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α-Human-ANP response to preanesthetic volume expansion and subsequent renal transplantation in diabetic and nondiabetic uremic patients

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Abstract. α-Human atrial natriuretic peptide (ANP) concentrations were measured in 11 diabetic patients with uremia and in 16 nondiabetic uremic controls undergoing renal transplantation after preanesthetic volume expansion with 1000 ml saline solution within 10 min. Two diabetic and seven nondiabetic patients received grafts from living donors and the rest from cadaveric donors. Volume expansion induced a significant increase in the cardiac filling pressures ($P < 0.001$), which were kept at that level especially at declamping, which was preceded by mannitol infusion. The baseline mixed venous ANP levels were significantly higher in the diabetic (252 ± 6 pg/ml) than in the nondiabetic group (103 ± 14 pg/ml; $P < 0.05$). In the nondiabetic group, ANP increased to 177 ± 40 pg/ml as a response to volume loading ($P < 0.05$); it was not clearly changed in the diabetic group. Arterial ANP increased from 267 ± 55 to 343 ± 75 pg/ml in the diabetic group ($P < 0.05$ and from 102 ± 17 to 147 ± 31 pg/ml in the nondiabetic group ($P < 0.05$). During transplantation, mixed venous ANP decreased to 125 ± 55 pg/ml in the diabetic and to 80 ± 10 pg/ml in the nondiabetic group ($P < 0.001$). About 30% of circulating ANP was taken up by the transplant irrespective of postoperative graft function. Two patients in each group showed delayed diuresis requiring postoperative dialysis therapy (22% of all cadaveric transplantations). ANP levels at declamping had no correlation to the outcome of kidney function.

Key words: ANP levels, in kidney transplantation – Kidney transplantation, ANP levels – Diabetes mellitus, ANP levels, in kidney transplantation

Since its characterization and purification, great interest has been focused on atrial natriuretic peptide (ANP) and its role in regulating glomerular and tubular function after renal ischemia [9, 19]. Exogenous ANP does not seem to prevent acute renal failure in cadaveric kidney transplantation [2, 24, 27]. ANP plasma levels have been shown to increase after intravenous volume expansion in conscious humans [25]. ANP level in plasma decreases during hemodialysis in uremic patients [3, 11] and it may remain low during subsequent renal transplantation. There is a clear need for further studies on the effect of ANP in association with renal transplantation [10]. ANP response to intravascular volume loading is normal in non-uremic diabetic patients with microangiopathy [7], but the response in patients with long-term diabetes and with uremia has not been evaluated. We, therefore, compared the effect of volume-stimulated plasma ANP levels during renal transplantation in diabetic uremic patients and those with a primary kidney disease.

Patients and methods

Twenty-seven uremic patients undergoing renal transplantation participated in the trial. Eleven of the patients had diabetes mellitus-related nephropathy and uremia and 16 uremia of other than diabetic etiology. The study protocol was approved by the Hospital Ethics Committee and informed verbal consent was obtained from all patients. Two patients in the diabetic and seven in the nondiabetic group received a kidney from a living related donor; the rest received a kidney from a cadaveric donor (Table 1). The patients fasted for at least 8 h before the operation. Antihypertensives, calcium channel blockers, and angiotensin converting enzyme inhibitors were discontinued 8 h before the study. The last hemodialysis was performed within 24 h before the operation. If the patient was on continuous ambulatory peritoneal dialysis, the dialysis was continued until the operation to keep the plasma potassium value below 5.0 mmol/l.

The transplant recipients receiving a cadaver graft were selected on the basis of their HLA-A, -B, and -DR compatibility; a maximum of two mismatches were accepted in A and B loci and one in DR. Immunosuppressive therapy with azathioprine, methylprednisolone, and cyclosporine was standardized. In the nine grafts from living related donors, four donors were HLA-identical siblings and five non-HLA-identical. Initial immunosuppression in the HLA-identical cases was azathioprine and methylprednisolone. In the non-HLA-identical cases, donor-specific blood transfusions together with azathioprine were given before operation. Perioperative antibiotic prophylaxis was with cefamandole.

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Table 1. Demographic patient data. All values expressed as mean ± SEM

	Diabetic group	Nondiabetic group
No. of patients	11	16
Age (years)	37 ± 2	38 ± 3
Sex (M/F)	5/6	3/13
Weight (kg)	64 ± 2	68 ± 4
Duration of diabetes mellitus (years)	26 ± 5	0
Type of dialysis (CAPD/hemodialysis)	8/3	10/6
Donor (living/cadaver)	2/9	7/9

Table 2. Hemodynamic response to volume expansion and changes during renal transplantation. All values expressed as mean ± SEM. HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure

	HR (beats/min)	MAP (mm Hg)	PCWP (mm Hg)	CVP (mm Hg)
Diabetic group ($n = 11$)				
Before volume expansion	83 ± 6	123 ± 5	7 ± 1	1 ± 0.2
After volume expansion	85 ± 5	130 ± 5	13 ± 1**	4 ± 0.6*
45 min after induction	73 ± 1	93 ± 6**	12 ± 1	6 ± 1
Before declamping	67 ± 4	94 ± 6	13 ± 1	4 ± 1
5 min after declamping	67 ± 4	86 ± 4	12 ± 2	6 ± 0.3
Nondiabetic group ($n = 16$)				
Before volume expansion	78 ± 4	113 ± 4	7 ± 1	3 ± 1
After volume expansion	83 ± 4	118 ± 4	13 ± 1**	7 ± 1**
45 min after induction	76 ± 4	87 ± 3**	11 ± 1	7 ± 1
Before declamping	70 ± 4	86 ± 3	11 ± 1	7 ± 1
5 min after declamping	71 ± 4	80 ± 3	12 ± 1	9 ± 1

* $P < 0.01$; ** $P < 0.001$ from baseline

The patients were premedicated with diazepam 0.2 mg/kg p.o. After arrival in the operating theater the right internal jugular vein was cannulated under local anesthesia and a pulmonary artery balloon tip catheter (Swan-Ganz 7F, American Edwards Laboratories) was advanced into the pulmonary artery in five patients in the diabetic and in seven in the nondiabetic group. A central venous line was inserted in six patients in the diabetic and in nine in the nondiabetic group. A radial artery for continuous pressure monitoring and a peripheral vein for drug administration were cannulated under local anesthesia. Thereafter fast volume-loading was carried out with a crystalloid potassium-free solution (Fysioring, Orion Ltd, Finland: Na^+ content 130 mmol/l) over 10 min in order to double the baseline pulmonary capillary wedge pressure (PCWP) or central venous pressure (CVP). Then the patients were anesthetized with thiopental 4 mg/kg and fentanyl 0.15–0.2 mg. Anesthesia was maintained with isoflurane and 66% nitrous oxide in oxygen and analgesia with fentanyl. Muscle relaxation for endotracheal intubation and surgery was achieved with vecuronium.

Heart rate (HR), mean arterial pressure (MAP), PCWP, and CVP were recorded before and after the volume expansion and before and 5 and 15 min after declamping of the renal vessels. Intravascular pressures were electronically obtained at the midthoracic level. Ten minutes before declamping, 200–300 ml 15% mannitol was infused into the central line. Cardiac filling pressures were kept at about the levels obtained after volume expansion throughout the transplantation, especially before and after declamping. No fluids other than the crystalloid fluids were used. The interval from the induction of anesthesia to the connection of the graft circulation was 130 ± 44 min (mean ± SEM) in the diabetic group and 139 ± 20 min in the nondiabetic group.

Blood samples for the measurements of α-human atrial natriuretic peptide (ANP), plasma renin activity (PRA), and antidiuretic hormone (ADH) were drawn from the proximal port of the pulmonary catheter or from the central venous line, and from the radial artery before and after the volume loading and before and 5 and 15 min after declamping of the graft vessels. These variables were also assessed in the renal venous blood 5 and 15 min after connection of the graft circulation. Samples were placed into prechilled propylene tubes containing EDTA and the tubes were immediately immersed in ice until centrifuged at −4 °C and stored at −70 °C. Plasma lactate and lactate dehydrogenase (LDH) were measured from the blood sampled from the radial artery before and from the renal vein 5 and 15 min after the declamping. The concentrations of ANP, PRA, and ADH were determined with the method descibed by Hynynen et al. [14]. In the diabetic group, blood glucose was kept below 12 mmol/l with 50 IU short-acting insulin added to 500 ml 5% glucose infused at a rate of 10–40 ml/h. In the recovery room, sodium concentration in the primary post-transplantation urine was assessed. PCWP was kept at a level of 8–10 mm Hg and CVP at 4–6 mm Hg. Kidney function was considered to be immediate if diuresis was 0.5–1 ml/kg/h, with subsequent decrease of creatinine within 2 days. If needed, furosemide was administered intravenously to maintain diuresis above 0.5 ml/kg per hour.

Student's unpaired t-test was used for statistical analysis of the differences in the variables between the groups. The changes within a group were assessed with Student's paired t-test. The results are expressed as mean ± SEM. A P value of less than 0.05 was considered statistically significant.

Results

The two groups were comparable with respect to age, weight, and preoperative dialysis therapy. In the diabetic group, the patients had had diabetes mellitus for 26 ± 5 years (Table 1). Preoperative diuresis was 1010 ± 360 ml/24 h in the diabetic and 850 ml ± 210 ml/24 h in the nondiabetic group. Three patients in the diabetic and none in the nondiabetic showed cardiac enlargement in the preoperative chest X-ray ($P < 0.05$). Preoperative CVP was 1 ± 0.2 mm Hg in the diabetic and 3 ± 1 mm Hg in the nondiabetic group. Volume expansion was performed with 968 ± 106 ml fluid in the diabetic and 927 ± 82 ml fluid in the nondiabetic group. PCWP and CVP increased significantly as a response to volume loading in both groups ($P < 0.001$). In all patients, the volume loading was completed within 9 ± 1 min. MAP decreased similarly in both groups from the baseline after induction of anesthesia ($P < 0.001$; Table 2). The total amount of fluid given during anesthesia was 3650 ± 225 ml in the diabetic and 3567 ± 254 ml in the nondiabetic group.

The initial preoperative ANP levels in mixed venous ($P < 0.05$) and arterial blood ($P < 0.01$) was significantly higher in the diabetic (252 ± 60 and 267 ± 55 pg/ml) than in the nondiabetic group (103 ± 14 and 104 ± 17 pg/ml respectively). In the nondiabetic group, ANP in mixed venous increased significantly compared to the baseline (103 ± 14 pg/ml) after volume loading (177 ± 40 pg/ml; $P < 0.05$); the corresponding figures in the diabetic group were 252 ± 60 and 258 ± 57 pg/ml, respectively (difference not significant). The ANP in arterial blood after volume loading was 147 ± 31 pg/ml in the nondiabetic and 343 ± 75 pg/ml in the diabetic group ($P < 0.05$ from the baseline in both groups).

During the transplantation, mixed venous and arterial blood ANP decreased in both groups despite continuous volume replacement, in the diabetic group to 124 ± 55 and

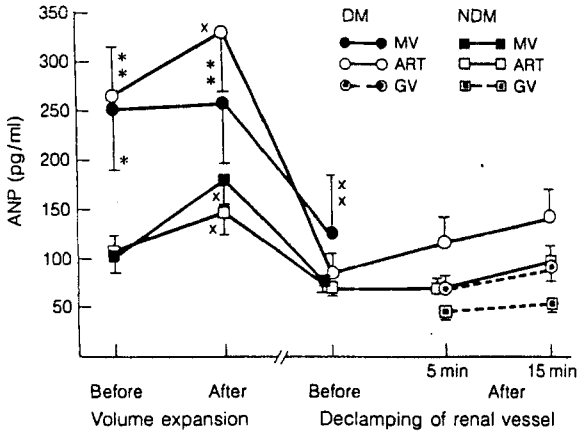

Fig. 1. α-Human atrial natriuretic peptide (ANP) during renal transplantation. Plasma concentration measured from mixed venous *(MV)*, radial artery *(ART)*, and from the vein of the transplanted kidney *(GV)*. Mean ± SEM values are given for 11 diabetic *(DM)* and 16 nondiabetic *(NDM)* uremic patients. * $P < 0.05$, ** $P < 0.01$ between the groups. Changes within a group: x $P < 0.05$. Significant decrease in all groups: xx $P < 0.001$

85 ± 17 pg/ml, respectively and in the nondiabetic group to 80 ± 10 and 81 ± 6 pg/ml ($P < 0.001$), respectively. At declamping, ANP was higher in the blood from the radial artery than in that from the renal vein (Fig. 1). ANP was taken up by the transplant at a rate of 28 ± 8% in the diabetic and 36 ± 7% in the nondiabetic group (graft vein concentration as percentage of arterial concentration).

No significant differences were found in PRA (Table 3) or in concentrations of ADH (Table 4) at any study point. Arterial lactate concentrations were significantly higher in the diabetic (1.3 ± 0.3 mmol/l) than in the nondiabetic group (0.7 ± 0.1 mmol/l; $P < 0.05$) before declamping (Table 5).

In both groups, the lactate concentration in the graft vein was significantly higher in the kidneys from cadaveric donors (1.7 ± 0.2 mmol/l) than in those from living donors (0.7 ± 0.1 mmol/l; $P < 0.001$). At declamping, blood glucose was 12 ± 5 mmol/l in the diabetic and 7 ± 1 mmol/l in the nondiabetic group ($P < 0.001$). After declamping of the renal vessels, immediate and adequate perfusion of the graft was seen in all patients. The mean cold ischemia time in cadaveric transplantations was 28 ± 4 h in the diabetic and 33 ± 2 h in the nondiabetic group. Sodium concentration in the primary post-transplantation urine was 92 ± 3 mmol/l in the diabetic and 90 ± 6 mmol/l in the nondiabetic group.

In the recovery room, severe or moderate swelling was seen in the eyelids, face, arms, fingers, and legs especially of the diabetic patients. Neither clinical nor radiological signs of pulmonary edema were noted at any phase of the study in any patient.

After cadaveric transplantations (18 cases), temporary dialysis therapy was required in two patients in the diabetic and in two in the nondiabetic group (delayed diuresis in 22% of all cadaveric transplants). In these four patients with nonfunctioning grafts, creatinine levels increased from 831 ± 97 to 937 ± 96 μmol/l within 2 days. Urine production was 266 ± 150 ml on the 1st and 285 ± 134 ml on the 2nd postoperative day. In these four patients, ANP was taken up by the transplants at a rate of 39 ± 6% at declamping. In transplantations from living donors (9 cases) kidney function started immediately after re-establishment of the graft circulation. In these patients, creatinine levels decreased from 745 ± 62 to 104 ± 10 μmol/l ($P < 0.001$) in 2 days with urine production of 5952 ± 1312 ml on the 1st and 6131 ± 1460 ml on the 2nd postoperative day. After cadaveric transplantations with immediate graft function (14 cases), the figures were: creatinine levels in the first 2 days, 727 ± 49 and 312 ± 54 μmol/l ($P < 0.001$); urine production, 4275 ± 129 ml on the 1st day and 4368 ± 890 ml on the 2nd day.

Discussion

Our results show that plasma ANP levels did not correlate to the outcome of kidney function. Preanesthetic volume expansion and moderate hydration combined with mannitol infusion before declamping were associated with a low incidence of delayed diuresis. ANP response to preanesthetic hydration was obtained in the nondiabetic patients. In the diabetic patients, ANP response was seen in the arterial circulation, reflecting that the response was about similar in nondiabetic and diabetic patients. ANP levels

Table 3. Plasma renin activity (ng/ml h) during transplantation. All values expressed as mean ± SEM. CV, Central vein; PA, pulmonary artery; RA, radial artery; GV, graft vein

	CV or PA	RA	GV
Diabetic group ($n = 11$)			
Before volume expansion	2.7 ± 0.3	2.9 ± 0.5	–
After volume expansion	3.3 ± 0.5	2.6 ± 0.3	–
Before declamping	2.5 ± 0.2	3.2 ± 0.2	–
5 min after declamping	–	3.2 ± 0.5	2.8 ± 0.3
15 min after declamping	–	3.1 ± 0.4	2.7 ± 0.2
Nondiabetic group ($n = 16$)			
Before volume expansion	2.9 ± 0.3	2.6 ± 0.2	–
After volume expansion	2.5 ± 0.2	2.6 ± 0.3	–
Before declamping	2.6 ± 0.3	2.4 ± 0.3	–
5 min after declamping	–	2.6 ± 0.2	3.0 ± 0.2
15 min after declamping	–	2.9 ± 0.3	3.1 ± 0.4

Table 4. Concentrations of antidiuretic hormone (ADH) (pg/ml) during transplantation. All values expressed as mean ± SEM. Number of patients in brackets. CV, Central vein; PA, pulmonary artery; RA, radial artery; GV, graft vein

DM (5)	CV or PA	RA	GV
Before volume expansion	7 ± 0.2	9 ± 0.04	
After volume expansion	7 ± 1	5 ± 0.6	
Before declamping	20 ± 9	12 ± 5	
5 min after declamping		11 ± 4	38 ± 28
15 min after declamping			16 ± 6
NDM (8)			
Before volume expansion	10 ± 3	10 ± 3	
After volume expansion	8 ± 3	7 ± 3	
Before declamping	17 ± 8	17 ± 6	
5 min after declamping		22 ± 7	13 ± 5
15 min after declamping			22 ± 7

Table 5. Concentrations of lactate and lactate dehydrogenase during transplantation. All values expressed as mean ± SEM. D, Declamping; LDH, lactate dehydrogenase. * $P < 0.05$ between the groups

	Before D		5 min after D		15 min after D	
	Lactate (mmol/l)	LDH (U/l)	Lactate (mmol/l)	LDH. (U/l)	Lactate (mmol/l)	LDH (U/l)
Diabetic group ($n = 11$)						
Radial artery	1.3 ± 0.3*	270 ± 19				
Graft vein			1.6 ± 0.3	313 ± 20	1.4 ± 0.3	312 ± 30
Nondiabetic group ($n = 16$)						
Radial artery	0.7 ± 0.1	220 ± 20				
Graft vein			1.4 ± 0.2	297 ± 30	1.1 ± 0.1	275 ± 27

decreased in all patients during the later course of transplantation despite continuous volume loading. The transplants took up about 30 % of circulating ANP irrespective of postoperative graft function.

ANP levels have been shown to be elevated in uremic patients undergoing chronic dialysis therapy [1, 6, 11, 16–18, 20, 23, 29, 30] and, especially, in patients with heart failure [3, 8, 28]. Immediately after hemodialysis, however, the plasma concentrations of ANP have been observed to decrease [11, 13, 23]. It has also been postulated that the chronic increase and fluctuations in ANP levels in chronic renal failure make the plasma ANP level a poor indicator of the fluid balance [17, 20]. In our nondiabetic patients, the preoperative ANP levels were approximately normal [28]; only in the diabetic patients were the ANP levels clearly elevated. This is probably due to the cardiac enlargement in three of our diabetic patients [28] and chronic cardiac failure often seen in diabetes-related uremia [12]. Our nondiabetic patients responded to the rapid volume loading by a rise in ANP. A similar response was seen in arterial samples from the diabetic patients. Uremic nondiabetic patients have a normal ANP response to volume expansion [5, 6, 20, 29] and to water immersion [15]. Diabetic patients with microangiopathy also have a normal response [7]. The ANP response in diabetic uremic patients needs to be further evaluated.

ANP levels decreased during the renal transplantation in all our patients to about 80 pg/ml, even in the diabetic patients with significantly higher preoperative ANP levels. This decrease may be due to peripheral vasodilatation caused by isoflurane [22], and intermittent positive ventilation may also affect ANP levels [5]. However, the arterial and cardiac filling pressures in our patients were clinically adequate throughout the operation, especially at the time of declamping. Although ANP levels decreased, the graft took up about 30 % of the circulating ANP and graft function was perfect in 78 % of the patients. Moreover, the grafts with nonimmediate function took up ANP at a similar rate. In dogs with acute renal ischemia, exogenous ANP significantly improved the glomerular filtration [9, 19]. Nyberg et al. [20] have demonstrated that ANP levels were high after renal transplantation. Our ANP levels started to increase 15 min after establishment of graft circulation. Unfortunately, ANP was not measured after the recovery from anesthesia, when the peripheral circulation has returned to a normal state [22]. Our results give evidence that with adequate cardiac filling and optimal renal perfusion, graft function is satisfactory [4] even if ANP levels are low. However, beneficial effects of mannitol [30] may be of importance. Also, the outcome of graft function depends on several other determinants [21].

In our study, PRA and ADH did not show any significant correlation to changes in ANP, agreeing with observations by Hynynen et al. [14]. As expected, plasma lactate concentrations from the graft vein were higher in the diabetic than in the nondiabetic patients, due to higher blood glucose values at the time of declamping. Also, cadaveric grafts gave higher lactate concentrations than those from living donors. This reflects the higher ischemia and greater metabolic changes [26] in cadaveric grafts.

In conclusion, optimal cardiac filling with adequate renal perfusion may be more important factors than certain ANP levels for the outcome of kidney function after renal transplantation.

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