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BRIEF REPORT

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Human natriuretic factor in cirrhotic patients undergoing orthotopic liver transplantation

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Abstract We measured the plasma levels of atrial natriuretic factor (ANF) during orthotopic liver transplantation (OLT) in eight adult patients with cirrhosis and ascites. The aim of this study was to determine whether significant differences in ANF concentration may be detected during the individual phases of OLT and to correlate these changes with hemodynamics. In each patient a hemodynamic assessment was achieved using a Swan-Ganz fiber optic catheter for continuous monitoring of cardiac output (CO), systemic vascular resistance index (SVRI), right filling pressure as assessed by central venous pressure (CVP), and left filling pressure by means of pulmonary arterial wedge pressure (PAWP). During reperfusion a clear-cut increase in ANF values was observed ($P < 0.05$). Concurrently, an increase in CVP ($P < 0.05$) and a decrease in SVRI were observed without any significant increase in diuresis. These data suggest that ANF might play a role in the development of the reperfusion syndrome.

Key words Liver transplantation, atrial natriuretic factor · Atrial natriuretic factor, liver transplantation

Introduction

Volume homeostasis is almost always impaired in cirrhotic patients due to abnormal sodium retention, which results in ascites formation [22] and hemodynamic changes, including high cardiac output (CO) and low systemic vascular resistance index (SVRI) [8].

Bernardi et al. [3] reported high plasma renin and aldosterone concentrations in these patients although no correlation between plasma aldosterone concentration and renal sodium excretion was demonstrated. It has been postulated that a deficiency of a putative circulating natriuretic factor [13, 16] or, alternatively, resistance to such a factor, may contribute to sodium retention.

Human atrial natriuretic factor (ANF) has been identified as a natriuretic and diuretic substance involved in the regulation of sodium and volume homeostasis in

response to changes in intravascular volume [1, 2, 14, 15]. Volume expansion, changes in posture, head-out-water-immersion, an increase in dietary sodium intake, mineralocorticoid, norepinephrine and angiotensin administration lead to a rise in ANF, whereas a fall in plasma ANF levels has been induced by furosemide administration and sodium depletion [6].

Various organs extract ANF from the blood, among them the liver and kidneys. Since the kidneys are the organs with the highest blood flow per gram of tissue, they appear to be one of the major sites of extraction. ANF has a short half-life, is not or is only very slowly broken down by circulating plasma enzymes, and is inactivated by "clearance" receptors and degraded by endopeptidase [19]. When ANF binds to its receptors, cGMP formation is also stimulated in humans, eliciting a cascade of cellular responses leading to vasodilatation and to inhibition of renin secretion and sodium transport in kidney cells [22].

ANF is a strong antagonist of angiotensin II [21]. As a consequence, in the presence of vasoconstriction secondary to angiotensin II, ANF results in a sudden drop in systemic arterial blood pressure through powerful vasodilatation. ANF is secreted by the cardiac atria in response to increased atrial pressure from stretching of the atrial wall [7–9]. In addition, other nervous, humoral, and hormonal factors are involved in its secretion [20].

During orthotopic liver transplantation (OLT), hemodynamics differ from phase to phase. In the preanhepatic phase, hemodynamic instability may occur because of decreased venous return due to surgical manipulation of the inferior vena cava (IVC). An additional acute decrease in preload can be caused by considerable blood loss or crossclamping. Moreover, marked hemodynamic instability is often observed at the reperfusion of the liver graft [18].

The aim of the present study was to evaluate the role of ANF during OLT in cirrhotic patients with ascites.

Materials and methods

We studied eight adult cirrhotic patients affected by Budd-Chiari syndrome ($n = 1$), cryptogenic cirrhosis ($n = 1$) postalcoholic cirrhosis ($n = 1$), and posthepatitis cirrhosis ($n = 5$) who were undergoing OLT. One of these eight patients was retransplanted for primary nonfunction (PNF). The average age of the patients was 37 ± 8 years; their weight was 65 ± 9 kg and height 172 ± 5 cm (mean ± SD). Careful laboratory and imaging work-up was carried out preoperatively and the diagnosis of cirrhosis was confirmed by preoperative biopsy in all patients.

Anesthetic induction and tracheal intubation were performed with 5 mg/kg thiopentone (Pentothal) and 1.5 mg/kg succinylcoline (Midarine) supplemented with 3–5 μ/kg fentanyl (Fentanest). Anesthesia was maintained with 55 % air and 45 % oxygen, with 0.8 %–1.5 % isoflurane (Forane) and fentanyl. Nitrous oxide was not used. Muscular relaxation was obtained with vecuronium (Norcuron). Ventilatory settings were adjusted (Servo ventilator 900 C) with adequate parameters of volume and frequency to maintain $PaCO_2$ between 31 and 35 mm Hg.

Dopamine (Revivan) alone was routinely infused at the rate of 3 μg/kg per minute, as all of these patients presented with a certain degree of renal impairment. No diuretics nor any other vasoactive drugs (i.e. catecholamines) were given during the operation. None of the patients was affected with cardiomyopathy. Four patients underwent venovenous bypass (Bio-pump, Biomedicus) during the anhepatic phase. The cannulated vessels included the portal, femoral, and axillary veins. The flow rate ranged between 1000 and 1800 ml/min.

Continuous monitoring of ECG, $ETCO_2$, and pulse oximetry (Oscar-Datex) was obtained and hemodynamic variables including saturation of mixed venous blood (SVO_2), heart rate (HR), central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary arterial wedge pressure (PAWP), and cardiac output (CO) measured by thermodilution were continuously provided by a Swan-Ganz fiber optic catheter (Oximetrix, Abbott). Calculated parameters such as cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), oxygen transport index (DO_2I), oxygen consumption index (VO_2I), and arteriovenous oxygen content difference (a-v DO_2) were also recorded. A cannula was inserted into the femoral artery for continuous monitoring of mean arterial blood pressure (MAP), and urine output was measured every 30 min using a urine bag connected to the catheter inserted into the bladder.

Blood samples from the cannulated radial artery were collected for ANF measurement. Hemodynamic and laboratory assessments were obtained at the induction of anesthesia (phase I), every 60 min during hepatectomy (phase II), every 30 min during the anhepatic phase (phase III), and 5 and 30 min after the reperfusion of the liver graft (phases IV and V). Diuresis during the last two phases was combined into a single 30-min measurement. The data were recorded as the mean ± SD value for each time point.

Statistical analysis of the results was obtained using Student's t-test for paired data, comparing each phase with basal values. A P value of 0.05 or less was considered significant.

Blood samples were centrifuged, refrigerated, and analyzed using the RIA 1 125 method (INCSTAR, Stillwater, Minn., USA). The normal values for ANF ranged between 21–49 pg/ml in our laboratory.

Results

Table 1 shows changes in the parameters studied in various phases of OLT. ANF concentration and both heart filling pressure and systemic vascular resistances are shown in bold characters. No differences in hemodynamic parameters were observed in patients with or without bypass.

A significant increase in ANF became evident 5 min after reperfusion of the liver graft (phase IV, $P < 0.05$). Concurrently, a significant increase in CVP ($P < 0.05$) and decrease in systemic vascular resistance index (SVRI) occurred. During the anhepatic phase (phase III), ANF levels appeared slightly elevated but did not reach statistical significance, whereas basal samples were within the normal limits in all patients. Diuresis did not change significantly during the entire procedure.

The values of CVP, ANF, and SVRI before and after reperfusion are plotted in Fig. 1.

Table 1 Hemodynamic, oxyphoretic and ANF concentration changes during orthotopic liver transplantation. Values indicate mean ± SD. $N = 8$ patients (*HR* heart rate, *MAP* mean arterial blood pressure, *CI* cardiac index, *CVP* central venous pressure, *PAWP* pulmonary arterial wedge pressure, *SVRI* systemic vascular resistance index, *PVRI* pulmonary vascular resistance index, VO_2 oxygen consumption index, DO_2I oxygen transport index, $a\text{-}vDO_2$ arteriovenous oxygen content difference, SVO_2 saturation of mixed venous blood. *n. a.* not applicable)

Phase	I (Basal phase)	II (Hepatectomy phase)	III (Anhepatic phase)	IV (5 min after reperfusion phase)	V (30 min after reperfusion phase)
ANF (pg/ml)	*38 ± 10*	*30 ± 12*	*50 ± 10*	*75 ± 10**	*40 ± 10*
HR (beats/min	105 ± 5	105 ± 10	111 ± 12	88 ± 10*	105 ± 10
MAP (mm Hg)	95 ± 20	90 ± 9	85 ± 10	75 ± 10*	89 ± 20
CI ($L \cdot min^{-1} \cdot m^{-2}$)	8.1 ± 1	7.8 ± 1.7	6.2 ± 1.8	7.5 ± 1.8	8.0 ± 2
CVP (mm Hg)	*5 ± 2*	*5 ± 1*	*4.5 ± 0.5*	*8.8 ± 1**	*6 ± 2*
PAWP (mm Hg)	7 ± 2	7 ± 1	6 ± 1.5	10 ± 2*	8 ± 1
SVRI(dyn · $cm^{-5} \cdot s^{-1} \cdot m^{-2}$)	*680 ± 170*	*620 ± 160*	*800 ± 195*	*580 ± 200*	*800 ± 160*
PVRI(dyn·$cm^{-5} \cdot s^{-1} \cdot m^{-2}$)	80 ± 4	95 ± 5	96 ± 7	99 ± 8	95 ± 6
VO_2 I ($ml \cdot min^{-1} \cdot m^{-2}$)	100 ± 20	103 ± 18	85 ± 10*	130 ± 30*	160 ± 20
DO_2 I ($ml \cdot min^{-1} \cdot m^{-2}$)	880 ± 100	800 ± 80	660 ± 90*	700 ± 80	1010 ± 90
a-vDO_2 (%)	1.9 ± 1.5	2 ± 1.1	2.5 ± 1.2	2.2 ± 1.1	2.1 ± 1.1
P_aO_2 (mm Hg)	140 ± 40	130 ± 35	180 ± 50	200 ± 40	150 ± 45
SVO_2 (%)	86 ± 3	88 ± 2	91 ±2*	88 ± 4	80 ± 5*
Diuresis (ml/30 min)	21.4 ± 4.3	23.8 ± 4.5	19.6 ± 4.3	n.a.	18.4 ± 4.4

* $P < 0.05$

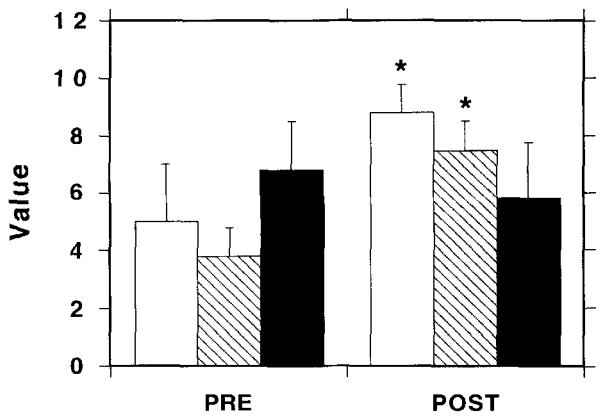

Fig. 1 CVP values (□), ANF concentrations (▨), and SVRI measurements (■) before (pre) and after (post) reperfusion in eight cirrhotic patients during liver transplantation. Size units as follows: SVRI ($dyn \cdot cm^{-5} \cdot s^{-1} \cdot m^{-2} \times 10^{-2}$), ANF ($pg/ml \times 10^{-1}$), CVP (mm Hg). * $P < 0.05$

Discussion

Liver transplantation is a complex surgical operation that involves major vascular derangements in addition to the hemodynamic baseline changes present in cirrhotic patients [4, 5, 10, 11]. A hyperdynamic circulation with high cardiac output and low vascular peripheral resistance is a pathophysiological characteristic of liver cirrhosis. Portal hypertension, hepatorenal relations, the renin-angiotensin-aldosterone (RAA) system, neurosympathetic tone, and the ADH hormonal status are all involved in these hemodynamic changes. More recently, primary peripheral vasodilation and arteriovenous shunts are thought to also play a role in the hyperdynamic circulatory changes that occur.

OLT has various hemodynamically relevant stages, from the induction of anesthesia of the clamping of the vena cava with or without venovenous bypass, to the anhepatic phase and, finally, to reperfusion of the graft with declamping of the vena cava. The latter critical phase is associated with additional stress on the hemodynamic circulation and can sometimes be responsible for the so-called reperfusion syndrome. This clinical condition can be fatal and has been described as hypotension, worsening low vascular peripheral resistance, bradycardia, and asystolia occurring after reperfusion of the graft [4, 18].

During the reperfusion phase of liver transplantation, the sharp increase in blood volume associated with declamping is responsible for the increased cardiac preload [18] that results in increased intraluminal pressure. This event, in our experience, is associated with an increase in ANF release. To the best of our knowledge, these data have never before been reported. The increase in ANF levels is also associated with a further decrease in peripheral vascular resistance but, in our experience, not with an increase in diuresis. The relationship between atrial stress, ANF release, decreased vascular resistance, and increased diuresis has been well described in other pathophysiological conditions [2, 11, 12, 17–21].

The lack of increase in diuresis during the reperfusion phase of OLT can be explained by different hypotheses. Cirrhotic patients may be affected by hemodynamic derangements that are resistant to ANF action, such as hyperactivation of RAA or sympathetic tone, which sometimes culminate in the hepatorenal syndrome. In addi-

tion, infusion of ANF does not always increase diuresis in such patients. Whether this is true insensitivity or down-regulation of receptors still remains to be determined [22].

It seems, therefore, reasonable to assume that a pathophysiological mechanism involving ANF may be responsible for both hypovolemia and altered sodium reabsorption, characteristic of cirrhotic patients. More data and further investigations, including concurrent monitoring of serum renin and aldosterone levels as well as urinary sodium concentration, are needed to adequately confirm whether ANF does, in fact, play a certain role in the development of the supposed reperfusion syndrome occurring in liver transplantation.

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