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Editorial

# Atrial natriuretic factor

## Possible implications in liver disease

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The pathophysiology of renal sodium retention and ascites formation in patients with cirrhosis of the liver has become progressively more complicated [1]. Conflicting theories of 'underfilling' and 'overflow' [2] have been developed to explain the afferent mechanisms of impaired volume homeostasis in cirrhosis. Investigations of efferent mechanisms proved to be equally perplexing. Stimulation of the Renin-Angiotensin-Aldosterone system may be of importance for sodium reabsorption [3], but there is increasing evidence that this is but one of several factors [4,5]. Thus, the impact of other hormonal and neural systems on sodium retention was investigated, such as the sympathetic nervous system [6,7], vasopressin [8], prostaglandins [9,10] and kallikrein-kinin [11]. For about two decades, the existence of a circulating natriuretic substance with digoxin-like immunoreactivity, with vasoactive and $Na^+/K^+$-ATPase inhibiting properties has been postulated [12–15]. A deficiency of this natriuretic substance was hypothesized to be relevant for fluid and electrolyte disturbances in chronic liver disease [16]. However, the inability to satisfactorily characterize and determine this putative natriuretic hormone rendered difficult the elucidation of its role [17].

**Atrial Natriuretic Factor (ANF) — a novel volume-regulating hormone**

As early as 1847, the heart was attributed an important role in volume regulation by inducing diuresis following the volume-loading of water immersion [18]: '. . . if the blood be thus driven (by water immersion) from the external and internal parts, what becomes of the blood? The heart and great vessels, it would seem, must be burdened. Such is to a degree the case; and it is perhaps the stimulus of this fullness and distension or its action on the elasticity of those great vessels and the heart that constitutes the reaction (which leads forth the urine in abundant effusion).' More than 100 years later, Gauer and Henry demonstrated that it was the atria which enhanced water and sodium excretion upon an increase in central blood volume [19,20]. Independently, and unaware of this physiologic research, workers performing electron-microscopic studies found multiple dense granules in the cytoplasm of atrial muscle cells [21,22]. Uniting the physiological importance of the atria with this morphological feature of secretory atrial myocytes, DeBold in 1981 found a natriuretic response to intravenous injection of atrial extracts

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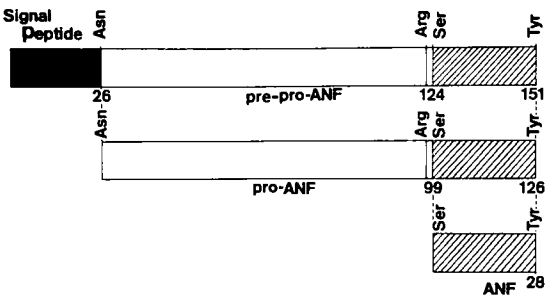


**Fig. 1.** Schematic representation of human ANF. Amino acid sequence is read from the amino (N)-terminus (left) to the carboxy (C)-terminus (right).

[23]. It took only 3 more years to identify the Atrial Natriuretic Factor (ANF) as a peptide (for a schematic representation of human ANF, see Fig. 1), and to date many of its important properties have been characterized.

For a better understanding of the possible implications of this novel volume-regulating hormone in liver disease, some significant features of ANF are summarized below (see reviews, Refs. 24–34, for comprehensive information).

The biosynthesis of human ANF resembles that of most secreted peptides: transcribed messenger RNA is translated to a 151-amino-acid pre-prohormone ANF-151 with a hydrophobic signal peptide at the N-terminus (Fig. 1), which is supposed to expedite transport across the endoplasmic reticulum. Subsequent to cleavage of the signal peptide, ANF-126, the prohormone is stored in secretory vesicles. ANF-126 is further processed enzymatically and secreted into the blood, where the biologically active C-terminal ANF-28 has been defined as the circulating hormone [27,35,36]. Increased dietary sodium intake has been shown to stimulate ANF release [37]. The initial observation that water immersion, increasing central venous pressure by shifting extracellular volume to the intrathoracic venous bed, rapidly increases ANF plasma levels in healthy human subjects [38] has been confirmed by several investigators [39,40,40a]. Elevation of atrial pressure has been demonstrated to prompt ANF release [41]. ANF plasma levels can be determined by RIA; however, plasma levels measured in different research laboratories in comparable groups of subjects may vary considerably (cf. Table 1). This may in part be due to different extraction procedures or tracer degradation. The 'International Collaborative Study of the Proposed International Standard for Atrial Natriuretic Factor on behalf of the American Heart Asso-

TABLE 1

ANF PLASMA LEVELS IN PATIENTS WITH CIRRHOSIS (Ci)

+/–A means (sub)group with/without ascites. Co: values in normal controls. *n*: number of subjects. Values are means ± SE, fmol/ml. 3 pg correspond to 1 fmol. Data in the table are basically taken from the referenced literature; data of several authors are supplemented by more recent information (personal communication).

| Author [Ref.] | Co | *n* | Ci | *n* | Ci+A | *n* | Ci–A | *n* |
|---|---|---|---|---|---|---|---|---|
| Barakat [64] | 9 ± 2 | 5 | 161 ± 63 | 5 | | | | |
| Bonkovsky [65] | 64 ± 4 | 11 | | | 46 ± 3 | 17 | 57 ± 3 | 12 |
| Burghardt [66] | 9 ± 1 | 17 | 9 ± 1 | 58 | 8 ± 1 | 18 | 9 ± 1 | 16 |
| Campbell [67] | | | | | 27 ± 6 | 4 | | |
| Epstein [68] | 8 ± 2 | 13 | | | 10 ± 3 | 8 | | |
| Fernandez-Cruz [69] | 28 ± 2 | 5 | | | 61 ± 9 | 8 | | |
| Gerbes [70] | 6 ± 1 | 22 | 9 ± 1 | 41 | 8 ± 1 | 10 | 8 ± 1 | 11 |
| Ginés [71] | 4 ± 1 | 13 | 14 ± 1 | 35 | | | | |
| Jüppner [72] | 33 ± 3 | 21 | 82 ± 10 | 33 | | | | |
| Morgan [73] | 9 ± 2 | 14 | | | 120 ± 23 | 7 | | |
| Nishiuchi [74] | 6 ± 1 | 54 | 46 ± 14 | 17 | | | | |
| Nozuki [75] | 23 ± 2 | 28 | | | 17 ± 4 | 5 | | |
| Renner [76] | 15 ± 1 | 106 | | | 31 ± 4 | 20 | 14 ± 3 | 10 |
| Shenker [77] | 16 ± 2 | 10 | | | 20 | 4 | | |

ciation/International Society of Hypertension/World Health Organisation' [42] will attempt to clarify the existing discrepancies. Furthermore, as antibodies recognize, to varying degrees, precursors or circulating fragments of ANF-28, characterization of the immunoreactivity determined is advisable, e.g., by HPLC techniques [43].

ANF binding sites have been found in renal glomerula as well as vasa recta, in cells of the adrenal zona glomerulosa, in vascular smooth muscle and endothelial cells and in various parts of the central nervous system. Cyclic guanosine monophosphate has been claimed to be the intracellular second messenger of ANF action [44]. Various physiologic actions of ANF in the organism are summarized in Fig. 2. Enhanced renal sodium and volume excretion are supposed to be in part due to an increase of the glomerular filtration rate as a result of alterations of renal hemodynamics induced by pre-glomerular vasodilation and post-glomerular vasoconstriction [45]. In part, actions at other renal sites may increase perfusion of the medullary papillary interstitial space. Indeed, ANF relaxes smooth muscles of different vascular sites with differing potency. Thus, infusion of ANF at doses not affecting systemic blood pressure can influence both renal and liver blood flow [46]. The observation that antisera to ANF reduce urinary sodium excretion and increase plasma renin activity [47] suggests a physiological role for this novel hormone in volume regulation.

Thus, it is by no means surprising that interactions with other hormonal systems involved in volume regulation have been reported: ANF counteracts the Renin-Angiotensin-Aldosterone axis [48] by reducing renin as well as aldosterone secretion and by relaxing angiotensin-constricted vessels [49–51]. It was speculated that ANF, elevated in primary aldosteronism [52], in turn might be stimulated by angiotensin

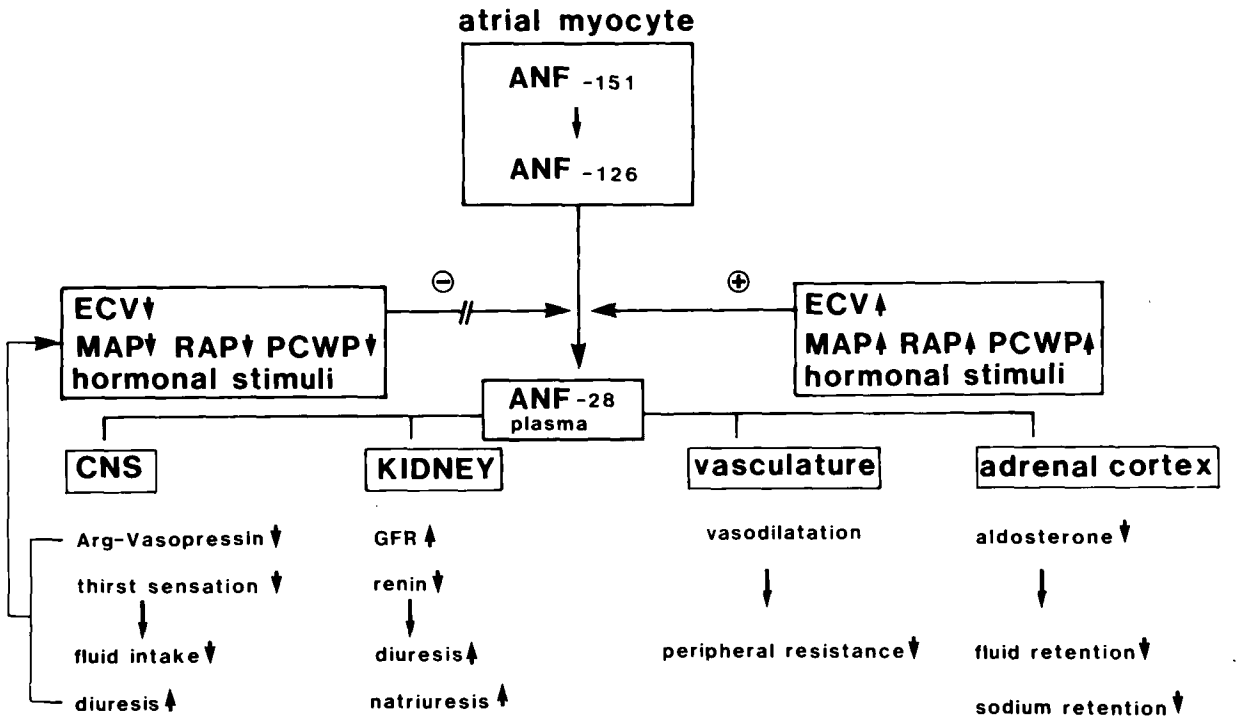


Fig. 2. Effects of ANF in the body. CNS = central nervous system, ECV = extracellular volume, GFR = glomerular filtration rate, MAP = mean arterial pressure, PCWP = pulmonary capillary wedge pressure, RAP = right atrial pressure.

II, thus explaining the natriuresis observed after angiotensin infusion [53]. ANF is stimulated by mineralocorticoid administration [54,55], thus being a potential mediator of the 'escape phenomenon'; though it certainly is not identical with the $Na^+/K^+$-ATPase-inhibiting natriuretic hormone, ANF seems to be an excellent candidate for the long-elusive 'third factor' [56]. A number of observations suggest interactions of ANF with the sympathicoadrenergic system: Infusion of norepinephrine provokes ANF release from isolated rat hearts [57], this stimulation being inhibited by alpha-adrenoceptor blockade with phentolamine [57]; ANF may prevent norepinephrine-induced acute renal failure [58] and may reduce norepinephrine-induced blood pressure elevations [59]; and a relationship to vasopressin is suggested by the observation of an increased ANF secretion following vasopressin infusion [60,61], whereas ANF administration inhibits stimulated vasopressin increase [62].

This brief outline of the characteristics of ANF helps explain why the discovery of this novel volume-regulating hormone, linking the heart – now known to be an endocrine organ – with kidney, adrenal cortex, microvasculature and the brain, has created so much excitement. Cardiologists, nephrologists and hepatologists are awaiting information on the possible impact of ANF in various diseases. This review will concentrate on the role of ANF in cirrhosis; in this pathologic state, the splanchnic and peripheral subcompartment are volume-overloaded, in contrast to the central volume-stimulation of congestive heart failure.

## Plasma levels

As mentioned above, in cirrhotic patients with splanchnic sequestration of extracellular volume, supporters of the 'underfilling' theory might expect a diminution of centrally effective blood volume, resulting in decreased stimulation of ANF release and thus in lower ANF plasma levels. In contrast, if one believes in the 'overflow' theory of increased effective blood volume, elevated ANF levels might be anticipated. The first report concentrating on ANF plasma levels in cirrhosis [63] demonstrated in 9 cirrhotics without and 10 with ascites that there was no absolute deficiency of plasma ANF as compared to controls. Concentrations in patients with ascites did not differ from those in the other cirrhotics. In the course of the year that has elapsed since the appearance of that report and the submission of this review, several groups have investigated ANF levels in cirrhosis (Refs. 64–77; cf. Table 1). Levels lower than in controls were reported by one group only [65], in cirrhotics with ascites. In all of the studies that evaluated the presence or absence of ascites, the ANF concentrations observed were not markedly different from normal in the cirrhotics without ascites [65,66, 70,76]. In patients with ascites, ANF values equal to [66,68,70,75,77], lower [65] or higher [67,69,72–74, 76] than normal have been found. Differences in a number of factors might cause such different results: plasma extraction, radioimmunoassay, posture of the subjects, restriction of dietary sodium and water, diuretic treatment, or possibly variations in hepatic and renal clearance of ANF [78]. The atrial content of ANF, estimated by bioassay, was found to be higher than normal in human cirrhotic subjects [79], but lower than normal in cirrhotic rats [80].

Patients with congestive heart failure, characterized by central volume overload, exhibit markedly elevated ANF levels ranging from several up to one hundred times higher than normal [43,81,82]. Interestingly, further characterization of the immunoreactive ANF by HPLC techniques revealed an immunoreactive component of higher molecular weight in some of these patients (Fig. 3). It was speculated that the rate of compensatory ANF secretion upon the volume stimulus exceeded the capacity of the processing enzymes, thus resulting in the release of immature ANF of possibly reduced biological activity [83]. However, the above-mentioned reports on markedly elevated ANF plasma levels in cirrhotic patients do not provide a further characterization of the immunoreactivity. High performance gel permeation chromatography of ANF in cirrhosis has been performed in a few patients (Ref. 83, Fig. 3) and revealed only trace amounts of higher molecular weight forms.

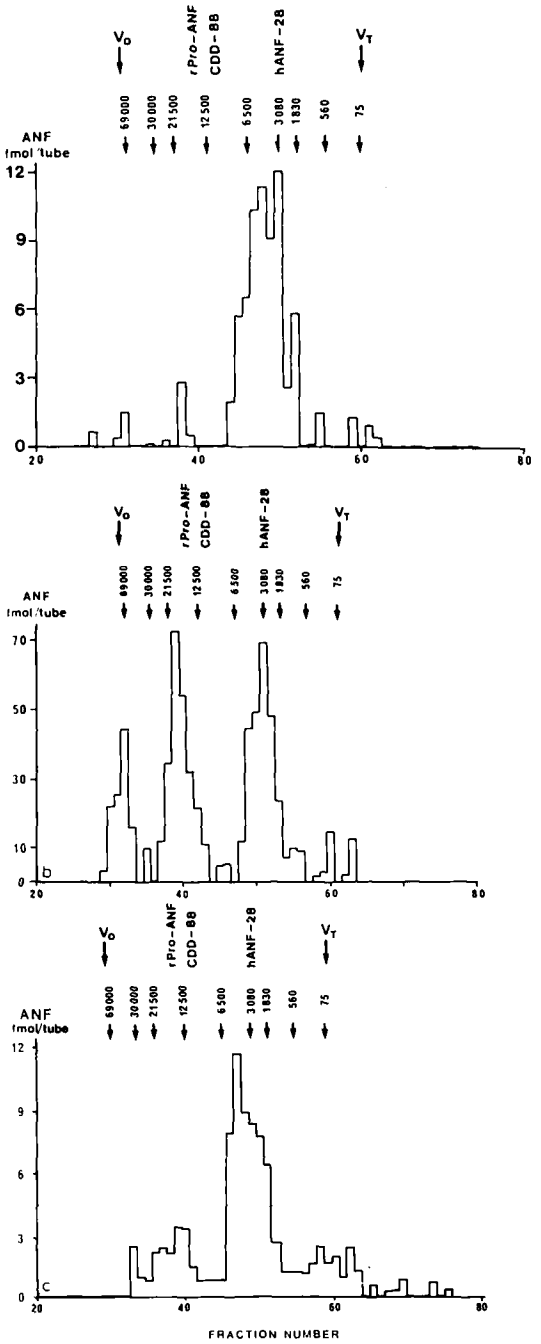


Fig. 3. Molecular weight pattern of immunoreactive ANF in a representative healthy subject (*a*), a patient with severe congestive heart failure (*b*) and a patient with cirrhosis (*c*). In healthy subjects, plasma ANF consists virtually exclusively of ANF-28. In patients with CHF, higher molecular weight forms can be found that are to be seen only in trace amounts in the cirrhotic patient. Molecular weight calibration of the TSK 125 Bio-Sil column is indicated at the top of the illustration.

## ANF release

Apart from inappropriate plasma levels or alterations of posttranslational processing, release of ANF to volume stimulation might be impaired. Head-out water immersion has been shown to be a useful model for investigating the response of the ANF system to acute volume stimulation in healthy subjects [38]. One-hour immersion in a thermoneutral bath induces a two-fold rise in ANF plasma levels (Fig. 4). Numerous investigations had shown that water immersion can also be conveniently used in cirrhotic patients [84] to study volume regulation. ANF release after 1-h immersion has been found to be normal in cirrhotics without ascites, but reduced to about one-half in the presence of ascites [85] (Fig. 5). These findings are at variance with another study demonstrating ANF increases twice as high as in normals in patients with ascites and edema [68]. Another group reported blunted ANF stimulation following water immersion in cirrhotics with ascites [69]. In view of a lack of increase in their control group, however, this assertion has been questioned [86].

## Renal response

The natriuretic response to elevated ANF following water immersion has been found to be variable

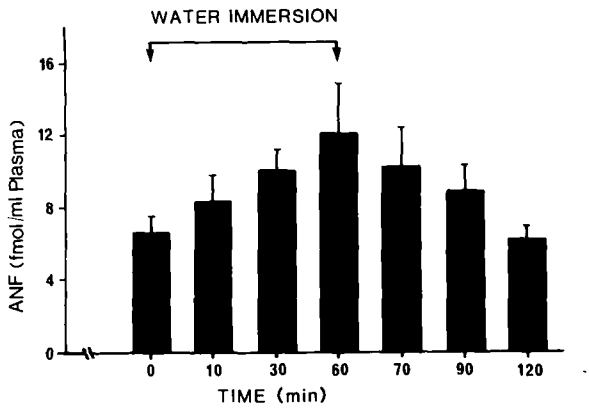


Fig. 4. ANF plasma levels before, during 60 min water immersion, and subsequent to immersion. Mean values and standard deviations of 12 healthy subjects.

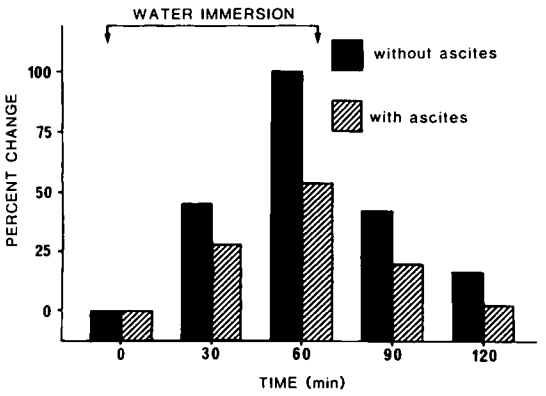


**Fig. 5.** Percent increase of plasma ANF during water immersion. Mean values of 7 patients with and 7 patients without ascites. Whereas cirrhotics without ascites exhibit normal increase, stimulation is blunted in patients with ascites.

[68,70]. Thus, stimulus-response coupling may be impaired in cirrhosis [87]. However, in patients with refractory ascites, insertion of a peritoneo-venous shunt increased ANF plasma levels, with a corresponding rise in natriuresis and diuresis [66,67]. Infusion of synthetic human ANF-28 in healthy subjects results in marked diuresis and natriuresis [88–90]. Similar beneficial effects have been observed in patients with cardiovascular disease, despite increased basal values [82,91]. The initial experience in a patient with refractory ascites, with infusion of 50 ng/kg/min for 60 min and resultant diuresis (Fig. 6) [92], encouraged other studies with therapeutic aspects. Eight of 14 cirrhotics responded to an i.v. bolus injection of 1 $\mu$g/kg with a significant increase of sodium excretion and urine flow, similar to the response of healthy controls [93]. Six patients, however, showed no marked effects. Plasma aldosterone was decreased in all cirrhotics, an effect that has not, as yet, been observed in all healthy subjects studied [89,90]. Renal response to ANF seems to be highly variable [94,95], and limited effects of continuous infusion have been reported [94]. At this early stage of investigation of ANF in liver disease, it seems impossible to make unequivocal conclusions as to any dysfunction of stimulus-response-coupling.

## Therapeutic aspects

Conventional diuretic therapy of ascites has been shown to involve hazards [96]. Thus, application of a naturally occurring diuretic hormone might seem promising. The diuretic, natriuretic and anti-hypertensive effects of ANF could be of therapeutic relevance in clinical practice, especially when long-acting analogues will be developed. In patients with end-stage heart failure on intensive care, i.v. ANF administration might prove helpful in improving cardiopulmonary hemodynamics (Arendt, R.M. and Gerbes, A.L., unpublished observation). Upon administering the peptide to cirrhotics, in whom the Renin-Angiotensin-Aldosterone system is often activated to

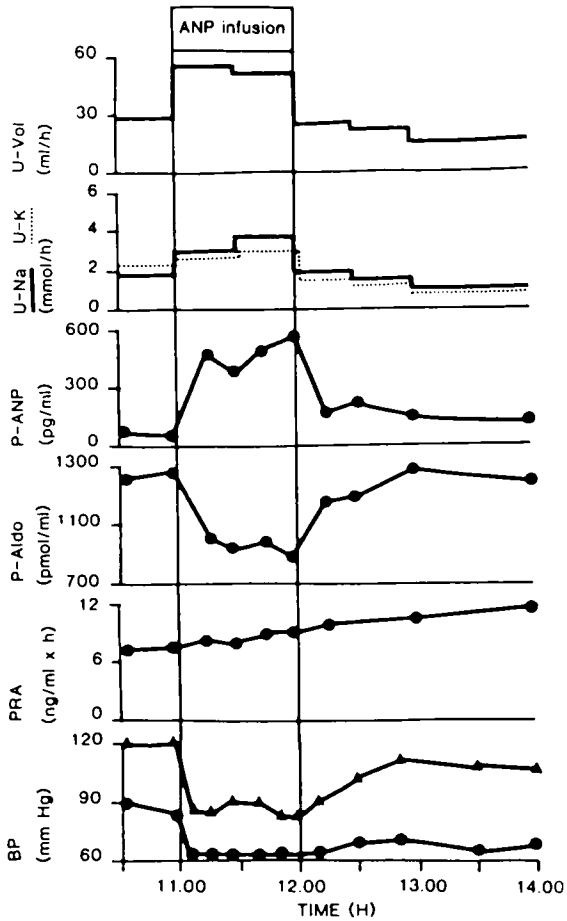


**Fig. 6.** Effects of ANF infusion in a patient with cirrhosis and ascites (from Ref. 92).

maintain their blood pressure, special attention should be given to the antihypertensive effects. Slight to marked decreases of mean arterial pressure following ANF injection have been observed [93]: 2–10 minutes after injection, mean arterial pressure decreased more markedly in cirrhotics (18 ± 5 mm Hg) than in controls (8 ± 4 mm Hg) [93]. However, with its modes of action differing from that of established diuretics [97], the therapeutic potentials of ANF should be studied in greater detail.

## Summary

The discovery of the first well-defined natriuretic hormone, the Atrial Natriuretic Factor (ANF), has prompted research on its impact on volume regulation in health and disease. The natriuretic, diuretic, and smooth muscle-relaxing properties suggest an important role of this novel hormone in pathophysiological states with sodium or volume retention, such as congestive heart failure or cirrhosis of the liver. Investigations on the implications of ANF in liver disease have been performed for little more than 1 year, and results are still controversial in many respects. At present, it seems very likely that there is no absolute deficiency of plasma ANF in patients with cirrhosis. Moreover, elevated plasma levels in cirrhotics with ascites have been reported by several groups. However, as yet, a molecular characterization of this increased immunoreactivity is still lacking. There is disagreement on the reduced release of and renal response to ANF in subgroups of cirrhotics; however, stimulus-response-coupling might be impaired. Further studies are needed to elucidate the pathophysiological implications and therapeutical potential of ANF in patients with chronic liver disease.

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