary arteriolar sphincters would be expected to predispose to edema formation.

To summarize, peripheral arterial vasodilation in cirrhosis causes arterial underfilling and adaptive neurohumoral responses that can become maladaptive in extreme circumstances. Specifically, the resultant ascites formation predisposes to spontaneous bacterial peritonitis, the renal vasoconstriction predisposes to the hepatorenal syndrome, and the increased splanchnic vasodilation and flow are major contributors to the portal hypertension and esophageal varices, all of which combine to increase morbidity and mortality in patients with cirrhosis. A therapeutic strategy to reverse these extrahepatic consequences of cirrhosis could be designed to attenuate these causes of morbidity and mortality in this disorder. Administering an orally active, long-acting V_1 agonist, β-blockers, or somatostatin to decrease splanchnic flow and an early prophylactic LeVeen peritoneovenous shunt should decrease the arterial underfilling in cirrhosis.[75] This approach should then suppress the neurohumoral responses to arterial underfilling and thereby prevent the hepatorenal syndrome; allow for aldosterone escape, thus preventing ascites formation and spontaneous bacterial peritonitis; and decrease splanchnic flow with a lowering of the portal pressure, thus diminishing the morbidity and mortality of esophageal variceal bleeding.

Pregnancy

Pregnancy is associated with a 30% to 50% increase in extracellular fluid, plasma, and blood volume and a 30% to 50% increase in cardiac output, GFR, and renal blood flow. Primary renal sodium and water retention

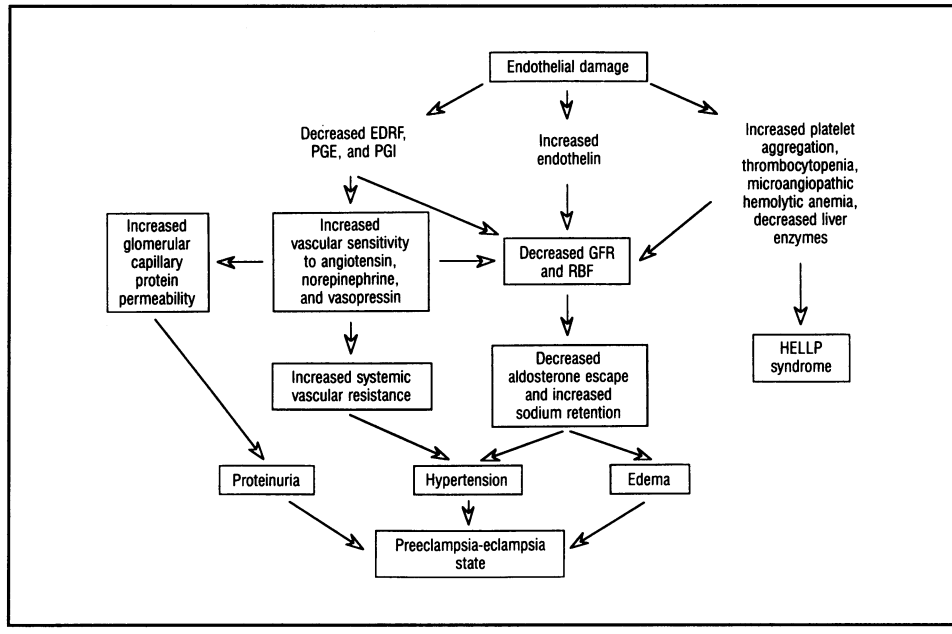

Figure 22.—The pathophysiologic schema for preeclampsia and eclampsia is shown (from Abraham et al[37] with permission). EDRF = endothelium-derived relaxing factor; GFR = glomerular filtration rate; HELLP = hemolysis, elevated liver enzymes, and low platelet count; PGE = prostaglandin E; PGI = prostaglandin I; RBF = renal blood flow

has been suggested to account for these changes associated with normal pregnancy. Several important factors, however, suggest that primary arterial vasodilation causing arterial underfilling with secondary sodium and water excretion occurs in pregnancy. For example, a fall in systolic and diastolic blood pressures occurs in the first trimester of pregnancy despite an increase in the blood volume.[76] The renin-angiotensin-aldosterone axis is activated early in pregnancy, an effect also expected with arterial underfilling due to peripheral arterial vasodilation,[77] whereas primary volume expansion would be expected to suppress these hormones. The increase in GFR and renal blood flow in pregnancy precedes the expansion of the blood volume,[78] thus suggesting primary renal vasodilation. Additional important findings in pregnancy are the "resetting" of the vasopressin-osmoreceptor[79] and the volume depletion-vasopressin relationships[80] in a direction suggestive of arterial underfilling due to systemic arterial vasodilation.

Emerging evidence suggests that nitric oxide mediates the peripheral arterial vasodilation of pregnancy. Long-term blockade of nitric oxide synthase with nitro-L-arginine methylester is associated with a return to normal of mean arterial pressures in pregnant rats compared with controls.[81] Moreover, in the same study, the administration of an L-arginine bolus was associated with a substantially greater fall in mean arterial pressures in pregnant than in nonpregnant rats. Hormones known to increase in pregnancy, such as estrogen and progesterone, have been shown to induce nitric oxide synthase in in vitro experiments.[82,83] Further support for a role for nitric oxide in the vasodilation of pregnancy derives from the correlation between urinary cyclic GMP, the secondary messenger of nitric oxide, and urinary nitrate excretion, a metabolite of nitric oxide.[84,85] Recent preliminary studies from our laboratory also have shown an effect of nitro-L-arginine methylester on the response of aortic rings without endothelium to phenylephrine in pregnant but not nonpregnant rats. The resistance to angiotensin, norepinephrine, and vasopressin that characterizes normal pregnancy has also been shown to be reversed by the blockade of nitric oxide synthase.[86] In Figure 21 is shown the hypothesis whereby nitric oxide-induced arterial vasodilation initiates arterial underfilling in pregnancy. Moreover, endothelial damage in pregnancy, perhaps due to a circulating toxin released from an ischemic placenta, may initiate the events leading to the preeclampsia-eclampsia state.[87] These events are shown in Figure 22, including increased sensitivity to pressor hormones, a decrease in the GFR and renal blood flow, and failure to escape from the sodium-retaining effect of aldosterone, all combining to cause proteinuria, hypertension, and edema—the hallmarks of the preeclampsia-eclampsia state.[88]

In conclusion, to quote John Masefield: "What is life, the thing of watery salt held in cohesion by unresting cells which work, they know not why, which never halt myself unwitting where their master dwells." Our unifying hypothesis of body fluid volume regulation indicates that "the master" dwells in the arterial circulation.

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