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Changes in circulating levels of atrial natriuretic factor (ANF) during orthotopic liver transplantation in humans

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Abstract Atrial natriuretic factor (ANF) is a 28 amino acid peptide secreted by the atrial cardiocytes. Clearance is via the lung (50%) and the liver (25%). The main stimulus to ANF secretion is atrial distension but vasoconstrictors, sympathetic stimulation, catecolamines and tachycardia are able to enhance its circulating blood levels. ANF blood concentrations were measured during orthotopic liver transplantation in six postnecrotic cirrhotic patients. Significant increases in ANF blood levels occurred at the end of the anhepatic phase ($P \leqq 0.02$ vs baseline) associated with low cardiac filling pressures ($P \leqq 0.02$ vs baseline) and increased systemic vascular resistances ($P \leqq 0.02$ vs preanhepatic phase). Aldosterone blood levels showed a similar behaviour, increasing significantly ($P \geqq 0.001$ vs baseline) at the end of the anhepatic phase. ANF fell after reperfusion of the graft and returned towards baseline values at the end of the procedure. Since most of the total body clearance of ANF is performed by the lungs, its sharp increase at the end of the anhepatic phase could be considered a counterregulatory response to vasoconstricting stimulation and to fluid-sparing mechanisms in the presence of relative hypovolaemia. Its decrease after reperfusion could be related to volume normalization and partly to the enhanced clearance performed by the newly grafted liver.

Key words Atrial natriuretic factor
Aldosterone · Liver cirrhosis
Orthotopic liver transplantation

Introduction

Abrupt modifications of the circulating blood volume are often responsible for opposite changes in venous return, cardiac output and tissue perfusion reported during the various phases of orthotopic liver transplantation (OLT). Hypovolaemia occurs frequently during hepatectomy (owing to the large blood loss) or after caval and portal clamping (secondary to decreased venous return), while increased venous return and an acute increase in cardiac filling pressures are sometimes recorded after reperfusion of the grafted liver [13].

In cases of absolute or relative hypovolaemia, the main physiological responses rely upon vasoconstricting stimuli, for example, activation of the sympathetic nervous system, stimulation of the renin-angiotensin-aldosterone axis and increased secretion of vasopressin [3]. In contrast, increased glomerular filtration rate, diuresis and natriuresis are enhanced in cases of hypervolaemia and/or increased cardiac filling pressures [8].

Atrial natriuretic factor (ANF), a 28 amino acid peptide secreted by atrial cardiocytes and cleared 50% by the lungs, 25–30% by the liver and splanchnic organs and 15–20% by the kidneys, contributes to this latter response. Its main actions are stimulation of diuresis and natriuresis and relaxation of vascular smooth muscles [4, 10, 21].

Increased blood levels of ANF are common in cirrhotic patients and have been ascribed to the enhanced release by cardiac atria. However, the half life, the total body excretion rate and particularly the hepatic-splanchnic clearance do not seem to be substantially different from those found in controls [7, 11, 21]. Increased levels of ANF secondary to reduced hepatic extraction, however, have been demonstrated in severe acute liver failure [14].

Few studies have dealt with ANF changes during OLT in cirrhotic patients and contradictory results have been reported. Black et al. [2] and Koller et al. [12] found that ANF levels decrease during the anhepatic phase and increase sharply after reperfusion. In both studies the circulating ANF levels were directly correlated with cardiac filling pressures. Di Mauro et al. [5], on the contrary, reported increasing ANF blood levels during the anhepatic phase and a sharp decrease after graft reperfusion, and no correlation was found between cardiac filling pressures and ANF blood levels, while its acute decrease after reperfusion was ascribed to increased clearance of the peptide performed by the newly grafted liver.

We report here and discuss the changes in ANF arterial blood levels found in postnecrotic cirrhotic patients undergoing OLT. Our findings contradict those reported by Black et al. [2] and Koller et al. [12] and are similar to those reported by Di Mauro et al. [5].

Materials and methods

Six adult patients (one female, five males) suffering from postnecrotic cirrhosis (Child B two patients, Child C four patients) and accepted for OLT were included in an ongoing study of renal function during the intraoperative period. The study was approved by the Scientific Committee of our hospital and all the patients gave their informed consent. Mean age was 45 ± 7 years and mean body surface area was $1.76 \pm 0.39\ m^{-2}$.

Standard anaesthetic and surgical techniques, including veno-venous bypass (VVBP) during the anhepatic phase, were used in all patients. Haemodynamic monitoring included heart rate (HR, beats/min), invasive (radial) arterial pressure (mm Hg), right atrial (RAP), pulmonary artery and pulmonary capillary wedge (PWP) pressures (mm Hg), cardiac output (CO, l/min) (thermodilution technique, Oxymetrix, Abbott), continuous mixed venous oxygen saturation (S_vO_2, %) (Oxymetrix 3 Swan Ganz Catheter, Abbott). Urinary output (UO) was measured hourly (ml/kg per h). Using standard formulae, systemic vascular resistances (SVR, dyn/s per cm^{-5}) and cardiac index (CI, l/m per m^{-2}) were calculated. Mean arterial pressure (MAP, mm Hg) was electronically derived from the invasive measurements of arterial pressure.

Together with the complete haemodynamic and metabolic profiles, arterial blood and urine samples were obtained for measurements of electrolytes and creatinine at the following times: after the induction of anaesthesia and right heart catheterization (baseline), 120 min after skin incision (preanhepatic phase), at the beginning of portal anastomosis (60–90 min following the vascular exclusion of the native liver and while on partial VVBP, anhepatic phase), 10 min after reperfusion of the graft (reperfusion) and at the end of the surgical procedure, usually from 120–150 min following reperfusion (neohepatic phase). Urine flow rate, when needed, was calculated by dividing urinary output by the duration in minutes of the interval between the scheduled samples. At the same times, additional arterial blood was drawn, immediately centrifuged and stored at −20 °C for later RIA determination of ANF (Eiken, Japan); mean blood ANF concentration in normal internal controls 54 ± 30 pg/ml, range of 9–100 pg/ml, aldosterone (normal values in our laboratory during clinostatism, 2–10 ng/dl) and creatinine clearance (CC, ml/min), sodium excretion (absolute and fractional, FeNa, %) was also calculated using standard formulae. Intraoperative diuretic stimulation included mannitol (60 mg/kg per h) and furosemide (20–100 mg when required).

Statistical methods

Data are reported as mean ± SD. ANOVA and linear regression analysis were used. Differences were considered significant for P values ≤ 0.05.

Results

Five patients successfully underwent OLT and survived for at least 3 months; one patient died on day 7 post-OLT. Total blood losses ranged from 1800 to 8000 ml. Median duration of the whole surgical procedure was 600 min (480–720 min). Arterial oxygen saturation was maintained above 98% in all patients throughout surgery (range 98.5–100%). Haemodynamic and hormonal data recorded during the various phases of OLT are shown in Table 1.

Baseline CC (range 80–130 ml/min) and UO (range 0.8–3.0 ml/kg per h) were within normal limits in all patients, while arterial ANF concentrations, as expected in cirrhotic patients, were higher than normal (range 130–170 pg/ml). Basal haemodynamic profiles were characterized by low SVR and high CI, while HR, MAP and filling pressures (RAP, PWP) were within normal limits. During the preanhepatic phase, progressive volume loading and low blood losses produced an elevation of RAP, PWP, CI, CC and UO; ANF, as expected, increased. Signifcant changes in CI (−32%), PWP (−40%) and SVR (+33%) occurred during the anhepatic phase in

Table 1 Haemodynamic and hormonal data recorded during the various phases of OLT (means ±SD) Renin activity (mean ±SD) was measured in three of the six patients (*HR* heart rate, *MAP* mean arterial pressure, *PWP* pulmonary wedge pressure, *CI* cardiac index, *SVR* systemic vascular resistance, *ANF* arterial natriuretic factor, *ALDOST* aldosterone, *FeNa* fractional sodium excretion, *CC* creatinine clearance)

	Baseline	Preanhepatic	Anhepatic	Reperfusion	End of surgery
HR (beat/min)	96 ±11	86 ±6	100 ±16	100 ±12	99 ±9
MAP (mmHg)	82 ±8	94 ±10	90 ±7	80 ±14	95 ±5
PWP (mmHg)	10 ±2	13 ±2	8 ±1*	11 ±2	11 ±2
CI (l/min per m^{-2})	5 ±1	6.6±4	5 ±1[b]	6.6±1.7	6.1±1.3
SVR (dyn/s per cm^{-5})	600 ±130	560 ±61	750 ±165[a]	500 ±235	600 ±250
ANF (pg/ml)	140 ±39	280 ±116	478 ±269*	152 ±94	125 ±39[a]
ALDOST	25 ±7.6	35.5±8	54 ±5[c]	48 ±2[c]	44 ±0.5[c]
FeNa (%)	0.5±0.3	2.2±1.6	3.5±2.8*	3.6±3.9*	3.4±2.8*
CC (ml/min)	120 ±16	140 ±29	80 ±30*	50 ±40*	40 ±38*
Renin (ng/ml per h)	3.2±1.8	12.4±7	17.7±8	20 ±14	9 ±4

* $P \leq 0.02$ vs baseline, [a] $P \leq 0.02$ vs preanhepatic, [b] $P \leq 0.01$ vs preanhepatic, [c] $P \leq 0.001$ vs baseline

spite of the use of VVBP. Arterial blood ANF levels increased further and significantly compared with the preanhepatic phase (+58%); the same trend was recorded for aldosterone (+50%). A marked deterioration in renal function (as evidenced by a significant fall in UO and CC) occurred during this phase.

High CI, low SVR and cardiac filling pressures at the upper normal limits were recorded early after reperfusion of the graft. Impairment in renal function with further significant decreases in CC persisted after reperfusion and were still present at the end of surgery in spite of markedly increased UO. Absolute sodium excretion did not change throughout surgery. FeNa increased significantly during the anhepatic phase and following reperfusion, and it was linked to the reduced CC. ANF fell sharply following reperfusion, and blood levels close to baseline were recorded at the end of the surgical procedure. ANF blood levels showed a fairly good correlation with aldosterone ($r = 0.52$, $P \leq 0.01$) throughout the whole surgical procedure. Plasma renin activity (ng/ml per h) measured by radioimmunoassay in only three of the six patients increased during the anhepatic phase (3.2±1.8 to 17.7±8) peaked early after reperfusion (20±14) and decreased at the end of surgery (9±4.2).

Discussion

Atrial distension and/or raised cardiac filling pressures after volume loading are the main stimuli for the endogenous release of ANF in normal subjects as well as in cirrhotic patients [11]. However, vasoconstrictive hormones [10], tachycardia [17], increased sympathetic nervous activity [6], vasopressin [19, 20] and hypoxia [1] have also been found to stimulate its secretion. In contrast, reduced levels of ANF are usually present with decreased atrial stretch and deficits in body fluids [10, 16].

Black et al. [2] and Koller et al. [12], studying ANF changes in patients undergoing OLT, found a direct correlation between cardiac filling pressures and ANF blood levels. ANF decreased during the anhepatic phase when cardiac filling pressures were lower. The decreased circulating levels of the peptide during this phase were ascribed to reduced atrial stretch. No correlation has been found between diuresis and ANF levels [2].

In contrast to these results, we found a steady increase in ANF levels during the anhepatic phase, a sharp decrease early after reperfusion and blood levels close to baseline at the end of surgery. Surprisingly, the haemodynamic profiles recorded in our patients during the anhepatic phase and after reperfusion were similar to those found by Black et al. [2] and Koller et al. [12]. Results similar to ours have been reported by Di Mauro et al. [5] who ascribed a postreperfusion decrease in ANF blood levels to an increased clearance of the peptide by the new liver.

Such conflicting results raise the possibility that more complex mechanisms than simple atrial distension are involved in the control of ANF secretion. Catecholamines and direct adrenergic stimulation have been shown both experimentally and clinically to stimulate ANF release by atrial cardiocytes. In an experimental model of hypovolaemic shock [18], haemorrhage of 40% of the blood volume significantly reduced MAP, RAP and CI and induced a significant increase in HR, catecholamines, renin activity and SVR. These changes were associated with a significant increase in ANF levels which returned to baseline after fluid resuscitation. ANF levels have been reported to increase substantially during surgery for phaeochromocytoma. The parallel changes in ANF and

catecholamines suggest a direct effect of high levels of endogenously released catecholamines on the stimulation of ANF release [6]. Markedly increased levels of ANF have been found by Putensen et al. [15] in untreated hypovolaemic trauma patients. Fluid resuscitation was able to normalize the high circulating levels of ANF, confirming in a clinical setting the findings reported by Shackford et al. in their haemorragic shock model [18]. The increase in ANF levels during hypovolaemia has been interpreted as a counterregulatory response to vasoconstriction and fluid-conserving mechanisms [15]. Reduced degradation of ANF during splanchnic hypoperfusion has to be considered as a possible coexisting mechanism able to increase ANF blood levels. The role of splanchnic clearance, however, may not be critical since most ANF total body clearance (almost 50%) seems to occur via the lungs, while renal and hepatic-splanchnic degradation account for only 15% and 20–25%, respectively [7].

High SVR, low cardiac filling pressures, decreased UO and significantly increased blood levels of aldosterone were present at the end of the anhepatic phase in all the patients we studied. A sympathetic response to relative hypovolaemia could be considered a likely cause for the observed haemodynamic and hormonal profiles. Renin activity, available for three of the six patients, increased during the anhepatic phase, possibly confirming this hypothesis. Thus, the increased levels of ANF during the anhepatic phase could reflect an enhanced release of the peptide, acting in a counterregulatory manner to vasoconstriction and fluid-conserving mechanisms. Since the liver has no major specificity for ANF degradation [7], the absence of hepatic clearance during the anhepatic phase should have played only a minor role in increasing blood levels of the peptide during this phase in the series reported by Black et al. [2] and Koller et al. [12] ANF levels during the anhepatic stage decreased). In our series, the sharp decrease in ANF recorded after graft reperfusion and blood levels close to baseline found at the end of surgery occurred in spite of higher filling pressures, larger CI and increased UO. There seem to be two most likely explanations. First, volume normalization could have reduced the vasoconstricting and fluid-sparing stimuli [15]. Second, the initial functional recovery of the liver, present in all patients, could have enhanced ANF clearance and possibly could have assisted, at least partly, in lowering circulating blood levels.

In conclusion, the main finding of our study was the sharp increase in ANF during the anhepatic phase. The small number of patients prevent us from drawing any definitive conclusion, but these results could reinforce the hypothesis that ANF is able to act as a physiological antagonist to endogenous vasoconstrictors and fluid-sparing hormones released during hypovolaemia.

References

1. Baertshi AJ, Adams JM, Sullivan MP (1988) Acute hypoxia stimulates atrial natriuretic factor secretion in vivo. Am J Physiol 255:H295–300
2. Black ST, Roberts LC, Sakai T, Duke PK, Whitten CW, Paulsen AW, Ramsay MAE (1992) Changes in circulating levels of atrial natriuretic peptide and antidiuretic hormone during orthotopic liver transplantation. Proceedings of 10th World Congress of Anaesthesiologists, The Hague, p 625
3. Bond RF, Johnson G (1985) Vascular adrenergic interactions during hemorragic shock. Fed Proc 44:281–289
4. DeBold AJ, Borenstein HB, Veress AT, Sonnenberg H (1981) A rapid and potent natriuretic response to intravenous injection of atrial myocardiac extracts in rats. Life Sci 28:89–94
5. Di Mauro P, Sala C, Beck E, Prato P, Morandini M, Langer M (1991) Role of the atrial natriuretic factor in hemodynamic changes related to liver reperfusion during liver transplantation. Proceedings of 4th LICAGE Meeting, Paris
6. Donckier J, Michel L, Collard E, Berbinschi A, Ketelslegers JM, Harvengt C, Buysschaert M (1988) Parallel changes of atrial natriuretic factor and catecholamines during surgery of pheochromocytoma. Am J Med 85:278–279
7. Gerbes AL, Vollmar AV (1990) Degradation and clearance of atrial natriuretic factor. Life Sci 47:1173–1180
8. Giannello P, Squifflet JP, Carlier M, Lambotte L, Ketelsleger JM, Alexandre GPJ (1990) Atrial natriuretic factor: a protective role after acute renal ischemia? Transplant Int 3: 41–46
9. Gines P, Jimenez W, Arroyo V, Navasa M, Lopez C, Tito L, Serra A, Bosch J, Sanz G, Rivera F, Rodes J (1988) Atrial natriuretic factor in cirrhosis with ascites: plasma levels, cardiac release and splanchnic extraction. Hepatology 8:636–642
10. Goetz KL (1988) Physiology and pathophysiology of atrial peptides. Am J Physiol 254:E1–E15

11. Henriksen JH, Bendtsen F, Gerbes AL, Christensen NJ, Ring-Larsen H, Sorensen TIA (1992) Estimated central blood volume in cirrhosis: relationship to sympathetic nervous activity, beta-adrenergic blockade and atrial natriuretic factor. Hepatology 5:1163–1170
12. Koller J, Wieser Ch, Furtwangler W, Kornberger E, Pomaroli A, Artner E (1991) Influence of hemodynamic changes during orthotopic liver transplantation on ANP and cGMP release. Proceedings of 4th LICAGE Meeting, Paris
13. Marquez JM, Martin D (1986) Anesthesia for liver transplantation. In: Winter PM, Kang YG (eds) Hepatic transplantation. Praeger, New York, Westport, London, pp 44–60
14. Moreau R, Hadengue A, Pussard E, Soubrane O, Sogni P, Gaudin C, Lebrec D (1991) Relationship between plasma atrial natriuretic peptide concentrations and hemodynamics and hematocrit in patients with cirrhosis. 13 Hepatology: 1036–1039
15. Putensen C, Mutz N, Pomaroli A, Lingnau W, Artner-Dworzak E, Puschendorf B (1992) Atrial natriuretic factor release durig hypovolemia and after volume replacement. Crit Care Med 20:984–989
16. Ramamoorti C, Rooney MW, Dries DJ, Mathru M (1992) Aggressive hydration during continuous positive-pressure ventilation restores atrial transmural pressure, plasma atrial natriuretic peptide concentrations and renal function. Crit Care Med 20:1014–1019
17. Rankin AJ, Courneya CA, Wilson N, Ledsome JR (1986) Tachycardia releases atrial natriuretic peptide in anesthetized rabbit. Life Sci 38:1951–1957
18. Shackford SR, Norton CH, Ziegler MG, Wilner KD (1988) The effect of hemorrhage and resuscitation on serum levels of immunoreactive atrial natriuretic factor. Ann Surg 207:195–200
19. Sonnenberg H (1986) Mechanisms of release and renal tubular actions of atrial natriuretic factor. Fed Proc 45:2106–2110
20. Sonnenberg H, Veress AT (1984) Cellular mechanisms of release of atrial natriuretic factor. Biochem Biophys Res Commun 124:443–449
21. Warner L, Storecki W, Blendis L, Epstein M (1993) Atrial natriuretic factor and liver disease. Hepatology 17:500–513