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Long-term renal preservation after brain death maintained with vasopressin and epinephrine

Y. Kinoshita[1], K. Yahata[1], T. Yoshioka[1], S. Onishi[2], and T. Sugimoto[1]

[1] Department of Traumatology and Emergency Medicine, Osaka University Hospital, 1-1-50 Fukushima-ku Fukushima, Osaka-shi, Osaka, Japan 553,
[2] Department of Pathology, College of Biomedical Technology, Osaka University, Osaka, Japan

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Abstract. In order to examine renal function after brain death, twenty-eight patients were randomly separated into two groups. The systemic blood pressure of ten patients was maintained with epinephrine alone (group 1). Eight of the ten patients experienced cardiac arrest within 48 h (range 6–87 h) despite the rather large dosage of epinephrine. Urine output was uncontrollable and renal function deteriorated progressively in this group. Eighteen patients were maintained with arginine vasopressin and epinephrine (group 2). Circulation was maintained with a smaller dosage of epinephrine than that given group 1 for at least 4 days (mean ± SD 16.5 ± 12.2 days). Urine output was controlled within the normal range and serum levels of blood urea nitrogen (BUN) and creatinine were normal for 14 days. Daily creatinine clearance was more than 80 ml/min. The combined administration of arginine vasopressin and epinephrine preserved the kidneys after brain death for more than a week. This method will be of great value in renal transplantation from brain-dead organ donors.

Key words: Brain death, maintenance of circulation – Epinephrine in brain-dead donors – Vasopressin in brain-dead donors – Donor maintenance, pharmacological

Renal function after brain death is one of the most important factors that determine whether renal transplantation will be successful. Carroll et al. [4] showed that kidneys that suffered significant hypotension delayed the onset of function in cadaver kidney transplants. Although certain vasoactive agents, such as catecholamines [13, 17] and phenoxybenzamine [7, 8], had been used in attempts to protect the kidneys from hypotension after brain death, patients usually experienced cardiac arrest within 48 h. This does not provide sufficient time to persuade patients' families to donate organs of their loved ones or to select the best recipients for those kidneys.

We recently succeeded in maintaining circulation after brain death with the combined administration of arginine vasopressin (ADH) and epinephrine for more than a week, and we were able to examine renal function in detail after brain death. In this study we report the clinical and pathological changes after brain death in kidneys maintained with epinephrine alone or with the combination of ADH and epinephrine.

Materials and methods

Twenty-eight brain-dead patients who were admitted to the Department of Traumatology of Osaka University Hospital from 1983 to 1988 were selected for this study. There were 22 males and 6 females.

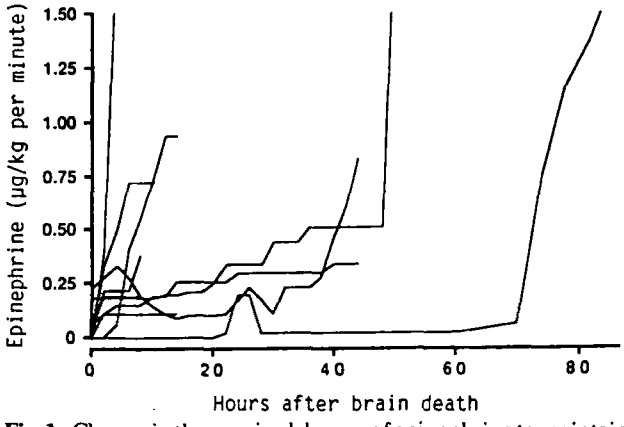

Fig. 1. Change in the required dosage of epinephrine to maintain the systolic blood pressure above 100 mm Hg in group 1

Offprint requests to: Y. Kinoshita

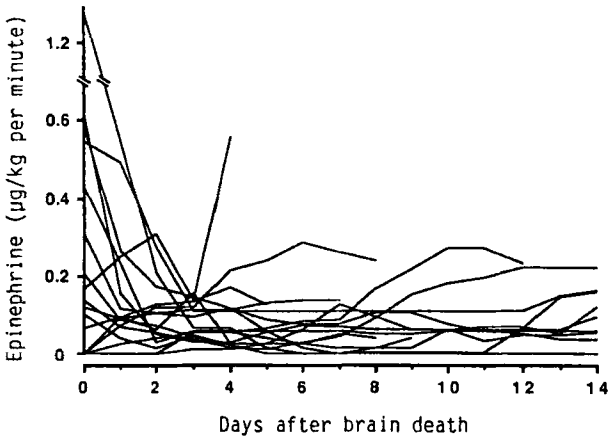

Fig. 2. Change in the required dosage of epinephrine to maintain the systolic blood pressure above 100 mm Hg in group 2 (ADH infused constantly at about 0.3 mU/kg per minute)

Their average age was 34 years (range 9–54 years). The etiology of brain death was severe closed head injury in all patients. The diagnosis of brain death was confirmed by the usual criteria [2, 14, 19], including deep coma, lack of brain-stem reflex, apnea, and isoelectric EEG, which continued for more than 6 h. Formal informed consent for long-term maintenance in order to examine the organ changes after brain death was obtained from all of the patients' families.

All cases had been maintained on a ventilator prior to brain death. Sufficient hydration was provided with rapid infusion of crystalloids and colloids to keep the central venous pressure up to 5 cm H_2O after confirmation of brain death.

The patients were separated into two groups by the methods of circulatory maintenance. Epinephrine was administered intravenously by an automatic syringe infusion pump to maintain the systolic blood pressure above the level of 100 mm Hg in ten patients who were admitted in 1983 and 1984 (group 1). Both arginine vasopressin (Pitressin, Park Davis Morris Plains, NJ) and epinephrine were simultaneously administered to maintain the systolic blood pressure above 100 mm Hg in 18 patients admitted from 1985 through 1988 (group 2). Arginine vasopressin (ADH) was infused constantly according to the hemodynamic state and to control the urine volume in an average dosage of 0.3 mU/kg per minute. Simultaneous infusion of epinephrine was adjusted to maintain the systemic blood pressure. Intravenous prophylactic antibiotics were given to all patients. No diuretics or steroids were used at all. There were no differences between the two groups in the methods of intensive care except for the vasopressin.

The duration from brain death to cardiac arrest and the required dosage of epinephrine to maintain the systemic circulation in the two groups were compared. Serum blood urea nitrogen (BUN), creatinine, and electrolytes were examined every day. Clinical data were obtained by standard methods. Creatinine clearance was calculated daily by urine collected via urethral catheter for 24 h in group 2.

Free water clearance was derived from the formula:

$$CH_2O = (1 - Uosmol/Posmol) \times UV \text{ (ml/min)}$$

Light microscopic examination of the kidney was done in 5 of the 18 patients in group 2 for whom an autopsy was authorized.

Table 1. Renal function of group 1. Values expressed as mean ± SD

Days after brain death	0 ($n = 10$)	1 ($n = 4$)	2 ($n = 2$)
Urine volume (ml/day)	2093 ± 2614	1968 ± 1350	1114 ± 1085
Blood urea nitrogen (mg/dl)	21.1 ± 4.1	37.3 ± 9.2	38.7 ± 12.4
Creatinine (mg/dl)	1.6 ± 0.3	3.1 ± 1.0	4.4 ± 2.5
Na (mEq/l)	154.0 ± 7.1	162.0 ± 8.1	160.2 ± 9.0

Results

The mean and standard deviation of duration from brain death to cardiac arrest was 31.6 ± 24.5 h (range 6–87 h) in group 1 and 16.5 ± 12.2 days (range 4–54 days) in group 2. It was not possible to maintain the circulation of any of the patients in group 1 even by increasing the dosage of epinephrine to prevent hemodynamic deterioration and eventual cardiac arrest (Fig. 1). The systemic circulation of all but two patients in group 2, however, could be maintained steadily for more than a week; both ADH and epinephrine were discontinued and the ventilator disconnected from these patients after getting the approval of their families.

The required dosage of epinephrine was relatively large during the first 2 days after brain death in some patients but could be decreased to less than 0.1 μg/kg per minute in most group 2 patients afterwards (Fig. 2). Only two patients in group 2 who required a rather large dosage of epinephrine experienced cardiac arrest with severe respiratory failure within a week after brain death.

All patients experienced diabetes insipidus before or after the onset of brain death. Urine output was uncontrollable in group 1; in group 2 it was well controlled in the range of 2500–3000 ml/day with continuous administra-

Table 2. Renal function of group 2. Values expressed as mean ± SD

Days after brain death	0 ($n = 18$)	1 ($n = 18$)	3 ($n = 18$)	5 ($n = 17$)	7 ($n = 15$)	10 ($n = 11$)	14 ($n = 10$)
Urine volume (ml/day)	3811 ± 1802	3074 ± 1728	2966 ± 1323	2479 ± 1299	2617 ± 1428	2298 ± 906	2572 ± 1340
Blood urea nitrogen (mg/dl)	16.6 ± 7.1	18.2 ± 8.0	13.2 ± 6.6	16.9 ± 11.6	21.4 ± 14.1	20.5 ± 10.6	22.2 ± 7.9
Creatinine (mg/dl)	1.1 ± 0.5	1.1 ± 0.4	0.9 ± 0.4	1.0 ± 0.3	0.9 ± 0.3	0.8 ± 0.2	0.9 ± 0.4
Creatinine clearance (ml/min)	63.7 ± 25.7	89.2 ± 33.7	95.1 ± 39.5	88.2 ± 39.8	87.7 ± 39.8	92.0 ± 33.1	87.6 ± 66.2
Free water clearance (ml/min)	− 0.9 ± 2.4	− 1.8 ± 1.2	− 1.7 ± 1.3	− 2.1 ± 1.8	− 2.3 ± 1.8	− 1.5 ± 1.0	− 1.5 ± 0.7
Na (mEq/l)	146.0 ± 8.3	150.3 ± 8.0	138.6 ± 10.1	132.4 ± 11.8	131.0 ± 12.2	129.2 ± 12.7	132.9 ± 8.3

Table 3. Light microscopic findings of the kidney. − none, + mild, + + moderate

Autopsy day after brain death	6	7	15	16	20
Glomerular alteration	−	−	−	−	−
Proximal tubulus					
vacuolation	+ +	+	−	−	−
desquamation	+	+	+	+ +	+
Distal and collecting tubulus cast	+	+ +	−	+ +	−

tion of ADH and epinephrine. Urine osmolarity was lower than serum osmolarity in group 1, but it was more than 500 mosmol/kg H_2O, and free water clearance (C H_2O) was always under − 1 ml/min in group 2.

The clinical data after brain death are summarized in Tables 1 and 2. The mean serum level of BUN increased progressively in group 1 but was kept under 20 mg/dl in the 1st week and increased slightly in the 2nd week in group 2. The mean serum level of creatinine deteriorated daily in group 1 but remained at the normal level for 14 days in group 2. Creatinine clearance decreased to 63.7 ml/min on the 1st day after brain death but recovered to more than 80 ml/min for 14 days in group 2. The mean serum level of sodium increased to more than 160 mEq/l in group 1; it was slightly high during the first 2 days and decreased gradually in group 2.

Urinalysis was almost normal and there were a few urinary tract infections with prophylactic antibiotics for 2 weeks in group 2.

Permission was given to perform an autopsy on five patients in group 2 after cardiac arrest. Macroscopically there were no particular changes except for slight edema and hemorrhagic spots in some kidneys. Histopathological changes in the kidneys were also minimal. Glomeruli were intact in all specimens. Vacuolation of proximal tubular epithelia was observed in three of the five specimens, and desquamation of epithelial cells into proximal tubular lumen was observed in all specimens. Acute tubular necrosis or cortical necrosis was not observed at all. Cast in distal or collecting tubular lumen was observed in three of the five specimens (Table 3).

Discussion

Renal ischemia due to prolonged systemic hypotension is one of the major causes of kidney damage after brain death. Carroll et al. [4] showed that preventing such hypotension improved the quality of cadaveric kidneys. However, catecholamines alone failed to maintain the systemic blood pressure and blood volume decreased as a result of uncontrolled diabetes insipidus. We showed that all but two patients in group 1 who were maintained with epinephrine alone experienced cardiac arrest within 48 h after brain death. On the other hand, the combined therapy of ADH and epinephrine succeeded in achieving long-term hemodynamic maintenance in group 2.

Our recent study [20] showed that both cardiac output and systemic vascular resistance decreased without any maintenance therapy after brain death. Epinephrine alone increased only cardiac output without a significant increase in systemic vascular resistance. ADH alone increased systemic vascular resistance with a slight decrease in cardiac output. Consequently, each of these drugs alone could not increase systemic blood pressure sufficiently. Yet, the combination of ADH and epinephrine not only increased cardiac output but also increased systemic vascular resistance twice as much as at baseline. We assume that there is some special interaction between ADH and epinephrine that increases vascular tone and that this effect leads to long-term hemodynamic maintenance after brain death.

In this report we examined the renal function of brain-dead patients whose hemodynamics were maintained with epinephrine alone or with a combination of ADH and epinephrine. For patients in group 1, who were maintained with epinephrine alone, urine output was uncontrollable. While systemic blood pressure was raised to obtain sufficient renal perfusion pressure, diluted urine overflowed by more than 300 ml/h and then suddenly stopped as systemic blood pressure dropped, due to hypovolemia. These patients finally experienced renal shutdown. The serum levels of BUN and creatinine progressively deteriorated. The serum level of sodium rose by hemoconcentration, due to the large volume of diluted urine.

In contrast, 0.3 mU/kg per minute ADH and a small adjusted dosage of epinephrine controlled not only systemic blood pressure optimally but also daily urine volume in the range of 2500–3000 ml in group 2. The serum level of BUN was normal for 2 weeks. The serum level of creatinine was also normal throughout our study. Although daily creatinine clearance dropped transiently the 1st day after brain death due to circulatory instability, it recovered and remained at more than 80 ml/min for 2 weeks. Urine osmolarity was more than 500 mosmol/kg H_2O, and free water clearance was also maintained under − 1 ml/min by the antidiuretic effect of ADH. These results prove that as long as the hemodynamics are maintained within the normal range, renal function after brain death can be well preserved for more than a week.

Brown et al. [3] discussed the effects of chronic intravenous or intrarenal infusion of ADH in dogs. A small dose of ADH (0.03 mU/kg per minute), which did not affect systemic circulation, caused a chronically positive cumulative water balance and increases in mean arterial pressure, glomerular filtration rate, urinary sodium, and potassium excretion. Smith et al. [18] also showed that an acute or chronic infusion of ADH increased the glomerular filtration rate, which is suggested to increase urinary sodium excretion. In this study, creatinine clearance was kept within the normal range and serum sodium decreased gradually in group 2. These changes were all in accordance with those experiments.

Though the combination of ADH and epinephrine raised systemic blood pressure, these drugs may actually reduce renal blood flow. Aviado et al. [1] showed that a large dose (3 μg/kg) of intravenous epinephrine reduced renal blood flow in dogs, and that is because α-receptors

are dominant in the kidney. Yet, Sato et al. [15] recently showed that a small dose of epinephrine did not change the renal blood flow since a marked increase in cardiac output canceled the decrease in the distribution of renal blood flow in patients following open-heart surgery. On the other hand, a large dose of intravenous ADH also has selective constrictor effects on different regional vascular beds. Schmid et al. [16] showed that 2 mU/kg per minute of intravenous ADH significantly increased renal blood flow from baseline, indicating a redistribution of cardiac output to the kidney from other beds in the dog model. In other experiments, intravenous ADH (0.1–4 mU/kg per minute) did not reduce renal blood flow in the dog [10] or rat [9] model. We did not measure renal blood flow directly, but we did obtain well-controlled urine output and normal creatinine clearance. It was suggested that the small dosage of ADH and epinephrine that we used in this study did not reduce renal blood flow.

Although our combined administration was able to preserve the kidney, ADH might injure other organs for transplantation, such as the liver and pancreas, because of a decrease in mesenteric blood flow [16]. However, we reported that GPT did not rise in brain-dead patients [11] without severe traumatic shock, and serum amylase (not shown) did not change significantly throughout our study.

The epithelial cells of the renal tubules, particularly those in the proximal segments, are vulnerable to ischemia [5, 6, 12]. Unless oliguria is observed, acute tubular necrosis is commonly found in shock patients. In the histopathological examination at autopsy, we observed no glomerular alteration and mild proximal tubular changes in some specimens without any findings of acute tubular necrosis. Vacuolation of proximal tubulus was found in three of the five specimens. Desquamation of proximal tubular cells suggested injuries and rapid turnover of proximal tubular epithelia. Because only 5 of the 28 patients could be examined, we were unable to obtain clear results. However, we assumed that these proximal tubular changes were mainly influenced by hypotension at the onset of brain death and that they were in the process of recovering from shock.

In 1983, Schneider et al. [17] reported the effects of the combination of dopamine and ADH on the preservation of donor kidneys. As far as we know, this was the first clinical trial using both ADH and a catecholamine. They gave 5–10 IU ADH intramuscularly every 6–8 h if the patient showed evidence of diabetes insipidus. They did not examine the effects of both drugs on the kidneys, and the duration from brain death to kidney removal in their study was fairly shorter than that in our study. It should also be noted that intermittent intramuscular injection of ADH may lead to hemodynamic derangement.

Thus, our study was the first trial to maintain renal function for more than a week by the continuous administration of ADH and epinephrine. We showed that epinephrine alone could not preserve the kidneys after brain death, but that the combination of ADH and epinephrine did succeed in long-term preservation of the kidneys. We conclude that this new method will be of great value in kidney donation from brain-dead patients.

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