A unifying hypothesis of body fluid volume regulation

The Lilly Lecture 1992

Many disease states are associated with perturbations in sodium and water balance. Thus, an understanding of body fluid regulation, as modulated by renal sodium and water excretion, has substantial implications for the practice of clinical medicine. The purpose of this article is to present a unifying hypothesis of body fluid volume regulation [1–5]. This hypothesis presumes the presence of normal intrinsic renal function in which extrarenal reflexes influence renal sodium and water excretion. Effects of acute or chronic renal parenchymal disease in causing sodium and water retention will therefore not be considered.

In normal subjects an increase in sodium and water intake is associated with an expansion of extracellular, interstitial and plasma volume. The normal response to this volume expansion is an increase in renal sodium and water excretion until restoration of normal total body sodium and water is achieved. It is the recognition of this normal response which has emphasised the clinical paradox of continued renal sodium and water retention which occurs in several clinical disorders in spite of expansion of extracellular, interstitial and plasma volume [1,2]. The study of these oedematous states, including cardiac failure, cirrhosis and pregnancy, has led to our proposal of a unifying hypothesis of body fluid volume regulation [1–5].

Cardiac failure

Earlier studies of cardiac failure led to two divergent proposals for the observed renal and water retention (Fig. 1). Starling [6] in Great Britain proposed the backward theory of cardiac failure in which venous congestion increases capillary pressure and causes transudation of fluid and electrolytes into the interstitium with oedema formation and plasma volume depletion. The decrease in plasma volume then initiates renal sodium and water retention. Peters [7], in the United States, also favoured this theory of cardiac failure and suggested that colloid administration would be the preferred treatment for cardiac failure. Stead and Ebert [8] challenged the backward theory of cardiac failure and proposed the forward theory of cardiac failure in which cardiac dysfunction would initiate renal sodium and water retention, resulting in plasma volume expansion. These workers therefore proposed that venesection should constitute the primary treatment of cardiac failure. Until accurate measurements of plasma and blood volume were available, it was not possible to distinguish between the two opposing theories of cardiac failure. Borst [9], from the Netherlands, suggested that cardiac output constitutes the signal whereby renal sodium and water excretion is regulated; however, subsequent measurements demonstrated that several states of sodium and water retention, including cirrhosis, high-output cardiac failure and pregnancy, were actually associated with increases in cardiac output.

When accurate methods became available to measure the volume of fluid in various body fluid compartments, it became clear that plasma and blood volumes were frequently expanded in patients with cardiac failure, cirrhosis and pregnancy. Our hypothesis suggests that the relative integrity or fullness of the arterial cir-

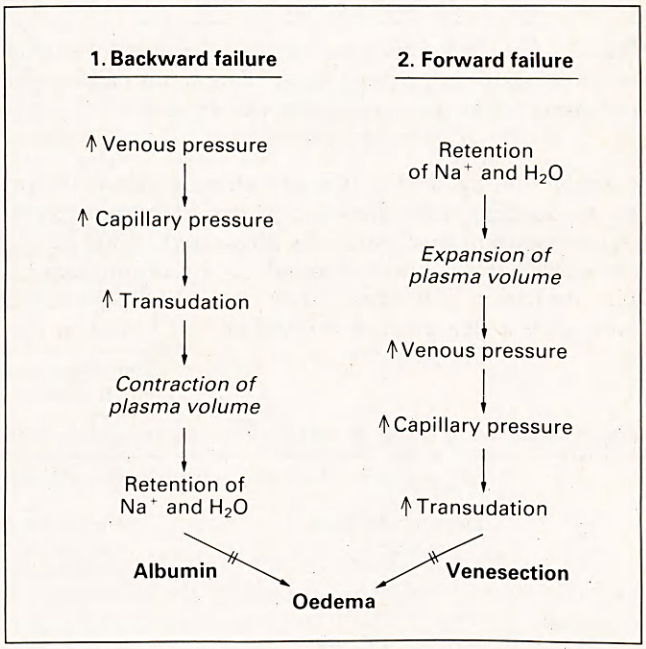


Fig. 1. *Backward (left) and forward (right) theories of heart failure* [7].

ROBERT W. SCHRIER, MD, *Professor and Chairman, Department of Medicine Head, Division of Renal Diseases and Hypertension, University of Colorado School of Medicine, Denver*

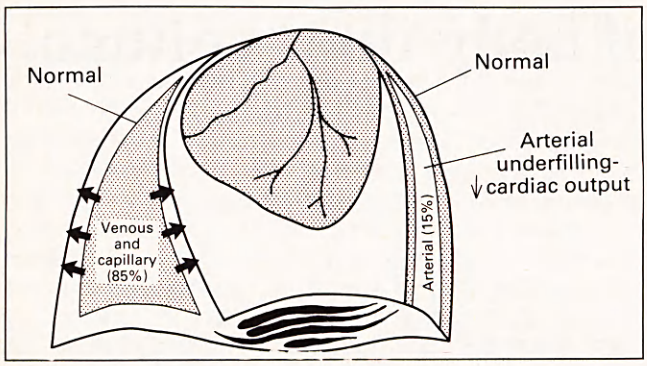
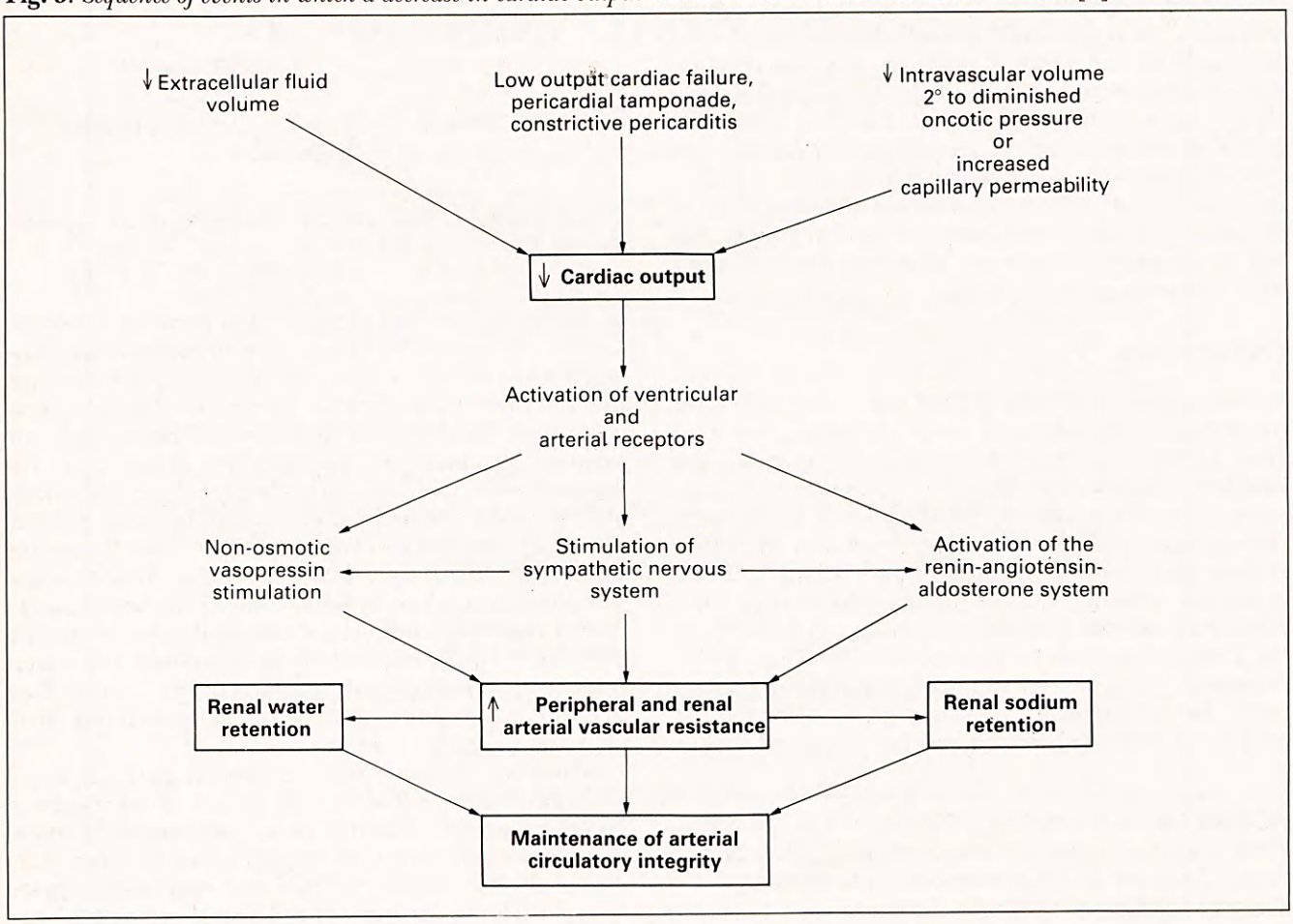


Fig. 2. *Total blood volume may be expanded because of venous congestion as arterial underfilling occurs due to either decreased cardiac output or arterial vasodilation.*

culation constitutes the primary afferent signal whereby the kidneys either increase or decrease their excretion of sodium and water. As illustrated in Fig. 2, an increase in the volume of blood on the venous side of the circulation may cause a rise in total blood volume even with a decrease in the volume of blood in the arterial circulation. This may occur because 85% or more of total blood volume has been estimated to be on the venous side of the circulation, while only 15% of the blood volume resides in the arterial circulation. A decrease in cardiac output is the most obvious reason for a decrease in arterial blood volume. But if this were the only afferent signal for underfilling of the arterial circulation, a unifying hypothesis of body fluid volume regulation would not be possible, given the previously cited oedematous disorders which are associated with increased cardiac outputs. A second determinant of the fullness of the arterial circulation is, however, the peripheral arterial vascular resistance and the compliance of the arterial vasculature. Peripheral arterial vasodilation therefore provides another afferent signal for arterial underfilling which causes renal sodium and water retention. Thus, with our unifying scheme of body fluid volume retention, either a decrease in cardiac output (Fig. 3) or peripheral arterial vasodilation (Fig. 4) may constitute the afferent signal for arterial underfilling, with the resultant renal sodium and water retention leading to expansion of total blood volume.

Fig. 3. *Sequence of events in which a decrease in cardiac output initiates renal sodium and water retention* [2].



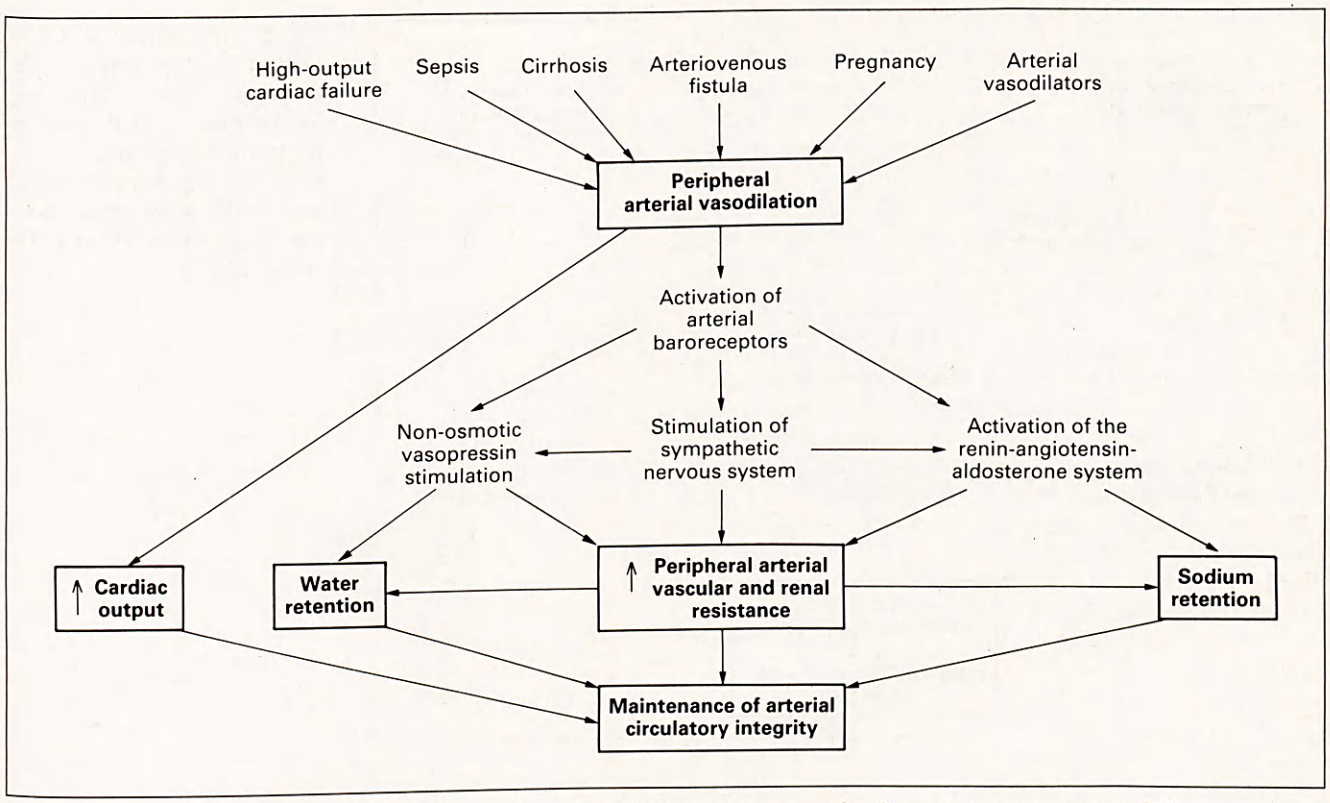


Fig. 4. *Sequence of events in which peripheral arterial vasodilation initiates renal sodium and water retention* [2].

Because of the speed of the compensatory efferent responses, arterial blood pressure is not a sensitive index of the presence of arterial underfilling in cardiac failure or cirrhosis. Rather, it is only with advanced disease states that the compensatory responses to arterial underfilling become insufficient to maintain mean arterial pressure. Moreover, even if sensitive methods for accurately measuring the volume of blood in the arterial circulation (generally less than 2% of total body fluid) were available, the absolute measured arterial blood volume could be greater than that of normal subjects in spite of relative arterial underfilling caused by peripheral arterial vasodilation.

Figure 5 shows the different afferent signals for low-output and high-output heart failure. Low-output failure causes arterial underfilling which is then associated with a compensatory increase in peripheral vascular resistance. In contrast, with high-output cardiac failure, as in beriberi or hyperthyroidism, primary peripheral vasodilation occurs and results in a rise in cardiac output secondary to afterload reduction. There is considerable evidence that the compensatory responses to arterial underfilling with low and high cardiac output are comparable [1].

Figure 6 demonstrates the haemodynamic and neurohumoral responses to progressive, low-output cardiac failure. It is known that pretreatment hyponatraemia correlates with high plasma renin activity and indicates a poor prognosis [10]. Similarly, in patients in cardiac failure high plasma renin activity and plasma norepinephrine in the absence of diuretic therapy are harbingers of high mortality [11,12]. Tritiated norepinephrine kinetic studies in patients with cardiac dysfunction have shown that plasma norepinephrine levels are raised because of increased release rather than decreased norepinephrine clearance, findings which are compatible with adrenergic stimulation [13]. With arterial underfilling secondary to cardiac dysfunction, it would be expected that renal sodium and water retention could progress and lead to pulmonary congestion and peripheral oedema.

Several receptor sites may sense arterial underfilling: they include the left ventricle, carotid, aortic arch, and renal baroreceptors. With arterial underfilling the sympathetic activation of renal beta-adrenergic receptors stimulates the renin-angiotensin-aldosterone system, and central adrenergic stimulation increases the non-osmotic release of vasopressin [1]. Thus, plasma aldosterone and vasopressin would be expected to be involved in the sodium and water retention of heart failure. In this regard, the specific receptor antagonist for aldosterone, spironolactone, increases sodium excretion in cardiac failure patients (Fig. 7) [14]. That aldosterone-mediated sodium retention is a compensatory response to arterial underfilling is supported by the finding that the spironolactone-induced natriuresis is associated with further stimulation of plasma renin activity and plasma norepinephrine and a

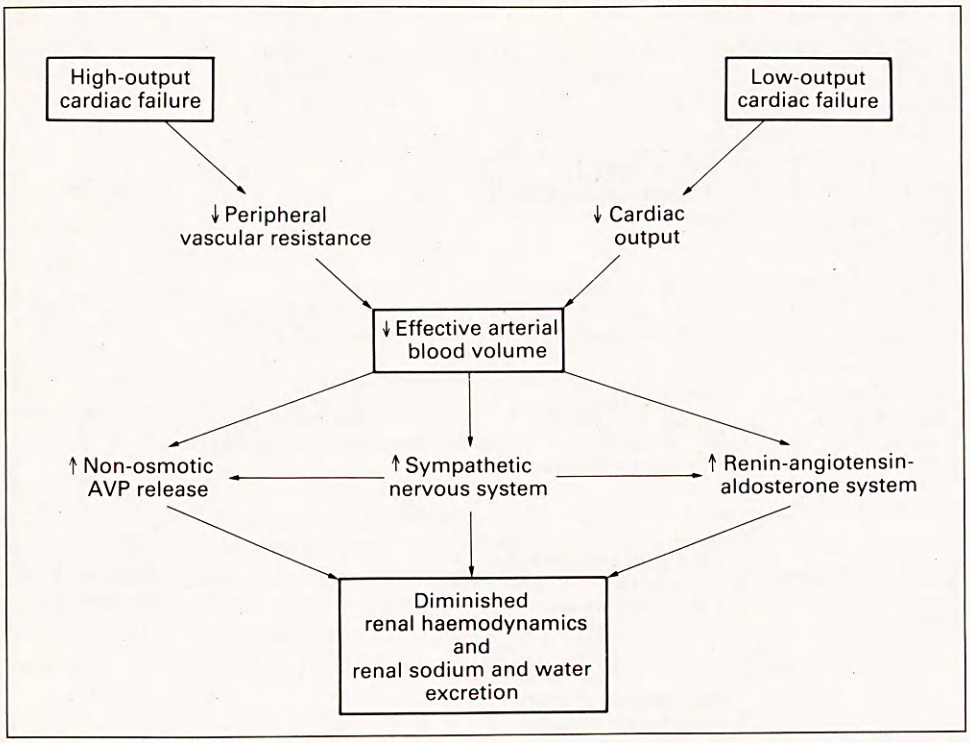


Fig. 5. *High-output and low-output cardiac failure.* Although the initiating 'underfill' event differs in high- and low-output failure, the subsequent pathways leading to renal sodium and water retention are similar [1].

decrease in plasma atrial natriuretic peptide (ANP) concentration [14].

An increase in plasma ANP is the earliest hormonal change in cardiac failure. However, the apparently normal plasma concentrations of renin, norepinephrine and aldosterone in patients with early cardiac dysfunction are actually abnormally high with respect to the observed plasma volume expansion, which in control subjects would suppress the concentration of these plasma hormones. Moreover, plasma ANP also suppresses plasma renin and aldosterone [15]; thus the increased plasma ANP may contribute to the 'normal' plasma concentrations of these hormones in early heart failure.

Using a sensitive radioimmunoassay, plasma vasopressin has been shown to be increased relative to the decreased plasma osmolality in patients with cardiac failure [16]. Moreover, a V_2 antidiuretic antagonist for vasopressin can completely reverse the abnormal water excretion in rats with acutely diminished cardiac outputs [17].

The arterial underfilling hypothesis also provides a potential explanation for: (1) the failure of such patients to escape from the sodium retaining effect of aldosterone, and (2) resistance to the natriuretic and diuretic responses to exogenous ANP. Arterial underfilling occurring secondary to either a decrease in cardiac output or peripheral arterial vasodilation activates mediators which decrease filtered sodium load and increase proximal tubule sodium reabsorption; together these effects diminish distal sodium delivery to the collecting duct site of action of aldosterone and ANP (Fig. 8). It is therefore proposed that diminished distal sodium delivery accounts for the ANP resistance [18] and impaired aldosterone escape which characterise heart failure [1,2]. ANP receptor down-regulation or ANP inactivation by increased neutral endopeptidase activity in the proximal tubule do not seem to account for ANP resistance in heart failure, since a linear correlation between plasma ANP and its secondary messenger, urinary cGMP, has been found in cardiac failure patients [19]. Studies in rats with experimental heart failure have also demonstrated that renal denervation reverses the resistance to ANP [20] (Fig. 9). Since proximal sodium reabsorption is enhanced by

Fig. 6. *Neurohumoral and plasma volume responses to progressive cardiac failure.* New York Heart Classification II, III and IV [3]. AVP = arginine vasopressin; NE = norepinephrine.

Cardiac index	Class II	Class III	Class IV
	↓	↓↓	↓↓↓
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

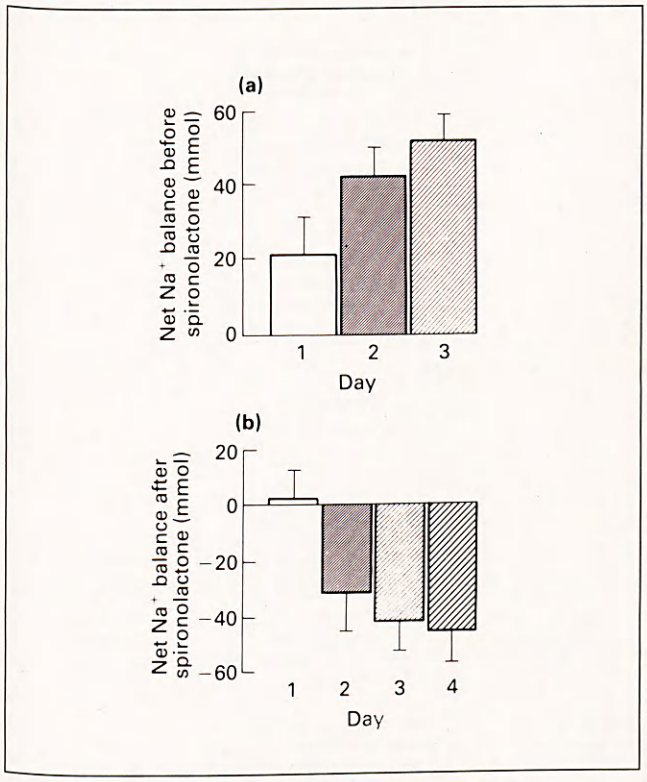


Fig. 7. *Reversal of Na^+ retention in congestive heart failure patients by aldosterone antagonism.* Net positive cumulative Na^+ balance by day for the periods before spironolactone (top panel) and net negative cumulative Na^+ balance after the initiation of spironolactone 400 mg/d (bottom panel). The increase in Na^+ excretion with spironolactone was significant ($p<0.01$) [14].

adrenergic stimulation, the effect of renal denervation to enhance ANP sensitivity in cardiac failure is also compatible with a role of distal sodium delivery.

The compensatory responses to arterial underfilling can become maladaptive in advanced cardiac failure (Fig. 10). Since effective cardiac inotropic agents are not readily available for clinical practice, small doses of angiotensin converting enzyme (ACE) inhibitors have been used to reduce cardiac afterload and thereby shift the cardiac output to a more beneficial part of the Frank-Starling curve. The CONSENSUS study has shown that in class IV cardiac failure patients (New York Heart Association classification) with the highest plasma concentrations of angiotensin II, norepinephrine, aldosterone and ANP, administration of the ACE inhibitor, enalapril, improves six-month survival [21] (Fig. 11). More recent studies in patients with less severe heart failure have also shown a benefit from ACE inhibition [22]. But if the dose of ACE inhibitor is too large, diminished vascular resistance may decrease blood pressure and obscure any improvement in cardiac function.

Cirrhosis

As with heart failure, two theories for sodium and water retention have been proposed: the 'underfilling hypothesis', in which plasma volume is thought to be decreased, and the 'overfill hypothesis', in which it is thought to be expanded (Fig. 12). With the classical 'underfilling hypothesis', ascites formation secondary to portal hypertension is believed to decrease plasma volume and cause secondary renal sodium and water retention [23]. Since plasma volume expansion ante-

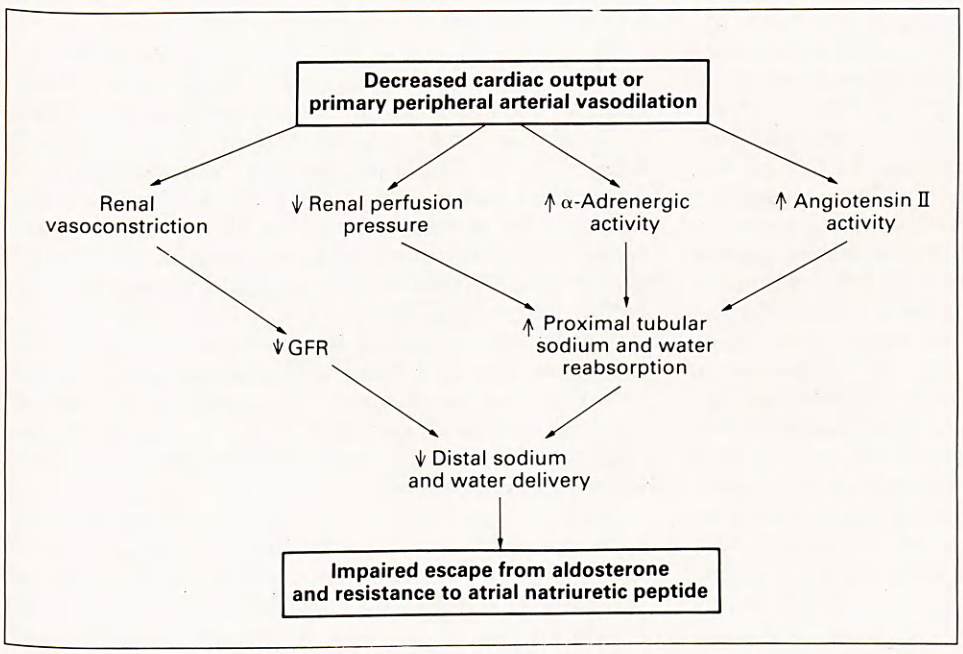


Fig. 8. *A decrease in cardiac output or peripheral arterial vasodilation can initiate events which diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to the natriuretic response to atrial natriuretic peptide (ANP)* [27].

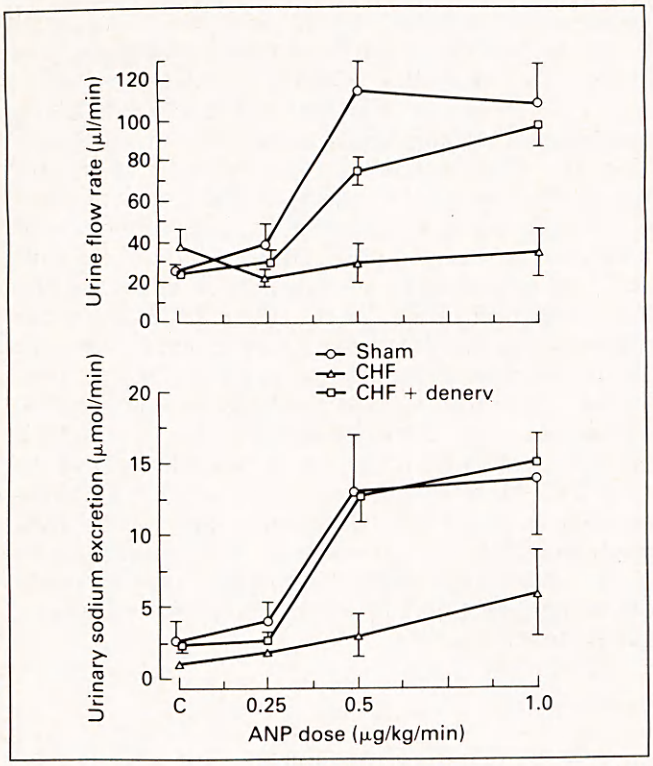


Fig. 9. *Effect of renal denervation (denerv) to reverse ANP resistance in experimental cardiac heart failure (CHF)* [20].

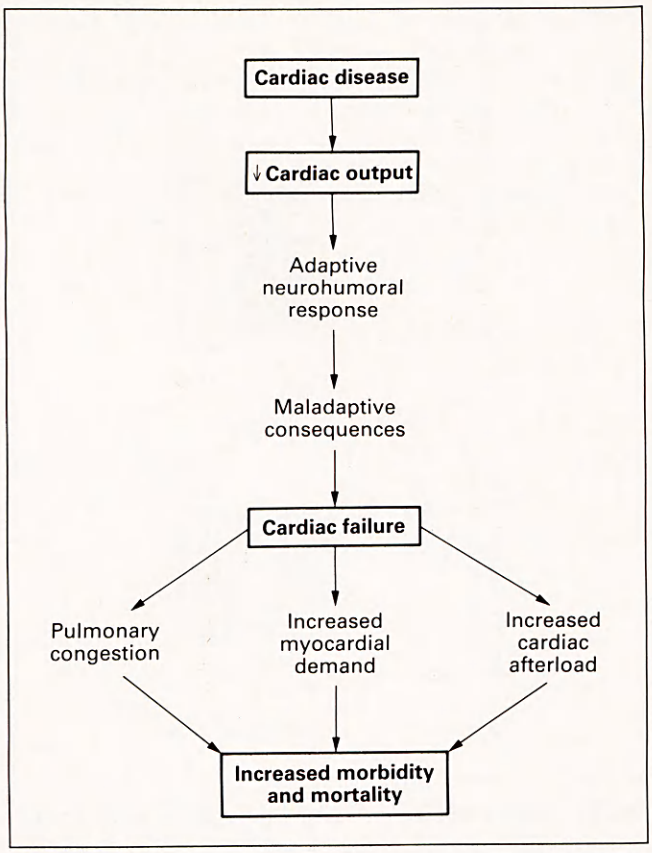


Fig. 10. *Compensatory responses become maladaptive in advanced cardiac failure* [3].

cedes ascites formation [24], the 'underfilling hypothesis' no longer seems tenable. Thus primary renal sodium and water retention, secondary to a hepatorenal reflex, has been proposed to lead to plasma volume expansion (both venous and arterial compartments) and cause overflow ascites in cirrhotic patients [24]. This 'overflow hypothesis' does not, however, explain the progressive stimulation of the neurohumoral profile which is observed in cirrhotic patients and is characteristic of arterial underfilling [1–4].

Since neither the 'underfilling' nor the 'overflow' hypothesis can adequately explain the spectrum of clinical states associated with cirrhosis, the 'peripheral arterial vasodilation hypothesis' has been proposed [4] (Fig. 13). With this hypothesis splanchnic vasodilation occurs early in cirrhosis and the resultant arterial underfilling stimulates sodium and water retention with plasma volume expansion prior to ascites formation. The normal plasma hormone concentrations in these compensated cirrhotic patients are relatively high for the degree of plasma volume expansion. The mediators of the early splanchnic vasodilation in cirrhosis are unknown but may include the opening of existing shunts, activation of vasodilating hormones, and ultimately the development of collateral vessels. As cirrhosis progresses, vasodilation occurs at other sites, including the skin, muscle and lung. As with cardiac failure, pretreatment hyponatraemia and high plasma concentrations of renin, norepinephrine and aldosterone bode a poor prognosis for the cirrhotic patient [4]. The highest plasma concentrations of these hormones and the lowest blood pressures occur as the decompensated cirrhotic patient with ascites progresses toward the hepatorenal syndrome.

The major detraction from the peripheral arterial vasodilation hypothesis is the finding that some compensated cirrhotic patients exhibit a low plasma renin activity and a greater natriuresis than normal subjects in the supine position [25] and with head-out water immersion (HWI) [26]. These findings can, however, be explained by centralisation of excessive splanchnic fluid in cirrhotic patients in the supine position or HWI. In this regard, the compensated cirrhotic patients who respond to HWI with an exaggerated natriuresis were those with the highest plasma ANP concentrations [26]. Moreover, compensated cirrhotic patients with low plasma renin activity in the supine position demonstrate normal or increased plasma renin activity in the upright position [Bernardi, personal communication].

As with other states of arterial underfilling, the neurohumoral responses to the peripheral arterial vasodilation of cirrhosis, such as the impaired aldosterone escape [27] and resistance to ANP [28], are associated with factors which diminish distal sodium

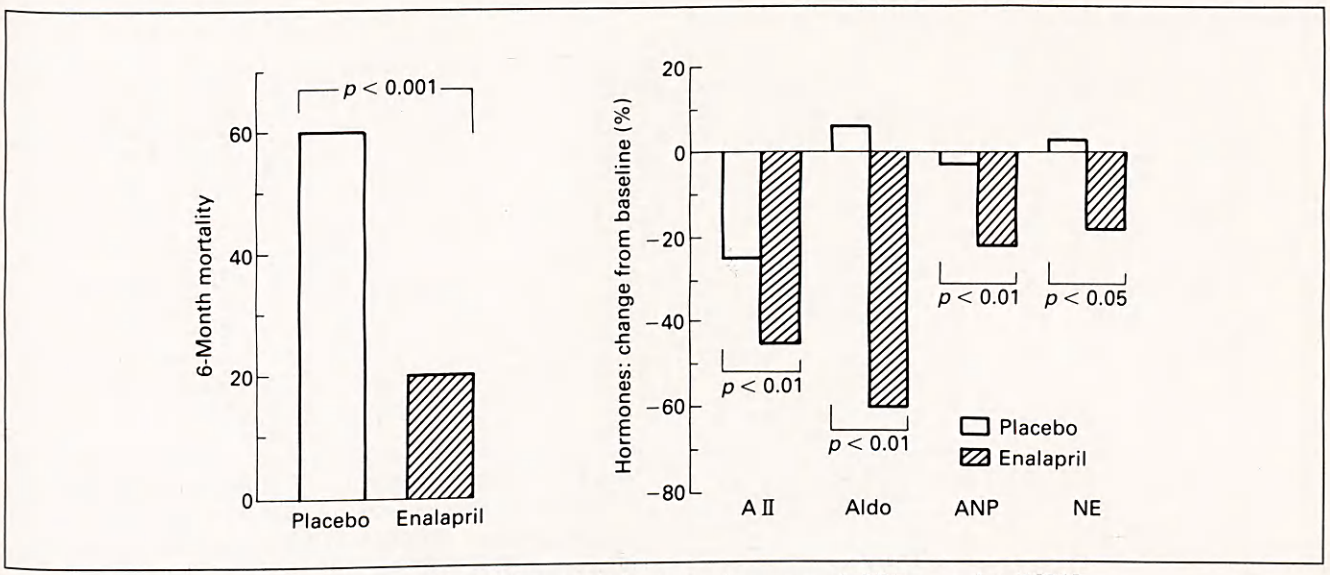


Fig. 11. *Prolongation of life in advanced heart failure with the converting enzyme inhibitor, enalapril* [21].

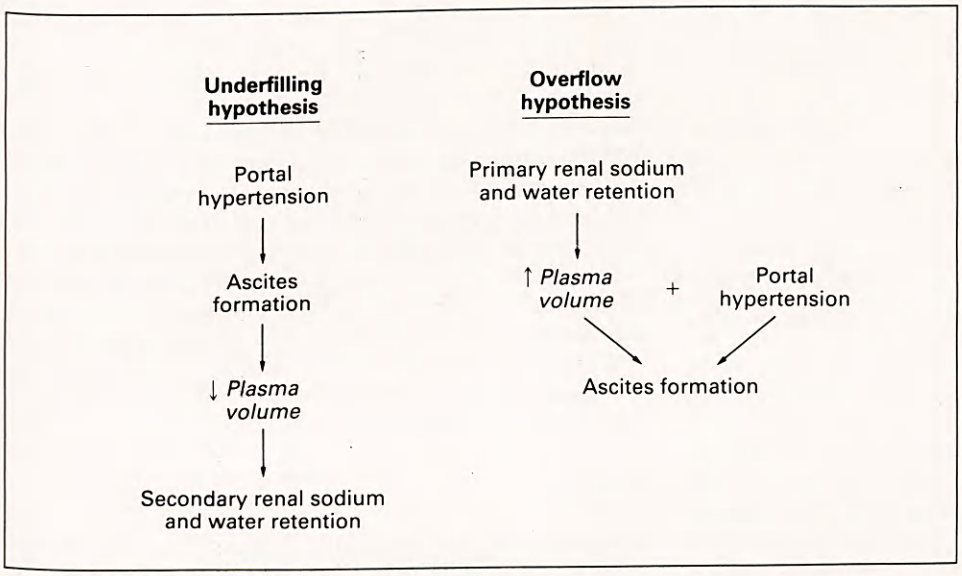


Fig. 12. *Underfilling (left) and overflow (right) hypotheses of renal sodium and water retention in cirrhosis* [3].

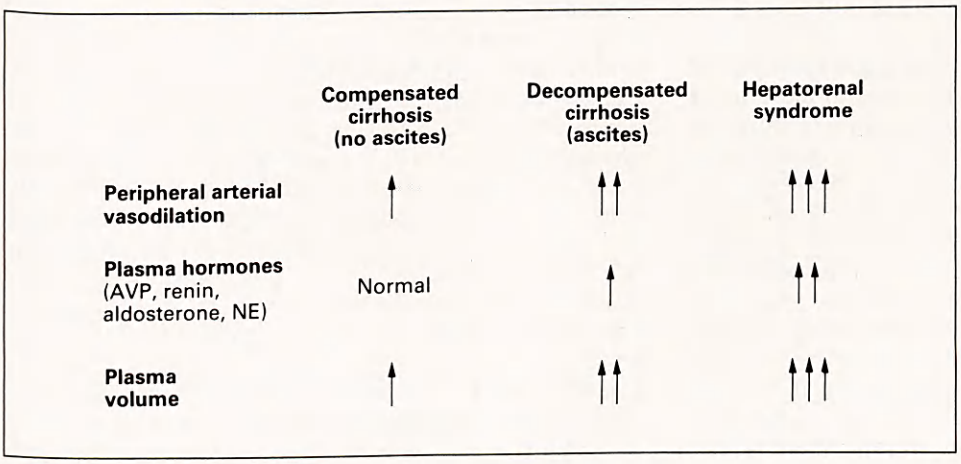


Fig. 13. *Peripheral arterial vasodilation hypothesis.* Normal plasma hormone concentrations indicate relative stimulation in the presence of plasma volume expansion. Hypoalbuminaemia may attenuate plasma volume expansion. AVP = arginine vasopressin; NE = norepinephrine. (Schrier RW, ed. In: *Manual of nephrology*, 3rd edn. Boston: Little Brown, 1990:1–19)

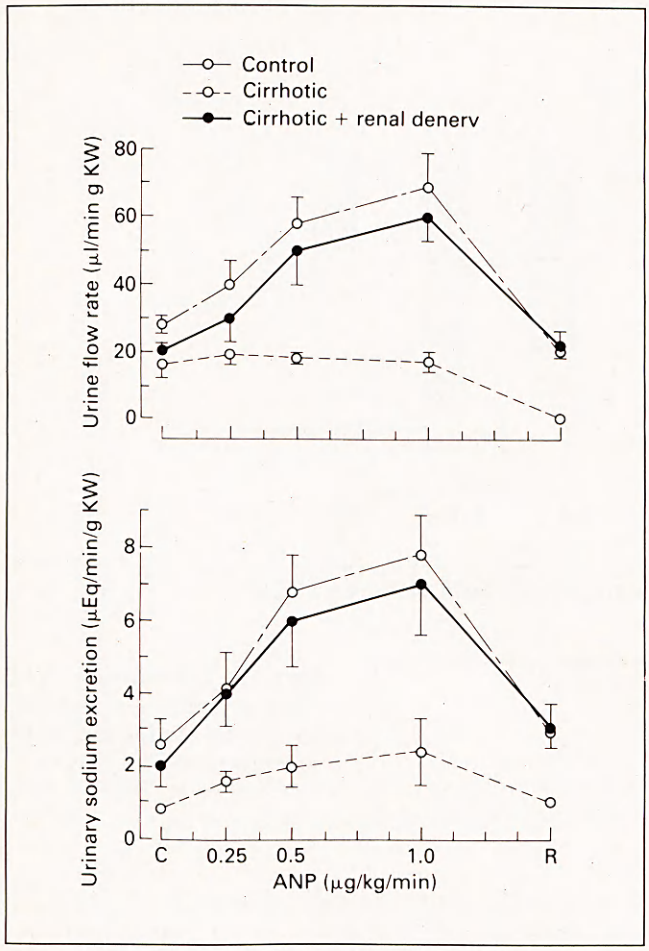


Fig. 14. *Effect of renal denervation (denerv) to reverse resistance to the natriuretic response to ANP* [29].

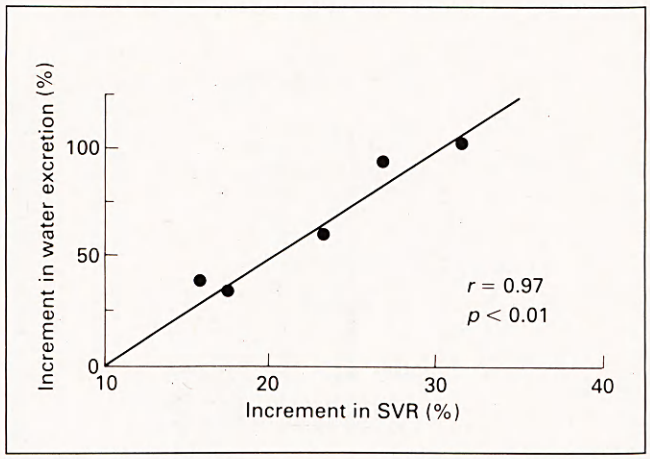


Fig. 15. *Correlation between the increase in systemic vascular resistance (SVR) and increase in water load excretion from immersion alone (HWI) to immersion with norepinephrine infusion (HWI + NE);* $r = 0.97$, $p<0.01$ [32].

delivery [27] (Fig. 8). As with experimental heart failure, renal denervation reverses the resistance to ANP in experimental cirrhosis [29] (Fig. 14). This finding supports a role for diminished distal sodium delivery in ANP resistance, particularly since Skorecki *et al* [28] have demonstrated a normal increase in urinary cGMP but no natriuresis in some cirrhotic patients infused with ANP.

The Barcelona group recently studied aldosterone escape in compensated cirrhotic patients without ascites [30]. They found that lower peripheral vascular resistances were present in those patients with impaired mineralocorticoid escape, but found no difference in liver enzymes, serum albumin, electrolytes, creatinine, and blood urea nitrogen levels between cirrhotic patients who escaped versus those who did not escape from the sodium retaining effect of mineralocorticoid hormone; nor were there differences in the hepatic venous pressure gradients between the two groups. Taken together, these findings do not support increased intrahepatic pressure as the primary determinant of sodium and water retention in cirrhosis [31], but do support the peripheral arterial vasodilation hypothesis [4].

The role of peripheral arterial vasodilation has been studied in decompensated cirrhotic patients with and without exogenous norepinephrine and HWI [32]. This combined manoeuvre acutely normalised renal sodium and water excretion in these ascitic patients. There was a statistically high correlation between the diuretic response and the increment in peripheral vascular resistance in these studies (Fig. 15), providing further support for the peripheral arterial vasodilation hypothesis. On this pathogenetic background, potential treatment strategies can be devised to decrease the morbidity and mortality in cirrhosis; one such theoretical strategy is shown in Fig. 16 [3].

Pregnancy

Pregnancy is associated with dramatic haemodynamic and humoral changes. Among them are a 30–50% increase in total plasma, blood and extracellular fluid volume, accompanied by a 30–50% increase in cardiac output, renal blood flow, and glomerular filtration rate. It has been suggested that the plasma volume expansion may account for the increase in renal haemodynamics; however, the rise in cardiac output, glomerular filtration rate and renal blood flow antecedes the plasma volume expansion in pregnancy [33] (Fig. 17). Another enigma of pregnancy is the stimulation of the renin-angiotensin-aldosterone system, a hormonal index of arterial underfilling. In non-pregnant individuals a 30–50% expansion of plasma volume would suppress the renin-angiotensin-aldosterone system.

There are also other characteristics of pregnancy that are not compatible with primary renal sodium and water retention leading to expansion of plasma

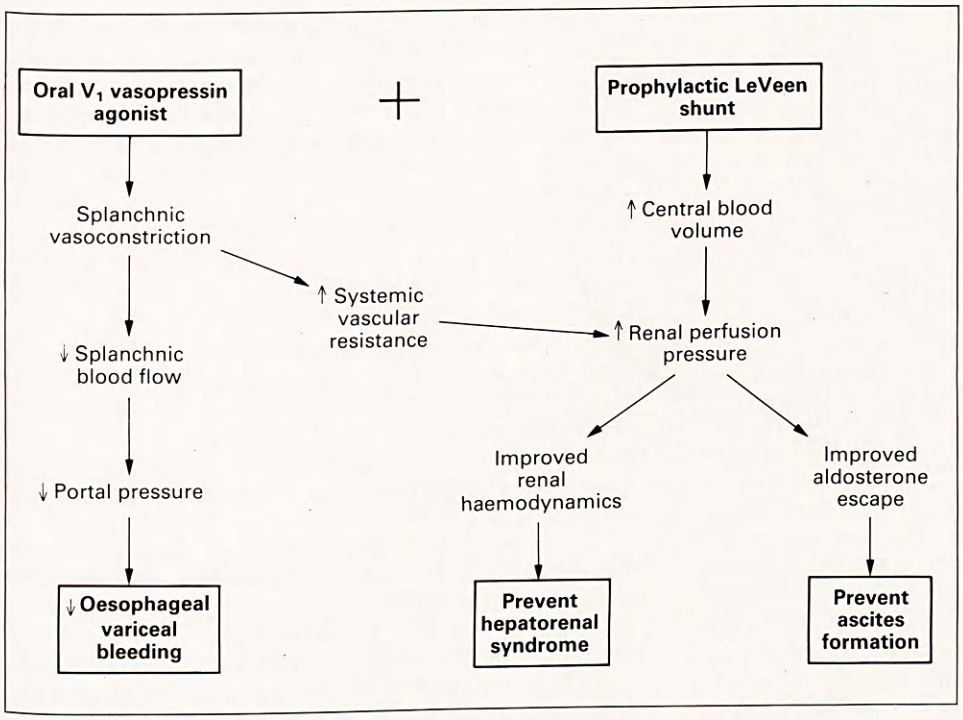
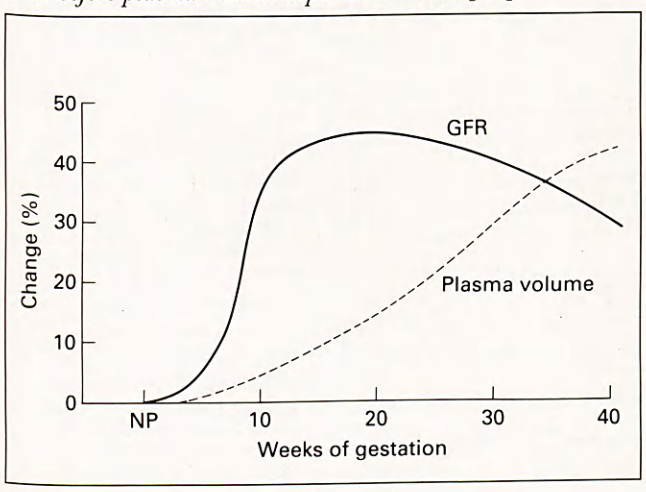


Fig. 16. *Proposed future treatment strategy for decompensated cirrhosis.* [3].

and extracellular fluid volume. We have recently proposed that primary peripheral arterial vasodilation is the major initiating factor in pregnancy to cause arterial underfilling and the resultant compensatory responses [5]. For example, in the first trimester of normal pregnancy blood pressure falls as cardiac output rises in association with a primary decrease in peripheral vascular resistance. In contrast, primary volume expansion with an increase in cardiac output and a secondary peripheral vasodilation would not explain the decrease in blood pressure which occurs during the first trimester of pregnancy. Moreover, primary peripheral arterial vasodilation is associated with stimulation of the renin-angiotensin-aldosterone system (Fig. 4), a normal occurrence in pregnancy [1].

Fig. 17. *In pregnant women glomerular filtration rate (GFR) rises before plasma volume expansion occurs* [33].



The most compatible explanation for the decrease in plasma sodium and osmolality which occurs in pregnancy is peripheral vasodilation and arterial underfilling. The increase in thirst and water intake that occurs in the first trimester of pregnancy [34] is another effect most compatible with arterial underfilling due to peripheral arterial vasodilation.

If the plasma volume expansion of pregnancy involves both the venous and arterial circulatory compartments, the blood volume threshold (ml/kg body weight) for the non-osmotic release of vasopressin during volume depletion should approximate that of the non-pregnant state. It has, however, been shown in the rat that the non-osmotic stimulation of vasopressin in pregnancy occurs at a blood volume which is 40% greater than in the non-pregnant state [35] (Fig. 18). Moreover, the expected blunting of the tubuloglomerular feedback with volume expansion in the rat also does not occur in pregnancy [36]. Either an angiotensin antagonist or an angiotensin converting enzyme inhibition [37] lowers blood pressure more in the pregnant than the non-pregnant rat [37]. Taken together, these findings are best explained by primary peripheral arterial vasodilation causing arterial underfilling, with secondary stimulation of the renin-angiotensin-aldosterone system. Hormonal and haemodynamic measurements in the pregnant baboon support this hypothesis [38].

In the absence of pre-eclampsia/eclampsia the sodium and water retention in pregnancy is not of the

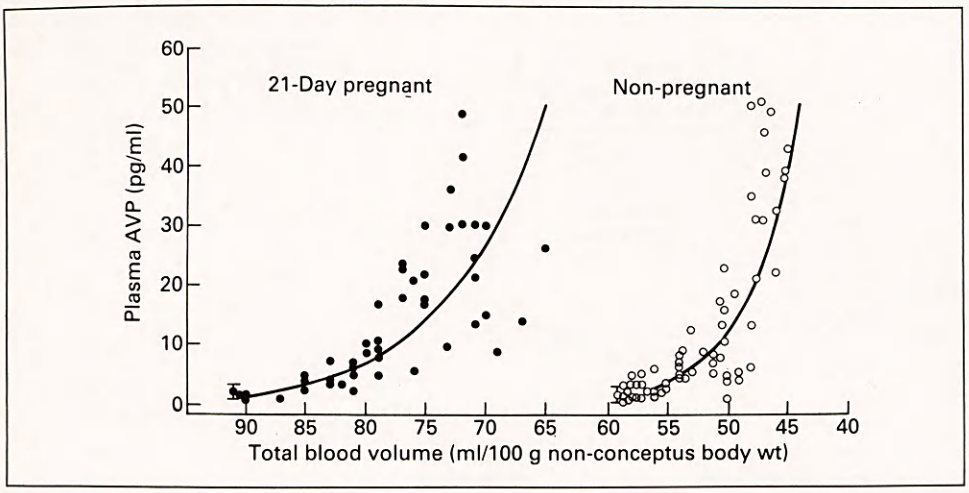
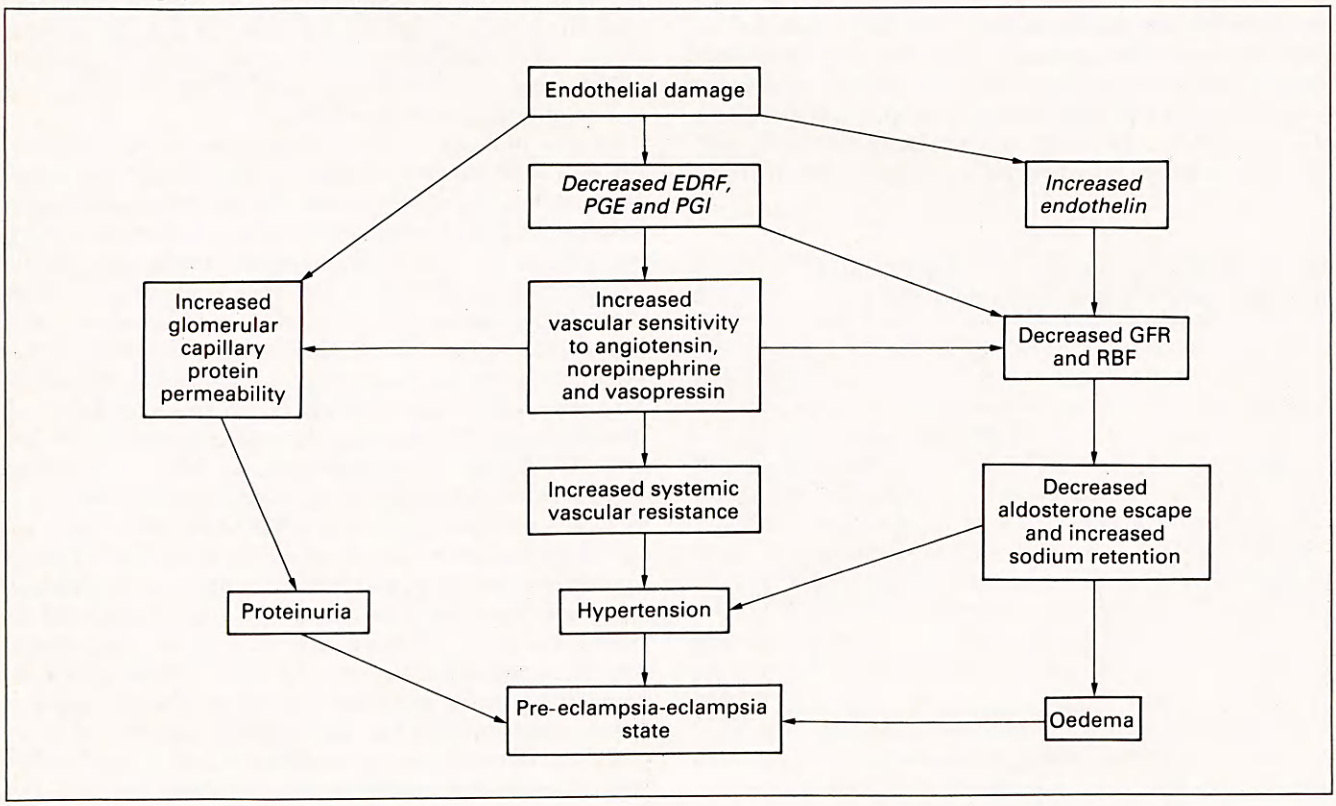


Fig. 18. *The rise in plasma AVP in response to hypovolaemia occurs at a larger total blood volume in pregnant rats than in nonpregnant rats* [35].

degree observed with other states of arterial underfilling, such as cardiac failure and cirrhosis, nor is there good evidence of impaired mineralocorticoid escape with normal pregnancy. The capacity to handle salt and water normally in pregnancy in spite of arterial underfilling most likely relates to the 30–50% increase in glomerular filtration rate and thus filtered sodium and water. Support for this interpretation comes from the observation that the more avid sodium and water retention occurs during pre-eclampsia/eclampsia, a state associated with a fall in glomerular filtration rate to non-pregnant levels.

It remains a major challenge to identify the factor(s) that mediate(s) the enhanced renal blood flow and glomerular filtration rate during pregnancy. Renal vasodilation not only antedates the blood volume expansion of pregnancy but also occurs in spite of peripheral arterial vasodilation, an event generally associated with reflex renal vasoconstriction. There is indirect evidence that the source of this potent renal

Fig. 19. *Pathophysiologic schema for pre-eclampsia and eclampsia* [5].



vasodilation of pregnancy may be the endothelium, since the fall in renal haemodynamics in pre-eclampsia/eclampsia is associated with glomerular capillary abnormalities known as glomerular endotheliosis. While a fall in vasodilating prostaglandins may be involved in pre-eclampsia/eclampsia, there is considerable experimental evidence that these hormones cannot be the sole mediator of the enhanced renal haemodynamics of normal pregnancy. Specifically, inhibition of prostaglandin synthesis does not reverse the high glomerular filtration rate and renal blood flow in the pregnant rat [39]. The results of the administration of antagonists of endothelium derived relaxing factor (EDRF) in the pregnant rat did not support a role for EDRF as the mediator of the systemic renal vasodilation of pregnancy [40]. Nevertheless, the increased circulating cGMP, the second messenger of EDRF, observed in pregnant rats is compatible with this mechanism [41]. The discovery of the nature of the systemic and renal vasodilator(s) of pregnancy could have important implications for the treatment of not only pre-eclampsia/eclampsia but also states of acute and chronic renal failure.

In summary, the understanding of the physiology of normal pregnancy in the context of our unifying hypothesis of body fluid volume regulation provides potential insights for the pre-eclampsia/eclampsia state. Figure 19 shows a suggestion for the pathogenesis of the pre-eclampsia/eclampsia state which is initiated by endothelial damage [5]. The hallmarks of pre-eclampsia/eclampsia, including the observed increased sensitivity to angiotensin, fall in glomerular filtration rate and renal blood flow, hypertension, oedema and proteinuria, can be explained by this hypothesis.

References

1 Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. *N Engl J Med* 1988;**319**:1065–72 (Part 1);1127–34 (Part 2).

2 Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med* 1990;**113**:155–9.

3 Schrier RW. An odyssey into the milieu intérieur: pondering the enigmas. *J Am Soc Nephrol* 1992; in press.

4 Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;**8**:1151–7.

5 Schrier RW, Briner VA. Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy: implications for pathogenesis of pre-eclampsia/eclampsia. *Obstet Gynecol* 1991;**77**:632–9.

6 Starling EH. *Fluids of body*. The Herter Lectures (New York, 1908). Chicago: WT Keener and Co, 1909.

7 Peters JP. The problem of cardiac edema. *Am J Med* 1952;**12**:66.

8 Stead EA Jr, Ebert RV. Shock syndrome produced by failure of heart. *Arch Intern Med* 1942;**69**:369–83.

9 Borst JG, deVries LA. Three types of 'natural' diuresis. *Lancet* 1950;**2**:1–6.

10 Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986;**73**:257–67.

11 Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation* 1981;**63**:645–51.

12 Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;**49**:1659–66.

13 Abraham WT, Hensen J, Schrier RW. Elevated plasma noradrenaline concentrations in patients with low-output cardiac failure: dependence on increased noradrenaline secretion rates. *Clin Sci* 1990;**79**:429–35.

14 Hensen J, Abraham WT, Durr JA, Schrier RW. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. *Am J Nephrol* 1991;**11**:44–6.

15 Lee ME, Miller WL, Edwards BS, Burnett JC Jr. Role of endogenous atrial natriuretic factor in acute congestive heart failure. *J Clin Invest* 1990;**84**:1962–6.

16 Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N Engl J Med* 1981;**305**:263–6.

17 Ishikawa S, Saito T, Okada K, Tsutsui K, Kuzuya T. Effect of vasopressin antagonist on water excretion inferior vena cava constriction. *Kidney Int* 1986;**30**:49–55.

18 Koepke JP, DiBona GF. Blunted natriuresis to atrial natriuretic peptide in chronic sodium-retaining disorders. *Am J Physiol* 1987;**252**:F865–71.

19 Hensen J, Abraham WT, Lesnefsky EJ, Levenson B, Groves BM, Schroder K, *et al.* Atrial natriuretic factor kinetic studies in patients with cardiac dysfunction. *Kidney Int* 1992;**42**:1333–9.

20 Pettersson A, Hedner J, Hedner T. Renal interaction between sympathetic activity and ANP in rats with chronic ischaemic heart failure. *Acta Physiol Scand* 1989;**135**:487–92.

21 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–35.

22 The SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293.

23 Papper S. The role of the kidney in Laennec's cirrhosis of the liver. *Medicine* 1958;**37**:299–316.

24 Lieberman FL, Denison EK, Reynolds TB. The relationship of plasma volume, portal hypertension, ascites, and renal sodium and water retention in cirrhosis: the 'overflow' theory of ascites formation. *Ann NY Acad Sci* 1970;**170**:202–6.

25 Trevisni F, Bernardi M, Gasbarrini A, Tame MR, Giancane S, Andreone P, *et al.* Bed-rest-induced hypernatriuresis in cirrhotic patients without ascites: does it contribute to maintain 'compensation'. *J Hepatol* 1992; in press.

26 Campbell PJ, Leung WM, Logan AG, Debowski TE, Blendis LM, Skorecki KL. Hyperresponsiveness to water immersion in sodium retaining cirrhotics: the role of atrial natriuretic factor. *Clin Invest Med* 1988;**11**:392–5.

27 Schrier RW, Better OS. Pathogenesis of ascites formation: mechanism of impaired aldosterone escape in cirrhosis. *Eur J Gastroenterol Hepatol* 1991;**3**:721–9.

28 Skorecki KL, Leung WM, Campbell P, Warner LC, Wong PY, Bull S, *et al.* Role of atrial natriuretic peptide in the natriuretic response to central volume expansion induced by head-out water immersion in sodium-retaining cirrhotic subjects. *Am J Med* 1988;**85**:375–82.

29 Koepke JP, Jones S, DiBona GF. Renal nerves mediate blunted natriuresis to atrial natriuretic peptide in cirrhotic rats. *Am J Physiol* 1987;**252**:R1019–23.

30 La Villa G, Salmeron JM, Arroyo V, Bosch J, Ginés P, García-Pagán JC, *et al.* Mineralocorticoid escape in patients with compensated cirrhosis and portal hypertension. *Gastroenterology* 1992;**102**:2114–9.

31 Unikowsky B, Wexler MJ, Levy M. Dogs with experimental cirrhosis of the liver but without intrahepatic hypertension do not retain sodium or form ascites. *J Clin Invest* 1983;**72**:1594–604.
32 Shapiro MD, Nicholls KM, Groves BM, Kluge R, Chung HM, Bichet DH, Schrier RW. Interrelationship between cardiac output and vascular resistance as determinants of effective arterial blood volume in cirrhotic patients. *Kidney Int* 1985;**28**:206–11.
33 Davison JM. Renal haemodynamics and volume homeostasis in pregnancy. *Scand J Clin Lab Invest* (Suppl) 1984;**169**:15.
34 Davison JM, Gilmore EA, Durr J, Robertson GL, Lindheimer MD. Altered osmotic thresholds for vasopressin and thirst in human pregnancy. *Am J Physiol* 1984;**246**:F105–9.
35 Barron WM, Stamoutsos B, Lindheimer MD. Osmoregulation during pregnancy in the rat: evidence for resetting of the threshold for vasopressin secretion during gestation. *J Clin Invest* 1981;**68**:337–46.
36 Baylis C, Blantz RC. Tubuloglomerular feedback activity in virgin and 12-day-pregnant rats. *Am J Physiol* 1985;**249**:F169–73.
37 Baylis C, Collins RC. Angiotensin II inhibition on blood pressure and renal hemodynamics in pregnant rats. *Am J Physiol* 1986;**250**:F308–14.
38 Phippard AF, Horvath JS, Glynn EM. Circulatory adaptation to pregnancy—serial studies of haemodynamics, blood volume, renin and aldosterone in the baboon (*Papio hamadryas*). *J Hypertension* 1986;**4**:773–9.
39 Conrad JP, Colpoys MC. Evidence against the hypothesis that prostaglandins are the vasodepressor agents of pregnancy: serial studies in chronically instrumented, conscious rat. *J Clin Invest* 1986;**77**:236–45.
40 Umans JG, Lindheimer MD, Barron WM. Pressor effect of endothelium-derived relaxing factor inhibition in conscious virgin and gravid rats. *Am J Physiol* 1990;**259**:F293–6.
41 Conrad KP: Possible mechanisms for changes in renal hemodynamics during pregnancy: studies from animal models. *Am J Kidney Dis* 1987;**9**:253–9.

Address for correspondence: Dr Robert W. Schrier, C281, University of Colorado School of Medicine, 4200 East 9th Avenue, Denver, CO 80262, USA.