Water retention and aquaporins in heart failure, liver disease and pregnancy

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Water retention in excess of total body sodium frequently occurs in patients with cardiac failure or cirrhosis and in pregnancy. In fact, hyponatraemia signifies a poor prognosis in cardiac failure and cirrhosis[1,2]. The mechanism for this hyponatraemia, however, has not been well defined. In the era when the antidiuretic hormone (ADH) bioassay was performed in ethanol-anaesthetized rats, consistent alterations in ADH could not be demonstrated in hyponatraemic patients with cirrhosis or heart failure. Therefore it was suggested that intrarenal, non-ADH-dependent, mechanisms accounted for the water retention in these oedematous disorders.

Another dilemma in understanding fluid balance in cardiac failure, cirrhosis and pregnancy relates to defining the afferent signals that could stimulate AVP release with resultant water retention. Expanded plasma volumes have been reported in all three conditions. This finding is typically associated with increased water excretion rather than water retention; thus, signals other than increased plasma volume must contribute to the water retention.

PREVIOUSLY PROPOSED MECHANISMS OF SODIUM AND WATER RETENTION

Backward versus forward cardiac failure

Two opposing theories have been proposed to explain the pathogenesis of water and sodium retention in cardiac failure (Figure 1)[3–5]. With backward failure[3,4], pump failure produces an increase in venous pressure with resultant transudation of fluid from the intravascular compartment to the interstitial space, oedema formation and decreased plasma volume. The diminution of plasma volume then stimulates renal sodium and water retention. This hypothesis was not compatible with the observed expanded plasma volumes in heart-failure patients. In contrast, with the forward failure theory[5], heart failure causes renal underperfusion with decreased sodium and water excretion and increased plasma volume.

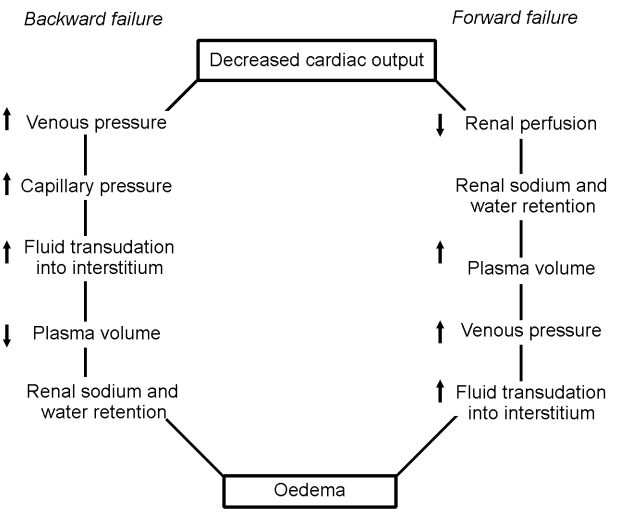

Figure 1 **Backward and forward theories of heart failure** [Modified by permission, from Peters JP, *Am J Med* 1952;**12**:66]

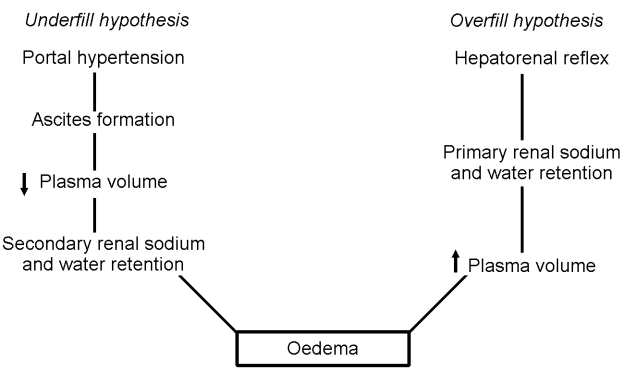

Figure 2 **Underfill and overfill hypotheses of oedema formation in cirrhosis** [Modified by permission, from Schrier RW, *J R Coll Physicians* 1992;**26**:295]

Overfill versus underfill hypotheses in cirrhosis

Overfill and underfill theories have been suggested to account for the water and sodium retention in cirrhosis (Figure 2)[6,7]. The underfill hypothesis proposes that portal hypertension produces transudation of fluid into the

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abdomen with ascites accumulation; this results in a decreased plasma volume which leads to renal sodium and water retention. In contrast, the overfill hypothesis suggests that a hepatorenal reflex induces primary renal water and sodium retention with expansion of plasma volume.

Overfill versus underfill hypotheses in pregnancy

Overfill and underfill hypotheses of water and sodium retention in pregnancy have also been proposed (Figure 3)[8]. With the overfill hypothesis, the threshold for osmotic and volume regulation alters in pregnancy, with resultant renal sodium and water retention and increase in plasma volume. Against this theory are observations of hypo-osmolality and activation of the renin-angiotensin-aldosterone system in pregnancy—findings more consistent with the underfill hypothesis.

Several developments have allowed these dilemmas in explaining the water retention in oedematous disorders to be more carefully studied. Specifically, a sensitive radio-immunoassay was developed to measure AVP[9], and methods became available to more accurately measure intravascular volume—i.e. total plasma or blood volume. The mechanisms whereby AVP causes urinary concentration have been better elucidated with the cloning of the vasopressin V_2 receptor on the basolateral membrane of the collecting duct[10] and the collecting duct water channels (e.g. aquaporin-2)[11]. Lastly, pharmacological antagonists to the antidiuretic action of AVP were developed, first for intravenous and then for oral use[12,13]. These technological advances have provided the means to test a unifying hypothesis on the water retention of cardiac failure, cirrhosis and pregnancy.

ARTERIAL UNDERFILLING HYPOTHESIS OF BODY FLUID VOLUME REGULATION

According to our unifying hypothesis, sodium and water retention is initiated by alteration of systemic and renal haemodynamics[14–16]. The focus is on the integrity of the arterial circulation. Approximately 85% of the plasma volume resides on the low-pressure venous side of the circulation, with the remaining 15% on the arterial side. Therefore, an expansion of total blood volume could occur with increases in the volume of the venous circulation, yet the kidney could sense arterial underfilling as the dominant afferent signal for renal sodium and water retention.

Low-output cardiac failure would result in arterial underfilling (Figure 4). By contrast, in pregnancy and cirrhosis, with their increased cardiac output, the arterial underfilling is a consequence of systemic arterial vasodilation (Figure 5). Such arterial underfilling is sensed by high-pressure baroreceptors in the ventricle, carotid artery

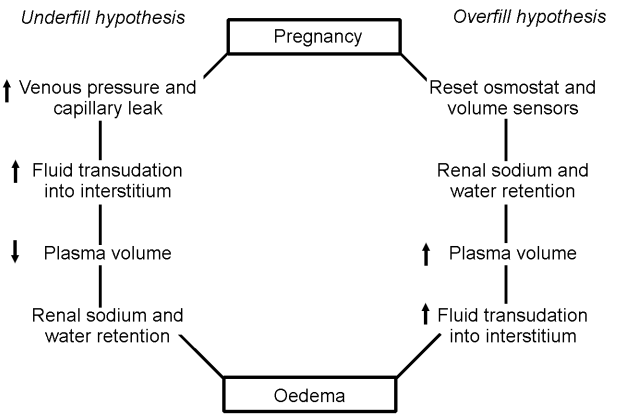

Figure 3 **Underfill and overfill hypotheses of oedema formation in pregnancy**

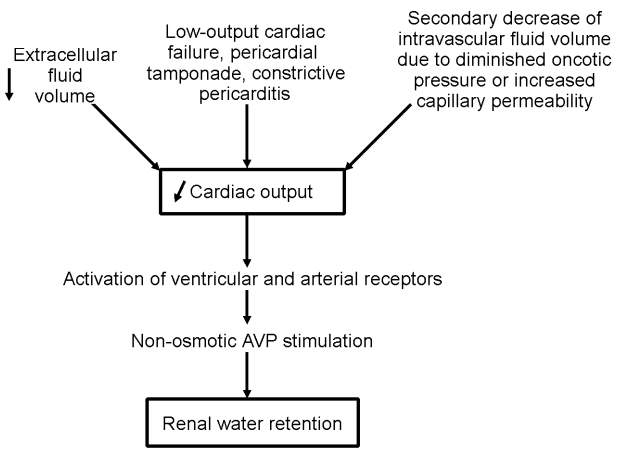

Figure 4 **Sequence of events in which a decrease in cardiac output initiates water retention** [Modified by permission, from Schrier RW, *Ann Intern Med* 1990;**113**:155]

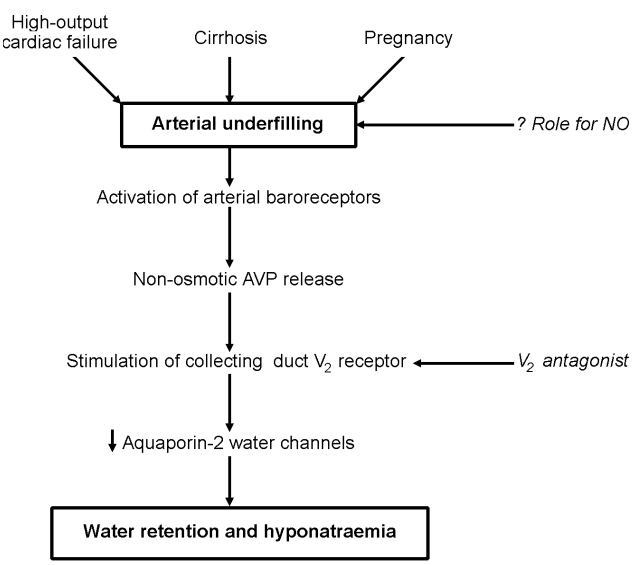

Figure 5 **Sequence of events in which peripheral arterial vasodilation initiates water retention** [Modified by permission, from Schrier RW, *J Am Soc Nephrol* 1992;**2**:1549]

and aortic arch and results in activation of the sympathetic nervous and renin-angiotensin-aldosterone systems as well as the non-osmotic release of AVP. The binding of AVP to its V_2 receptor on the basolateral membrane of the collecting duct produces a short-term translocation of the water channel, aquaporin-2 (AQP2), from cytosolic storage vesicles to the apical membrane through a cAMP-mediated pathway. This trafficking process increases the water permeability of the apical membrane of collecting-duct cells, thereby promoting water retention. In the long term, AVP controls AQP2 gene expression through a cAMP response element on the AQP2 promoter. Such regulation determines the quantity of AQP2 channels available for modulation of the apical membrane's water permeability.

On this background, we now review recent advances in our understanding of altered water metabolism in cardiac failure, cirrhosis and pregnancy.

CARDIAC FAILURE

Before the development of a sensitive AVP radioimmunoassay, the results of plasma AVP concentrations in patients with hyponatraemia and heart failure were conflicting. However, with use of the radioimmunoassay technique, osmotically inappropriate high concentrations of plasma AVP were consistently reported in patients with hyponatraemia and heart failure[9,17]. The degree of hyponatraemia and hypo-osmolality occurring in heart failure was sufficient to maximally suppress AVP in normal subjects, and yet plasma AVP was not suppressed. Moreover, hypothalamic AVP mRNA expression was found to be increased in a rat coronary ligation model of heart failure[18]. Therefore, non-osmotic, baroreceptor-mediated, stimulation of AVP was incriminated in heart failure.

The cloning of the vasopressin V_2 receptor[10] and the collecting-duct water channel AQP2[11], and the development of nonpeptide V_2 receptor antagonists[12,13], allowed examination of water metabolism in heart failure at a molecular level. Our laboratory demonstrated a significant upregulation of kidney AQP2 mRNA and protein expression in heart-failure rats with hyponatraemia[19]. This effect was associated with an increase in plasma AVP as measured by radioimmunoassay. Administration of an oral nonpeptide V_2 receptor antagonist reversed the impairment of water excretion and corrected hyponatraemia in heart-failure patients (Abraham WT, Martin P-Y, Xu L, Schrier RW. Unpublished). These effects of V_2 antagonism in heart-failure patients were associated with diminished urinary excretion of AQP2 water channels (Figure 6)[20]. In this regard, urinary AQP2 excretion has been found a reliable marker of apical membrane AQP2 in the collecting duct[21].

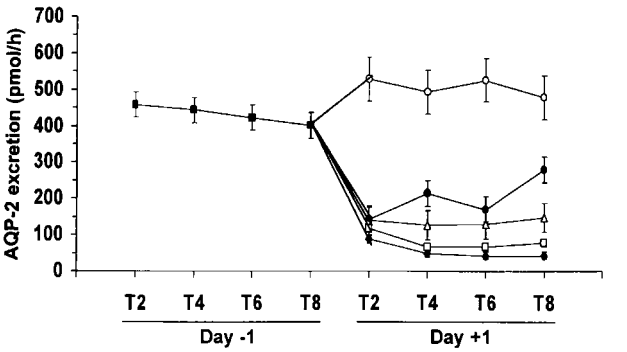

Figure 6 **Effect of VPA-985 administration on urinary AQP2 excretion of heart failure patients according to dose groups.** (X axis represents the collection periods. Day −1 is the baseline observation and day +1 is the study period. ■ Baseline; ○ Placebo; ● 30 mg; △ 75 mg; □ 150 mg; ◆ 250 mg) [Reprinted by permission, from Ref. 20]

CIRRHOSIS

As in heart failure, the rat bioassay for antidiuretic hormone did not incriminate AVP in the water retention of cirrhosis; but use of radioimmunoassay techniques revealed inappropriately high plasma AVP concentrations in hyponatraemic patients with cirrhosis[22]. Upregulation of hypothalamic AVP mRNA expression was also demonstrated in carbon-tetrachloride-induced cirrhosis in rats[23]. Increased renal expression of AQP2 mRNA and protein has been reported in cirrhotic rats[24] along with enhanced trafficking of AQP2 to the apical membrane of the collecting duct in cirrhotic animals[25]. Moreover, administration of V_2 receptor antagonists has been found to improve solute-free water excretion in rats with cirrhosis and ascites[26,27]. Kappa opioid agonists, which interfere with the central release of AVP, likewise increase renal water excretion in experimental cirrhosis[27–29]. Finally, a beneficial effect from V_2 receptor antagonists, in enhancing solute-free water excretion, has been reported in cirrhotic patients[13].

A proposed stimulus for the non-osmotic release of AVP in cirrhosis is arterial underfilling secondary to splanchnic vasodilation—the 'peripheral arterial vasodilation hypothesis'[14]. Our laboratory sought to determine whether the diminished systemic vascular resistance and the hyperdynamic circulation and altered water metabolism of cirrhosis could be reversed by inhibition of nitric oxide (NO). After administration of the nonspecific NO synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME) for seven days the hyperdynamic circulation of cirrhotic rats became normal[30]; and the same dose of L-NAME was associated with improved renal water and sodium excretion, correction of hyponatraemia and decreased ascites[31]. With L-NAME, plasma AVP in the cirrhotic rats returned to control concentrations, as did plasma renin activity and aldosterone concentration[31]. These results

implicate nitric oxide as an important mediator of peripheral arterial vasodilation and altered water metabolism in cirrhosis.

PREGNANCY

Normal pregnancy is associated with a 30–50% increase in total plasma and extracellular fluid volumes and a substantial rise in cardiac output. Hyponatraemia is also the rule. Some investigators have suggested that such hyponatraemia is due to resetting of an 'osmostat' whereby the osmotic regulation of vasopressin is normal but occurs around a lower plasma osmolality[32]. In contrast, the peripheral arterial vasodilation hypothesis suggests that arterial underfilling, due to a decrease in systemic vascular resistance, stimulates non-osmotic release of AVP with subsequent water retention and hyponatraemia[33].

By day 7 of gestation in rats, plasma osmolality has declined significantly and it then remains low throughout pregnancy (normal gestation 21–22 days)[34]. AVP concentrations, however, are not suppressed by this hypo-osmolality; in fact they tend to rise progressively in pregnancy[34]. Papillary AQP2 mRNA and protein rose early in pregnancy and remained above the non-pregnant level throughout. The effect of the non-peptide V_2 receptor antagonist OPC-31260 was then investigated. Papillary AQP2 mRNA was significantly suppressed by administration of OPC-31260 to rats at day 14 of pregnancy. In fact, the renal papillary concentration of AQP2 fell to the level of expression seen in non-pregnant rats receiving OPC-31260. These results therefore indicate that an increase in AQP2 water channels contributes to the water retention in pregnancy through a vasopressin V_2 receptor-mediated effect.

In human pregnancy, mean arterial pressure decreases by six weeks' gestation in association with an increase in cardiac output and plasma volume and a decrease in systemic vascular resistance[35]. The initiators of such physiological changes are not fully known. To evaluate the potential role of nitric oxide in mediating the peripheral arterial vasodilation in pregnancy, we investigated the constitutive NO synthase isoforms in the vasculature and hypothalamus of pregnant rats on day 20 of gestation and age-matched non-pregnant controls[36]. Neuronal NO synthase protein and mRNA were higher in the hypothalamus of pregnant rats, and endothelial NO synthase protein expression was also higher in both conductance arteries (aorta) and resistance arteries (mesenteric). These increases were associated with raised plasma AVP concentrations and by increased hypothalamic mRNA for AVP.

The effect of nitric oxide inhibition on systemic and renal haemodynamics was then studied[37]. In pregnant rats at day 14 of gestation, cardiac output was significantly higher than in non-pregnant controls as systemic vascular resistance (SVR) decreased and mean arterial pressure was unchanged. At day 14 of gestation, pregnant rats also had higher glomerular filtration rates (GFR) and renal plasma flow (RPF) than non-pregnant rats. When pregnant rats were given L-NAME from day 7 through 14 of gestation, values for cardiac output, SVR, GFR and RPF did not differ from those in non-pregnant animals. This study therefore indicated that, as in human pregnancy, primary peripheral vasodilation occurs early[35] and that the hyperdynamic circulation and glomerular hyperfiltration of normal rat mid-term pregnancy can be chronically reversed by NO synthase inhibition[37]. Despite these important systemic and renal haemodynamic changes with NO synthase inhibition in pregnancy, we were unable to reverse the hyponatraemia and water retention associated with normal rat pregnancy. This result suggested that pregnancy is associated with a stimulus for thirst and that the resultant polydipsia contributes to the hypo-osmolality of pregnancy.

CONCLUSION

In summary, we have proposed that water retention in cardiac failure, cirrhosis and pregnancy can be understood in the context of our unifying hypothesis of body fluid volume expansion. In our hypothesis, decreased cardiac output or peripheral arterial vasodilation stimulates renal sodium and water retention. Our laboratory has tested the hypothesis by cellular and molecular methods in animal models and human beings.

In cardiac failure, cirrhosis and pregnancy, techniques reveal high plasma AVP concentrations at plasma osmolalities that would normally suppress AVP to undetectable levels. Increased expression of kidney AQP2 water channels has also been demonstrated in cardiac failure, cirrhosis and pregnancy. Water retention and hyponatraemia can be reversed by V_2 receptor antagonists in cirrhosis and cardiac failure. Such antagonists also increase water excretion in pregnancy and clinical studies have shown that V_2 receptor antagonism is effective in patients with cardiac failure and cirrhosis.

Nitric oxide has been implicated as an important mediator of peripheral arterial vasodilation, leading to arterial underfilling in cirrhosis and pregnancy. Inhibition of NO synthases with L-NAME reverses the hyperdynamic circulations associated with these conditions. Moreover, NO synthase inhibition in cirrhosis reverses the impairment in sodium and water excretion.

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