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Fluid management and plasma renin activity in organ donors

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Abstract. Fluid management and assessment of organ perfusion in organ donors with hypotonic polyuria remain poorly investigated problems. In our protocol, urinary losses (565 ± 202 ml/h) were replaced volume for volume by 3.3% dextrose/0.3% natrium chloride solution (Baxter) with 20 mmol/l potassium chloride. Concentrated red blood cells were administered to maintain hematocrit at about 30%, and volume expansion (central venous pressure above 6 mmHg) was obtained by gelatin (Haemaccel) infusion. In all donors ($n = 9$), plasma electrolytes remained within normal limits despite hypotonic polyuria. Suppression of initial plasma renin activity (PRA; 9.7 ± 3.6 ng/ml per hour) was obtained by subacute volume expansion. In eight donors the hemodynamic status improved, dopamine administration, when used, was discontinued, and PRA decreased (2.3 ± 0.7 ng/ml per hour; $P < 0.05$). The only donor who failed to respond to fluid therapy had increased PRA (24.2 ng/ml per hour). During fluid challenge, an inverse relationship was demonstrated between mean arterial pressure and PRA in all nine donors ($r = -0.61$; $P < 0.001$), while there were no significant changes in blood urea, creatinine, or urine output. It is concluded that in organ donors, proper maintenance of the hemodynamic status and suppression of the renin stress response may be obtained by an adequate fluid management, involving both qualitative restoration and expansion of intravascular volume.

Key words: Donor management - Fluid management in donors - Plasma renin activity in donors.

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It has been reported that in organ donors, proper maintenance of oxygen delivery to organs involves both qualitative restoration and expansion of intravascular volume in such a way as to avoid excessive doses of dopamine and vasopressin [8, 11]. However, in such donors presenting with hypotonic polyuria, fluid management has been poorly investigated. Moreover, assessment of organ perfusion remains an unsolved problem. Serial assays of plasma urea and creatinine reveal little that is of interest, while in donors with diabetes insipidus or osmotic polyuria, urine output no longer reflects renal perfusion [3, 8]. Renin stress response has been described in the prerenal phase of acute renal failure and in abnormal conditions of renal perfusion, and it has been associated with a decrease in cortical perfusion [4, 9]. The aim of this preliminary study was to evaluate our recent protocol of fluid management and to analyze the observed changes in hemodynamic status, plasma electrolytes, and plasma renin activity during fluid challenge.

Materials and methods

Nine brain-dead, heart-beating donors presenting with hypotonic polyuria were studied. The mean age was 24 ± 7 years. The causes of brain death were: head trauma as a result of a traffic accident ($n = 7$), a gunshot wound ($n = 1$), and subarachnoid hemorrhage ($n = 1$). The brain death diagnosis was based on clinical examination and, when needed (i.e., in five donors), was confirmed by aortic arch angiography. The time that elapsed between brain injury and diagnosis of brain death ranged from 4 to 23 h (mean 9 ± 6 h). Upon diagnosis of brain death, all specific treatments were discontinued and the protocol of fluid management was started. Urinary losses were replaced volume for volume, using a

3.3% dextrose/0.3% natrium chloride solution (Baxter) with 20 mmol/l potassium chloride. Concentrated red blood cells were administered to maintain a hematocrit value of about 30%, and volume expansion (central venous pressure of at least 6 mm Hg) was obtained by infusing gelatin solutions (Haemaccel). At the beginning of the study, dopamine infusion (10÷20 μg/kg per minute) was needed in five donors. Continuous insulin infusion was used to limit excessive hyperglycemia (above 20 mmol/l). The core temperature of the donors was maintained at about 35°C by infusing warmed fluids, supplying heated gases from the respirator, and applying heating blankets.

The effects of fluid challenge on (1) plasma electrolytes and glucose; (2) the hemodynamic parameters of mean arterial pressure (MAP), central venous pressure (CVP), and blood lactate; (3) renal function, including diuresis, plasma urea, creatinine, and urine β2 microglobulin; and (4) plasma renin activity (PRA) were determined every 2 h during organ donor maintenance (8 h). PRA and urine β2 microglobulin levels were determined by radioimmunoassay (normal values 0.5-4.0 ng/ml per hour and 1.82-27.30 μmol/l, respectively). Results are expressed as the mean ± SEM. As statistical methods, we used the Wilcoxon signed rank test and the Spearman rank order correlation.

Results

Urinary fluid losses were 565 ± 202 ml/h; urine-specific gravity was 1003 ± 3. Cristalloid intake (3.3% dextrose/0.3% natrium chloride with 20 mmol/l potassium chloride) was 480 ± 160 ml/h. Natremia and kalemia remained within normal limits despite sustained polyuria; hyperglycemia was minimized (Table 1). Continuous infusion of insulin (1.5 ± 1 IU/h) was required in four donors. Intravenous intake of sodium (51 mmol/l) matched well with urinary losses (61 ± 21 mmol/l); change in natremia correlated with sodium balance ($r = 0.55$; $P < 0.01$). A wide variation in urinary losses of potassium (51 ± 45 mmol/l) was observed; change in kalemia correlated with potassium balance ($r = 0.33$; $P < 0.05$). During insulin infusion, two donors presented with transient hypokalemia requiring a potassium chloride supplement (40 mmol). During maintenance, the colloid (Haemaccel) requirement for obtaining a CVP of at least 6 mmHg was 1375 ± 515 ml; the blood requirement for maintaining hematocrit at about 30% was 1.5 ± 1 unit of red blood cells.

The initial hemodynamic status (MAP 68 ± 15 mmHg; CVP 2 ± 1 mmHg) improved in eight out of nine donors, resulting in the correction of the initial hypovolemic shock (Table 2). Dopamine infusion, when used, was discontinued (four donors) and PRA decreased (from 9.7 ± 3.6 to 2.3 ± 0.7 ng/ml per hour); there was no significant change in urine output, blood urea, creatinine, or urine β2 microglobulin (Table 3). Fifteen of the 16 kidneys removed were transplanted, resulting in a good initial function (urine output above 50 ml/h) in all but one case,

Table 1. Changes in mean plasma sodium, potassium, and glucose over the maintenance of nine donors (P = NS)

	Time from diagnosis of brain death (h)			
	2	4	6	8
Na (mmol/l)	144 ± 3	144 ± 4	143 ± 2	142 ± 4
K (mmol/l)	4.2 ± 0.3	4.7 ± 0.6	4.6 ± 0.6	4.3 ± 0.4
Glucose (mmol/l)	12.21 ± 2.22	14.43 ± 3.89	15.54 ± 3.89	15.54 ± 4.44

Table 2. Changes in hemodynamic status in eight donors who responded to fluid therapy. MAP, Mean arterial pressure; CVP, central venous pressure. * $P < 0.05$ with initial (T2) values

	Time from diagnosis of brain death (h)			
	2	4	6	8
MAP (mm Hg)	68 ± 15	88 ± 14	95 ± 13*	92 ± 8*
CVP (mm Hg)	2 ± 1	7.5 ± 1*	9 ± 1*	8 ± 1*
Lactate (mmol/l)	4.5 ± 1.6	3.3 ± 0.5	2.3 ± 0.6*	2.0 ± 0.2*

Table 3. Changes in blood urea, creatinine, plasma renin activity (PRA), urine β2 microglobulin (β2 M), and diuresis in eight organ donors who responded to fluid therapy. * $P < 0.05$ with initial (T2) values

	Time from diagnosis of brain death (h)			
	2	4	6	8
Urea (mmol/l)	6.31 ± 0.1	6.14 ± 0.1	5.81 ± 0.12	5.81 ± 0.12
Creatinine (μmol/l)	92 ± 18.6	92 ± 10.6	90.3 ± 7.1	86.7 ± 9.7
PRA (ng/ml per hour)	9.7 ± 3.6	4.6 ± 2.4	3.5 ± 1.4*	2.3 ± 0.7*
β2 M (μmol/l)	827 ± 400	745 ± 418	809 ± 418	618 ± 282
Diuresis (ml/h)	388 ± 148	600 ± 288	441 ± 206	471 ± 191

Table 4. Details of the one patient who failed to respond to fluid therapy. MAP, Mean arterial pressure; CVP, central venous pressure; PRA, plasma renin activity; β2 M, urine β2 microglobulin

	Time from diagnosis of brain death (h)			
	2	4	6	8
MAP (mm Hg)	90	80	60	50
CVP (mm Hg)	9	6	10.5	12
Lactate (mmol/l)	6.3	6.9	4.1	2.4
Urea (mmol/l)	5.81	5.64	6.31	6.47
Creatinine (μmol/l)	115	115	124	115
PRA (ng/ml per hour)	2.5	3.5	9.4	24.2
β2 M (μmol/l)	1454	1473	1373	1364
Diuresis (ml/h)	300	150	260	280

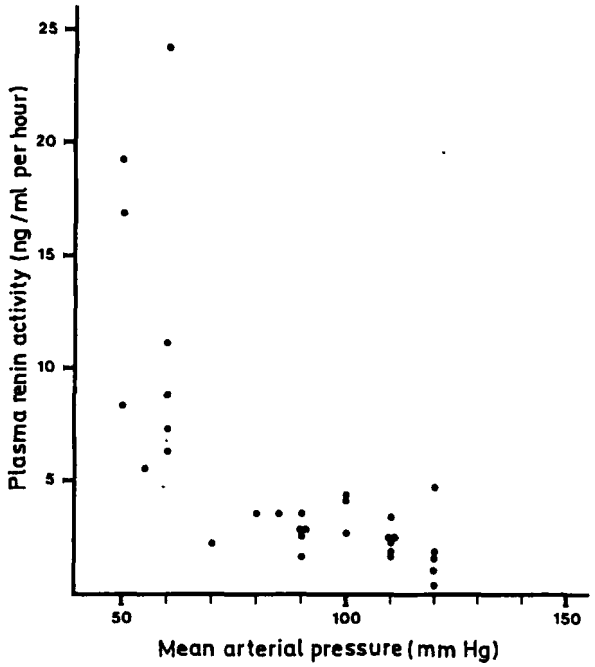

Fig. 1. Relation between mean arterial pressure and plasma renin activity in nine organ donors $r = -0.61$; $P < 0.001$

where a transient hemodialysis was required. Only one donor failed to respond to fluid therapy: moderate hypotension persisted despite high CVP and dopamine infusion at about 20 μg/kg per minute (Table 4). Interestingly, PRA increased from 2.5 to 24.2 ng/ml per hour while urine output, blood urea, creatinine, and urine β2 microglobulin remained unchanged (Table 4). One of the two kidneys that were removed never functioned; the other required transient hemodialysis. In the nine donors, PRA correlated negatively with MAP ($r = -0.61$; $P < 0.001$; Fig. 1).

A total of six livers, five hearts, one lung, and one pancreas were harvested from these nine donors. With the exception of the lung, which immediately developed an irreversible pulmonary edema, all resulted in good early graft function.

Discussion

Early graft function is dependent upon several factors, among them donor management, preservation and surgical technique, ischemia time, and receiver management. Thus, it is rather difficult to search for a direct correlation between the condition of the donor and early graft function. Moreover, due to the nature of this clinical work, it appears difficult to perform a randomized study with an adequate control group. However, it has been shown that kidneys from donors who have been maintained with high doses of dopamine and vasopressin have an increased incidence of acute tubular necrosis [11]. Adequate fluid management seems to be imperative in order to maintain proper organ perfusion without the administration of excessive doses of dopamine and vasopressin [8]. Yet, fluid management in organ donors is often referred to as "fluid replacement" or "volume expansion", with no indication of the fluid to be used.

Our protocol was intentionally designed to be quite simple so that it could be performed easily under difficult conditions, such as those involving the care of an unstable donor. Our fluid management allowed us to maintain proper hemodynamic parameters without having to administer dopamine and vasopressin. Circulatory status improved after volume expansion in eight out of nine donors: MAP increased, dopamine administration was discontinued, and blood lactate decreased. However, in all of the donors, urine output, plasma urea, and creatinine showed no significant changes during fluid challenge, thus failing to accurately reflect acute changes in renal perfusion.

Severe hypernatremia, hypokalemia, and hyperglycemia are complications that always occur in unstable donors who have been maintained by infusing normal saline and 5% dextrose solutions. Our fluid regimen allowed us to maintain serum electrolytes within normal limits despite hypotonic polyuria.

In eight donors, hemodynamic status improved after volume expansion while PRA decreased. The only patient who failed to respond to fluid therapy showed an increased PRA. In all nine donors there was an inverse relationship between MAP and PRA. The renin-angiotensin system seems to be implicated in the pathogenesis of acute renal failure (ARF) in humans [2]. In experimental studies in dogs, Huland et al. [6] found elevated levels of renin activity after warm ischemia. Kehoe et al. [9] have shown an association between PRA and renal dysfunction in patients at risk of developing ARF. The role played by the renin-angiotensin system in the pathogenesis of ARF is not exactly known; it is not clear whether an increase in PRA (renin stress response) is the result or the cause of the decrease in cortical perfusion [4]. Both the severity of hypotension (independent of urine output) and the need for prolonged dopamine administration have been associated with an increased incidence of post-transplant ARF [5, 11]. Our data show an inverse correlation between MAP and PRA. Moreover, as observed in chronic salt-loading and volume expansion [10], our results show that suppression of PRA

may be obtained by subacute volume expansion during donor maintenance. Some authors have demonstrated a beneficial effect of the renin-angiotensin inhibitors on the incidence of post-transplant ARF [1, 7]. It is possible that such treatments could be useful in donors who fail to respond to fluid therapy and in whom PRA is expected to be high.

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