Vasopressin Deficiency and Pressor Hypersensitivity In Hemodynamically Unstable Organ Donors

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Background—Solid organ donors often develop hypotension due to vasodilation, and recently we observed that a variety of vasodilatory states are characterized by vasopressin deficiency and hypersensitivity. Thus, we investigated the prevalence of vasopressin deficiency in hypotensive solid organ donors without clinical evidence of diabetes insipidus; we also investigated the vasopressor effect of vasopressin replacement in hypotensive donors.

Methods and Results—Fifty organ donors were evaluated for hemodynamic instability, (mean arterial pressure [MAP] ≤ 70 mm Hg despite the use of catecholamine vasopressors), and in those unstable donors who were not already receiving exogenous vasopressin, low-dose vasopressin was administered as a continuous infusion (0.04 to 0.1 U/min). MAP, catecholamine requirements, serum vasopressin, and serum osmolality were obtained before and after vasopressin administration. Ten patients meeting the enrollment criteria received vasopressin and MAP increased from 72.2 ± 3.5 to 89.8 ± 4.2 mm Hg, (P < 0.05), allowing for complete discontinuation of catecholamine pressors in 4 (40%) patients and a decrement in pressor dose in 4 (40%). Plasma vasopressin levels (2.9 ± 0.8 pg/mL) were low for the degree of hypotension.

Conclusions—Hemodynamically unstable organ donors without clinically apparent diabetes insipidus display a defect in the baroreflex-mediated secretion of vasopressin. In these patients, low-dose vasopressin significantly increases blood pressure with a pressor response sufficient to reduce catecholamine administration. (Circulation. 1999;100[suppl II]:II-244–II-246.)

Key Words: vasoconstriction ▪ transplantation ▪ blood pressure

The scarcity of organ donors for clinical transplantation is exacerbated further by hemodynamic instability due to vasodilation in otherwise suitable brain-dead candidates. Catecholamine vasopressors are frequently required to maintain arterial pressure but may result in end organ hypoperfusion and myocardial depression. Thus, an alternative to catecholamine pressors for the salvage of marginal donors experiencing hemodynamic instability is highly desirable and an area of increasing clinical interest.

The failure of the autonomic nervous system in brain death results in a defect in several vasoconstrictor systems that maintain vascular tone. Catecholamine deficiency in autonomic failure is well known, but a defect in the baroreflex-mediated secretion of vasopressin secretion is also a hallmark of this condition.1,2 In 1956, Wagner and Braunwald demonstrated patients with autonomic failure to be exquisitely sensitive (hypersensitive) to the vasoconstrictor effects of arginine vasopressin [AVP], whereas minimal vasopressor effects were demonstrable in normal subjects.3

More recently, we have discovered that vasodilatory shock in many clinical settings, including sepsis, postcardiopulmonary bypass, and following phosphodiesterase inhibitor infusion, is also characterized by vasopressin deficiency.4–6 Further, replacement of the hormone with low-dose intravenous infusion restored arterial pressure and reduced catecholamine requirements.4,5 AVP therefore represents an intriguing hormone because although its infusion (at doses up to 0.4 U/min) has no effect in normal subjects, a marked pressor response clearly exists when the blood pressure is threatened.4

These findings, together with older studies suggesting that vasopressin administration improves circulatory stability in organ donors, prompted us to investigate both the prevalence of vasopressin deficiency in solid organ donors and the effect of vasopressin replacement in those donors who are hypotensive.7,8

Methods

From July 1997 through February 1998, 50 consecutive brain-dead organ donors were evaluated after confirmation of appropriate informed consent. The diagnosis of brain death was confirmed by all of the following criteria: deep coma, apnea, lack of brain stem reflexes, and a silent electroencephalogram. The study was approved by the Institutional Review Board of Columbia University, and no
TABLE 1. Patient Demographics in the Entire Cohort (n = 50)

<table>
<thead>
<tr>
<th>Donor</th>
<th>Age</th>
<th>Cause</th>
<th>Serum Osm</th>
<th>Baseline AVP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Trauma</td>
<td>330</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>Trauma</td>
<td>295</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Trauma</td>
<td>321</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>SAH</td>
<td>304</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>CVA</td>
<td>313</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>Anoxia</td>
<td>277</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>Trauma</td>
<td>348</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>Trauma</td>
<td>256</td>
<td>5.8</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>SAH</td>
<td>279</td>
<td>2.8</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>Overdose</td>
<td>314</td>
<td>8.2</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>SAH</td>
<td>323</td>
<td>5</td>
</tr>
</tbody>
</table>

(Age represents age range). Complete data were available in 11 patients and 10 received AVP (donor number 11 did not receive AVP because of lack of availability).

The clinical characteristics of the 11 study subjects are described in Table 2. The cause of brain death included a typical array of lesions. As described, despite a serum osmolality >290 mOsm in all patients and hypotension requiring catecholamine vasopressors, the plasma AVP level was <4 pg/mL in 8 (72.7%) and ≤8 pg/mL in all 11 patients. The relatively low plasma AVP levels in the setting of shock indicate a defect in the baroreflex-mediated secretion of vasopressin. Further, the osmotic secretion of vasopressin was also impaired in at least 5 patients (patients 1, 2, 4, 5, and 7), with levels less than expected for the degree of hyperosmolality. However, one of these patients was sufficiently deficient to manifest clinically overt DI.

The administration of low-dose vasopressin to 10 hypotensive donors resulted in an increase in MAP from 72.2 ± 3.5 to 89.8 ± 4.2 mm Hg (P < 0.05) (as depicted in Figure 2). This increase was of sufficient magnitude to allow complete discontinuation of catecholamine pressors in 4 (40%) patients and a decrement in pressor dose in 4 (40%). In 2 patients, the commencement of low-dose AVP had no hemodynamic effect. Catecholamine pressor requirements are represented in Figure 3. This hemodynamic response to AVP correlated with a significant rise in plasma AVP concentration (from 2.9 ± 0.8 to 63.3 ± 25.0 pg/mL, P < 0.05), with exogenous vasopressin, as reflected in Figure 4. No untoward sequelae were noted in

Results

The distribution of the entire cohort of brain-dead organ donors (n = 50) is represented in Figure 1: demographics of this entire cohort are demonstrated in Table 1. Thirty-four (68%) donors were hemodynamically stable at the time of evaluation and 16 (32%) required catecholamine vasopressors to maintain mean arterial pressure (MAP) ≥70 mm Hg. Of the 16 hemodynamically unstable patients, 4 (25%) were already receiving AVP. All 11 remaining patients satisfied the other inclusion criteria (with the exception of one patient who succumbed to a cardiac arrest just before organ procurement).
Our findings suggest the presence of a defect in the baroreflex-mediated secretion of vasopressin in hemodynamically unstable donors who are without clinically apparent DI (ie, marked hypotension in the setting of normo- or hyperosmolality) failed to increase plasma AVP concentrations appropriately. Further, hormone replacement therapy with AVP significantly increased blood pressure such that concurrently administered catecholamine vasopressors could be discontinued or reduced. Together, these findings underscore the need for a mixed V1/V2 agonist in treating the donor population.

The doses of AVP used in this study (0.04 to 0.1 U/min) are similar to those that Kinoshita has demonstrated to be nonleterious to myocardium by histopathology, and we found no differences in posttransplant myocardial contractility between recipients of hearts from AVP-treated and untreated donors.9 The remarkable tissue survival benefit demonstrated in previous clinical studies of brain-dead patients, together with our current findings of a baroreflex-mediated defect of AVP secretion and pressor hypersensitivity to exogenous hormone, strongly support the use of low-dose AVP in any brain-dead organ donor with hypotension in the setting of normal cardiac function. The efficacy of this intervention for hemodynamically marginal donors as a strategy to significantly expand the donor pool will be the subject of ongoing investigations.

**Acknowledgment**

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**References**

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