High Copeptin Concentrations in Umbilical Cord Blood after Vaginal Delivery and Birth Acidosis

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Context: The pituitary-secreted nonapeptide arginine-vasopressin (AVP) is unstable and therefore unsuited for diagnostic use, but its secretion can be estimated by measuring copeptin, the C-terminal portion of the AVP precursor (pro-AVP).

Objective: Our objective was to investigate perinatal factors affecting copeptin concentrations in infants at birth and at 3 d of life.

Design and Setting: We conducted a prospective cross-sectional study at a tertiary university hospital.

Patients: Copeptin plasma concentrations were evaluated in 177 infants at birth, including 117 paired arterial/venous umbilical cord and 102 venous blood samples obtained at 3 d of life.

Main Outcome Measure: Copeptin concentrations were determined by a C-terminal pro-AVP luminescence immunoassay.

Results: Arterial umbilical cord copeptin concentrations were consistently higher than matched venous ones (median 18 vs. 10 pmol/liter, \( P < 0.001 \)), but both values were closely related (\( R_s = 0.825; \ P < 0.001 \)), and both were negatively related to arterial umbilical cord pH (\( R_s \) arterial/venous = \( -0.578/0.639; \ P < 0.001 \)). Although exceedingly high copeptin concentrations were observed after vaginal birth in umbilical cord arterial [median (5–95% range) = 1610 (85–5000) pmol/liter] and venous [793 (6–4836) pmol/liter] plasma, copeptin concentrations were low after primary cesarean section [arterial/venous = 8 (3–907)/5 (5–504) pmol/liter]. Postnatal body weight loss was associated with increased copeptin concentrations at 3 d (\( R_s = 0.438; \ P < 0.001 \) and both \( R_s = 0.289 \) and \( -0.309; \ P < 0.001 \)).

Conclusion: Vaginal birth is associated with a large release of copeptin that exceeds all values published so far, including those in critically ill adult patients with shock or brain injury. Thus, vaginal birth is arguably the most intense stressor in life. (J Clin Endocrinol Metab 95: 5091–5096, 2010)
Crucial integration of a variety of neural and endocrine events is a prerequisite for the successful adaptation to extrauterine life. Parturition evokes a dramatic surge in stress hormones facilitating the transition of the newborn to air breathing, cardiovascular adaptation, thermogenesis, and glucose and water homeostasis.

The nonapeptide arginine-vasopressin (AVP), also known as antidiuretic hormone, is one of these stress hormones. AVP was first reported to be increased in cord blood more than 30 yr ago (1, 2). However, the measurement of AVP levels is laborious and for clinical use unsuited because of its instability and short half-life. AVP derives from a larger precursor peptide (provasopressin) together with two other peptides, neurophysin II and copeptin. Copeptin is released in an equimolar ratio to AVP, circulates in plasma without physiological activity, and is highly stable especially after Ca$^{2+}$ chelation by EDTA, and easy to measure (3).

This study aimed to evaluate copeptin concentrations in paired samples of arterial and venous cord blood of newborn infants as well as in venous blood collected 3 d after birth.

**Subjects and Methods**

The study was carried out between July and September 2009. After obtaining written informed consent, pregnant women presenting for delivery at the University Hospital Zurich, Switzerland, were included. The study was approved by the institutional review board.

Of the 177 infants studied, 141 (80%) were term (37–41 completed weeks of gestational age), 21 were near term (35 or 36 wk), and 15 had a gestational age of 32–34 wk. Twenty-four (13.6%) infants were twins, and three (1.7%) triplets. Sixty-two wk), and 15 had a gestational age of 32–34 wk. Twenty-four completed weeks of gestational age), 21 were near term (35 or 36

**TABLE 1.** Selected characteristics of mothers and their infants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Venous plasma, umbilical cord (n = 143)</th>
<th>Arterial plasma, umbilical cord (n = 117)</th>
<th>Venous plasma, d 3 (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant sex</td>
<td>78 (55)</td>
<td>69 (59)</td>
<td>60 (59)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant birth weight (g)</td>
<td>&lt;2000</td>
<td>11 (8)</td>
<td>6 (5)</td>
</tr>
<tr>
<td></td>
<td>2000–3000</td>
<td>47 (32)</td>
<td>38 (31)</td>
</tr>
<tr>
<td></td>
<td>3001–4000</td>
<td>77 (54)</td>
<td>66 (56)</td>
</tr>
<tr>
<td></td>
<td>&gt;4000</td>
<td>8 (6)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Infant gestational age at birth</td>
<td>Preterm 32–37</td>
<td>32 (22)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>(completed weeks)</td>
<td>Term 37–41</td>
<td>111 (78)</td>
<td>91 (78)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>Cesarean section primary</td>
<td>74 (52)</td>
<td>63 (54)</td>
</tr>
<tr>
<td></td>
<td>Cesarean section secondary</td>
<td>26 (18)</td>
<td>23 (20)</td>
</tr>
<tr>
<td></td>
<td>Spontaneous vaginal</td>
<td>30 (21)</td>
<td>23 (20)</td>
</tr>
<tr>
<td></td>
<td>Instrumental vaginal</td>
<td>13 (9)</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>

Results are shown as n (%).
Results

Paired umbilical cord arterial and venous plasma copeptin concentrations were closely related \((n = 117; R_s = 0.825; P < 0.001)\). Copeptin concentrations were consistently higher in arterial than in venous samples \((\text{median 18 vs. 10 pmol/liter, } P < 0.001)\). Copeptin concentrations measured at 3 d of life \([n = 102; M (5–95\% \text{ range}) = 14.0 (5.5–56.6) \text{ pmol/liter}]\) were significantly \((P < 0.001)\) lower than copeptin concentrations in either umbilical cord arterial or venous plasma. There was not a correlation of copeptin concentrations in paired samples of arterial umbilical cord plasma and d 3 venous plasma \((n = 54; R_s = -0.061; P = 0.664)\) or in paired samples of venous umbilical cord plasma and d 3 venous plasma \((n = 68; R_s = -0.133; P = 0.281)\).

Analyzing copeptin concentrations in respect to clinical dates revealed a significant \((P < 0.001)\) inverse correlation of copeptin concentrations in both arterial umbilical cord plasma and venous umbilical cord plasma with umbilical artery pH \((R_s = -0.639 \text{ and } -0.578, \text{ respectively})\) and umbilical artery base excess \((R_s = -0.643 \text{ and } -0.638, \text{ respectively})\), as shown in Fig. 1. Apgar scores at 5 and 10 min of life and hematocrit in umbilical cord blood as well as mothers’ blood loss during delivery did not correlate with copeptin concentrations in any plasma samples, neither arterial and venous umbilical cord plasma nor plasma samples drawn at d 3.

The mode of delivery affected copeptin concentrations in arterial and venous umbilical cord plasma very strongly \((P < 0.001)\) (see Fig. 1) but had no impact on copeptin concentrations in d 3 venous plasma. The distributions of copeptin concentrations in arterial and venous umbilical cord plasma with respect to the various delivery modes are summarized in Table 2.

Gestational age was found to be directly related with copeptin concentrations in arterial and venous umbilical cord plasma \((R_s = 0.377 \text{ and } 0.416, \text{ respectively}; \text{both } P < 0.001)\) but not with copeptin concentrations in d 3 venous plasma. However, birth weight depicted only a weak correlation to copeptin concentrations in venous umbilical cord plasma \((R_s = 0.183; P = 0.029)\) but not with copeptin concentrations in either arterial umbilical cord plasma or d 3 venous plasma. This finding of lower copeptin concentrations in umbilical cord blood of infants born preterm or with low birth weight was mainly attributed to the fact that the percentage of deliveries by cesarean section was significantly higher in preterm infants \((31 \text{ of } 36, 86\%\) than in term infants \((83 \text{ of } 141, 59\%, P = 0.003)\).

The maximal weight loss in postnatal adaptation occurred between d 2 and 5, on average at d 3. Intravenous fluid was administered in eight infants, all of whom weighed less than 1800 g at birth and therefore received iv fluid following institutional guidelines. Only 40 infants of the study population were exclusively breastfed, 62 received some additional hydrolyzed starch solution, and 67 received formula milk with or without mother’s milk.

There was an inverse relation between maximal weight loss and copeptin concentrations in arterial as well as in venous umbilical cord plasma \((R_s = -0.309 \text{ and } -0.289, \text{ respectively}; \text{both } P = 0.001)\), indicating increased postnatal weight loss in infants with low copeptin concentrations at birth. Then we compared copeptin concentrations in venous umbilical cord plasma in all infants subdivided in groups with mild \((2–5\%, n = 33)\), moderate \((6–7\%, n = 51)\), and severe maximal \((8–12\%, n = 53)\) postnatal weight loss. Copeptin concentrations at birth were significantly higher in infants with mild compared with moderate or severe maximal postnatal weight loss \((P = 0.017 \text{ and } P < 0.0001, \text{respectively}; \text{Fig. 2A})\).

Maximal weight loss correlated directly with copeptin concentrations in venous plasma drawn at 3 d of life \((R_s = 0.438; P < 0.001)\) but not with sodium concentrations, hematocrit, or bilirubin at d 3. All infants with copeptin values from d 3 were subdivided in groups with mild \((n = 29)\), moderate \((n = 36)\), and severe maximal \((n = 37)\) postnatal weight loss. Copeptin concentrations at d 3 were significantly higher in infants belonging to the group with severe compared with mild or moderate maximal weight loss \((P < 0.0001 \text{ and } P = 0.011, \text{respectively}; \text{Fig. 2B})\).

There was not a relation between maximal weight loss and gestational age at birth or between maximal weight loss and birth weight.
Significant statistical differences were noted between the following groups: mild (37) and strong (53) loss. Data are presented as median (interquartile range) and whisker (5–95% range) plots. Significant statistical differences were noted between the following groups: mild vs. moderate (P = 0.017) and mild vs. strong (P < 0.0001). No significant difference was noted between moderate vs. strong (P = 0.27).

**Discussion**

Until now, copeptin had been studied exclusively in adults. These studies were done with respect to changes in plasma osmolality, in settings of mild to life-threatening physical stress, and in various diseases. Normal copeptin concentrations in healthy adults were consistently reported to be about 5 pmol/liter, as reviewed by Morgenthaler et al. (4). Water deprivation has been shown to increase copeptin concentrations 4-fold [M 19.9 (± SD 4.8) pmol/liter] (5), and severe stress, e.g., extubation of surgical patients, was found to result in a 10-fold increase [M 67.5 (interquartile range 37.8–110) pmol/liter] (6). The most pronounced surges in copeptin hitherto described were in patients suffering from shock, either septic [M 375 (range 59–1572) pmol/liter] (7) or hemorrhagic [M 269 (range 241–456) pmol/liter] (8). These 20-fold increased copeptin concentrations in adults suffering from life-threatening events are still far below the copeptin concentrations we measured in healthy, naturally delivered infants. Determination of copeptin concentrations in all these studies investigating adults was performed by the same C-terminal pro-AVP luminescence immunoassay as applied here, allowing for a direct comparison. Thus, vaginal delivery provokes a unique surge in copeptin plasma concentration (Fig. 1) incommensurable with all reported changes in copeptin concentrations in adult patients.

Hypoxia has been described to augment a strong AVP release within a short time in various animal models (9–13), and similarly, perinatal asphyxia in humans has been found to trigger a decisive AVP response (14, 15). Because also normal vaginal delivery in humans has been shown to trigger AVP release (1, 2), some investigators have come up with the hypothesis that fetal AVP release may effectively reduce placental blood flow during uterine contraction. This could contribute to acute fetal stress and hypoxia even during normal labor (16–18). However, our finding that copeptin concentrations in umbilical cord plasma are orders of magnitude (on average 500 times) higher in infants delivered vaginally compared with those delivered by elective cesarean section indicate that vaginal birth is the largest stressor for the body found so far, e.g., larger than brain trauma, ischemic stroke, or severe shock in adults (7, 8, 19, 20).

**TABLE 2. Copeptin intervals in arterial and venous umbilical cord plasma**

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>n</th>
<th>Median copeptin (pmol/liter)</th>
<th>95% reference interval (pmol/liter)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean primary</td>
<td>63/73</td>
<td>8/5</td>
<td>3–907/5–504</td>
<td>&lt;0.01/&lt;0.01</td>
</tr>
<tr>
<td>Cesarean secondary</td>
<td>23/27</td>
<td>14/11</td>
<td>4–2240/2–2260</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Vaginal spontaneous</td>
<td>23/30</td>
<td>1610/634</td>
<td>82–5000/6–5000</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Vaginal instrumental</td>
<td>8/13</td>
<td>1786/1324</td>
<td>1786–5000/90–4900</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
</tbody>
</table>

Results are shown as arterial/venous.

* Significance between cesarean primary and with each other mode of delivery.

**FIG. 2.** A, Correlation of copeptin in venous umbilical cord plasma with maximal postnatal weight loss. Maximal postnatal weight loss is grouped in mild (2–5%, n = 51), moderate (6–7%, n = 51), and strong (8–12%, n = 53) loss. Data are presented as box (interquartile range) and whisker (5–95% range) plots. Significant statistical differences were noted between the following groups: mild vs. moderate (P = 0.017) and mild vs. strong (P < 0.0001). No significant difference was noted between moderate vs. strong (P = 0.27). B, Correlation of copeptin in venous plasma at d 3 with maximal postnatal weight loss. Maximal postnatal weight loss is grouped in mild (2–5%, n = 29), moderate (6–7%, n = 36), and strong (8–12%, n = 37) loss. Data are presented as box (interquartile range) and whisker (5–95% range) plots. Significant statistical differences were noted between the following groups: mild vs. moderate (P = 0.011) and mild vs. strong (P < 0.0001). No significant difference was noted between moderate vs. severe (P = 0.054).
significant positive and moderate correlation of copeptin levels in arterial and venous cord blood with gestational age, there was no consistent relationship with birth weight. A closer view on this finding reveals that the high percentage of cesarean sections within the group of preterm infants (86%) accounted for their overall low copeptin levels. After adjusting for vaginal delivery and secondary cesarean section, the difference between term and preterm infants disappeared. This is in line with previous findings investigating AVP (16, 21). One important limitation of our analysis is the small group of premature infants included, and there were no infants under 32 wk gestational age, which represent the most vulnerable group of patients in neonatal intensive care units.

AVP orchestrates a magnitude of actions covering well-understood mechanisms including water retention and maintenance of blood pressure but also recently discovered roles in social behavior (22). Thus, it is intriguing to assume that AVP is involved in postnatal physical and behavioral adaptation (e.g. bonding). Reports linking elevated AVP at birth with delayed voiding (23, 24) are in support of the inverse relation of high copeptin in umbilical cord blood and minor postnatal weight loss we found in this study (Fig. 2A). This may offer an explanation why infants born by cesarean section are prone to dehydration more frequently than infants delivered vaginally (25). Increased rates of breathing disorders after cesarean delivery are common (26, 27), and it is tempting to speculate that low AVP after cesarean delivery is involved in compromised postnatal pulmonary adaptation. In contrast to peripheral vasculature, AVP leads to vasodilatation of pulmonary vasculature under hypoxic conditions through AVP receptor-mediated endothelial release of NO (28, 29). In addition, type II pneumocytes express AVP receptors and have been shown to secrete surfactant when exposed to AVP (30, 31). Thus, physiological hypoxia during vaginal birth causing a robust AVP release may prepare infants for successful postnatal adaptation, whereas infants delivered by primary cesarean section (that is before the onset of labor) have no relevant AVP release and are thus less well prepared to resume respiratory oxygenation.

Even exceedingly high copeptin concentrations at birth returned to near-normal values at d 3 of life; there was no correlation between concentrations at both time points. This is in agreement with data from AVP analyses (16, 21, 32, 33) and from copeptin analyses in adults with acute myocardial infarction (34). Already 24 h after pain onset, copeptin concentrations normalized in the majority of patients. Moreover, the inverse correlation of copeptin concentrations at d 3 and dehydration as indicated by the infants’ weight loss implicates an intact osmotic AVP regulation (Fig. 2B). Copeptin concentrations at d 3 were in about the same range as documented for adults during adaptation to dehydration (5). Thus, we conclude that after releasing AVP at birth, there are neither unusual low copeptin concentrations afterward nor a hampered osmotic AVP regulation.

Although an increased AVP secretion at the time of birth appears to be beneficial with respect to lung function and water retention, the magnitude of the surge after normal vaginal delivery is surprising. Several hypotheses may be invoked. First, newborns might require disproportionately high AVP concentrations because of low receptor expression or receptor affinity in target tissues. Second, AVP has a pivotal role in adaptation after birth, warranting the effort. Third, AVP is released in high concentrations for binding to AVP receptor-expressing neurons, pituitary gland cells involved in ACTH release, and for oxytocin receptor activation linked to bonding (22). There is indeed a fast-growing wealth of data uncovering evolutionary conserved function of vasopressin in modulating complex social behavior and cognition.

Recent data have revealed copeptin as a novel, independent prognostic marker in adult patients with ischemic stroke (20) and with severe injury after brain trauma in adults (19). In these settings, copeptin was shown to be superior to various markers such as protein S-100B and neuron-specific enolase in predicting severity level and outcome (20). Severe perinatal asphyxia damages brain in a manner similar to ischemic stroke resulting in hypoxic-ischemic encephalopathy, and neonatologists are looking for novel independent prognostic markers to guide clinical decision making with respect to applying therapeutic hypothermia and counseling parents. Further studies may explore whether extremely high copeptin concentrations at birth or kinetic changes of copeptin concentrations after birth may herald poor outcome.

Acknowledgments

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