Distributive failure in the microcirculation of septic patients

Boerma, E.C.

Citation for published version (APA):

Download date: 21 Sep 2020
Sublingual microcirculatory flow is impaired by the vasopressin-analogue terlipressin in a patient with catecholamine-resistant septic shock

E. C. Boerma\(^1,2\), P. H. J. van der Voort\(^2\) and C. Ince\(^1\)

1. Department of Physiology, Academic Medical Centre, University of Amsterdam, The Netherlands
2. Department of Intensive Care, Medical Centre Leeuwarden, The Netherlands

Abstract

For many decades arterial blood pressure regulation has been an important issue in the treatment of septic shock. The pathogenesis of this persistent hypotension is complex and multifactorial, but inability of vascular smooth muscle to contract in the presence of vasoconstrictive agents, seems to be a key factor. Many mechanisms have been proposed to account for this failure, including nitric oxide (NO) overproduction and vasopressin deficiency (1). However, improvement of outcome due to intervention in these mechanisms fails to be reported, despite restoration of blood pressure.

Recent studies of the microcirculation in humans by means of orthogonal polarization spectral (OPS) imaging have opened challenging new perspectives to study the microcirculation (2,3). We report a case in which sublingual OPS imaging was performed upon administration of terlipressin in a patient with catecholamine-resistant septic shock. It indicates that much caution should be taken when considering such potent vasoconstrictor when correcting blood pressure during shock.
Case report

An 80-year old woman was presented with fever (40.7°C), a declining level of consciousness and a few petechiae, all developing within a few hours. Positive cultures with Neisseria meningitides of both spinal fluid and blood confirmed the diagnosis meningococcal meningitis/sepsis. Prompt antibiotic treatment and dexamethasone 10 mg iv 4 times daily was started.

Within the first hour of admittance mechanical ventilation, aggressive fluid resuscitation and the use of catecholamines was needed. No overt purpura fulminans developed. A decreased P/F ratio (37 kPa), an elevated creatinine level (132 μmol/L) and thrombocytopenia (81.10⁹) indicated multiple organ dysfunction. Despite increasing doses of norepinephrine a mean arterial pressure of 60 mm Hg could not be maintained and the patient became oliguric. Sublingual OPS imaging was performed and analyzed semi-quantitatively as described elsewhere (3).

At baseline overall microcirculatory flow was well preserved, without evidence of heterogeneity. The light guide of the OPS device was fixed in a steady position, avoiding pressure artefacts, and a single bolus of 1 mg terlipressin was given intravenously. Over a 60-minute period OPS imaging was performed real-time and recorded at 20 minute intervals. Hemodynamic parameters were measured at the same time points, extended with t = 2 and 3 hours (Table).

Within 10 minutes a rise in mean arterial pressure and urinary output occurred. The patient developed an intense pallor and the peripheral perfusion index (PFI), derived from the pulse oxymetry signal (Intellivue MP70, Phillips Medical Systems), fell to an undetectable low range with a strong rise of the central-to-toe temperature difference (ΔT). OPS-imaging samples after three consecutive periods of twenty minutes each showed a dramatic decrease in small-vessel (10-25μm) numbers and eventually a complete stand-still of flow (fig.1 and 2).

Six hours after the administration of terlipressin the blood pressure declined again and the patient died within 24 hours as a result of irreversible shock.
Chapter 3

Fig. 1 Proportion of perfused capillaries using orthogonal polarization spectral imaging before (base) and 20, 40, 60 minutes respectively after a bolus of 1 mg terlipressin iv.

Fig. 2 Representative orthogonal spectral images obtained before (upper panel) and 60 minutes after (lower panel) administration of 1 mg terlipressin iv. (objective 5x, on screen 325x)
Discussion

Vasopressin is a vasoactive hormone with a range of vasomodulatory activities. The vasopressin analogue terlipressin has a higher V1a/V2 receptor ratio and is long-acting as compared to vasopressin (4,5). The complexity of its physiologic effects could be explained by four known mechanisms of action: activation of V1 vascular receptors, modulation of ATP-dependent K⁺ channels, modulation of NO and potentiation of adrenergic agents. Whether vasopressin causes vasodilation or vasoconstriction depends on the vascular bed, model, dose, and duration of exposure (4).

Up to date the role of vasopressin on survival in patients with septic shock remains to be established. No randomised controlled trials in humans with mortality as primary endpoint were performed. In two studies with different endpoints, mortality was reported (6,7). A recent Cochrane review calculated a relative risk on survival of vasopressin versus placebo in these 2 studies (N=58) to be 1.04 (95% CI 0.06-19.33) (8).

Data on the effects of vasopressin administration on splanchnic microvasculature seem to be conflicting. Low-dose vasopressin in a sepsis model limited the increase in ileal pCO₂-gap, as compared to norepinephrine (9). In humans low-dose vasopressin was demonstrated to improve macrohemodynamics with preservation of the gastric tonometry Pr-aco₂ gap (6), but the same group reported high incidences of ischemic skin and tongue lesions. High-dose vasopressin in norepinephrine-dependent patients with septic shock caused a significant rise in gastric pCO₂-gap, indicating splanchnic hypo perfusion (10). Low-dose terlipressin increased ileal microcirculation in endotoxic rats (4). However, high-dose terlipressin has been reported to increase portal hypertension, to reduce splanchnic blood flow in several animal models (4) and to increase L-lactate concentrations in the human rectal mucosa (11).

This case report outlines the potential contradictive effects of a vasopressin-analogue within a patient with septic shock. On one hand mean arterial blood pressure, with an expected rise in cerebral perfusion pressure (12), is restored. We also observed a rise in urine production. This might be the result of an indirect effect via rise of perfusion pressure, or a possible direct effect of vasopressin, either due to increased water permeability in the collecting duct by stimulation of V2 receptors, or by counter-acting sepsis-induced V2-receptor and aquaporin-2 content down-regulation in the kidney (13). On the other hand the perfusion of the skin is markedly reduced, base deficit continues to rise and sublingual microcirculatory flow comes to a stand still (table, fig.1). Thus, OPS imaging might provide a substrate for earlier observations of skin necrosis (14) and a decline of gut mucosal circulation (11,15).
Table Hemodynamic, tissue perfusion and acid-base parameters (MAP mean arterial pressure, HR heart rate, CVP central venous pressure, ΔT central-to-toe temperature difference, PFI peripheral perfusion index, BE base excess)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>20 min</th>
<th>40 min</th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>58</td>
<td>78</td>
<td>80</td>
<td>80</td>
<td>100</td>
<td>105</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>98</td>
<td>96</td>
<td>96</td>
<td>98</td>
<td>108</td>
<td>119</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>ΔT (°C)</td>
<td>1.7</td>
<td>2.3</td>
<td>8</td>
<td>12.5</td>
<td>12.8</td>
<td>13.4</td>
</tr>
<tr>
<td>PFI</td>
<td>6.3</td>
<td>4.8</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Urine output (ml/h)</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>110</td>
<td>165</td>
</tr>
<tr>
<td>Dopamine (µg/kg/min)</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Noradrenaline (µg/kg/min)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3.7</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Fluid balance (ml)</td>
<td>+6149</td>
<td>-</td>
<td>-</td>
<td>+6284</td>
<td>+6390</td>
<td>+6145</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td>-11.8</td>
<td>-</td>
<td>-</td>
<td>-12.7</td>
<td>-</td>
<td>-15.9</td>
</tr>
</tbody>
</table>

With the same technique Dubois et al reported little or no effect of low dose vasopressin on sublingual microcirculation in a patient with distributive shock (3). That different effects on the microcirculation with the same class of vasopressor agents can be observed is an important observation, especially in the light of the finding that persistent depressed sublingual microcirculation predicts non-survival (16). Associated with the marked decrease of capillary perfusion an increment of ΔT and drop in PFI was found. Both indicators of microcirculatory impairment are associated with poor clinical outcome (17,18). It is therefore important to notice that in our patient considerable doses of the vasoconstrictor norepinephrine were used to maintain a minimum level of mean arterial pressure. Although equivalent to doses in other OPS-studies (2,3) we observed in this setting no hampering of flow in the absence of terlipressin.

From our and Dubois’ study (3) it is clear that generalized conclusions about the action of vasopressin on the microcirculation should be made with caution. Dosage, the vasopressin-analogue used, circulating volume, severity of illness and genetic repertoire contribute to its effects. With all its limitations, including the absence of cardiac output- and SvO2 measurements, our study shows that, although effective in correcting severe hypotension, terlipressin can be deleterious to microcirculatory perfusion. Monitoring the microcirculation may provide a useful tool to titrate vasopressin in critically ill septic patients.

References


