

# Does positive pressure ventilation increase arginine vasopressin in preterm neonates?

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## Abstract

**Aim**—To examine the effect of intermittent positive pressure ventilation (IPPV) on plasma arginine vasopressin concentration (pAVP) in preterm neonates.

**Methods**—Thirty five neonates were classified, at the time of blood sampling, into three groups: unstable ventilated; stable ventilated; and stable non-ventilated. A modification of an extraction method for pAVP was developed for use in studies on very small babies, and sampling methods were compared.

**Results**—The pAVP (median, range) was similar in the ventilated (1.85 pmol/l, 0.5 to 3.4) and non-ventilated (2.0, 0.5 to 2.6) stable babies, but was significantly higher (5.7, 1.1 to 25) in the unstable group. There was an inverse correlation between systolic blood pressure and pAVP concentration.

**Conclusions**—This study shows that in preterm neonates pAVP concentration is affected by the clinical condition and blood pressure, but not by treatment with IPPV.

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Keywords: arginine vasopressin; assisted ventilation; systolic blood pressure

Arginine vasopressin (AVP) is released in response to osmotic and non-osmotic stimuli in humans and most animals. Non-osmotic stimuli are numerous but the most potent include hypotension and hypovolaemia. It has been suggested that intermittent positive pressure ventilation (IPPV) is a cause of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) in adults.<sup>1-4</sup> In neonates, SIADH has been reported in mechanically ventilated neonates with pneumothorax.<sup>5, 6</sup> AVP is reported to be increased in preterm neonates receiving mechanical ventilation for respiratory distress syndrome secondary to surfactant deficiency (RDS).<sup>7, 8</sup> It is common practice in some neonatal units for ventilated neonates to receive routinely restricted fluid volume. This study was performed to examine the effect of IPPV on plasma concentration of arginine vasopressin (pAVP) in preterm neonates.

Under normal circumstances the concentration of the anti-diuretic hormone AVP is very low in human plasma. Measurement necessitates a large volume of plasma, an extraction procedure, and a sensitive assay. The large sample volume required poses major problems in studies of neonates. We therefore developed a modification of an extraction procedure<sup>9</sup> to permit measurement of pAVP on small samples (50–100 µl of plasma), if sampling was performed at a time when other biochemical measurements were required. Only some neonates have an arterial sampling line in situ and it is therefore not considered justifiable to insert one purely for study purposes, so sampling methods were compared.

## Methods

Thirty five preterm babies in a regional neonatal unit in Newcastle upon Tyne were studied (table 1). All were nursed in enclosed incubators and given fluid volumes according to the unit's normal protocol (increasing stepwise from 80 ml/kg birthweight/day on day 1 to 150 ml/kg on day 5).

The babies were classified into three groups: stable, non-ventilated; stable, ventilated; unstable (all of whom were also ventilated). The categorisation was determined according to the following criteria, and carried out at the time of blood sampling and with knowledge of the blood gas results (which were immediately available) and before any other results had been obtained:

- A stable baby was one who:
- (i) was considered well on general clinical examination;
  - (ii) had blood results: pH > 7.25 and pCO<sub>2</sub> < 8 kpa;
  - (iii) had a "normal" blood pressure within published ranges<sup>10-12</sup> which was not consistently falling;
  - (iv) had had no "events" during the previous 24 hours, defined as anything untoward, such as pneumothorax, clinically suspected or confirmed infection, cardiovascular collapse, etc.

Any baby not fulfilling all of these criteria was classified as "unstable."

Blood was sampled when it was clinically required for measurement of electrolytes. An indwelling arterial line was used if present (in all the ventilated and some of the non-ventilated babies), otherwise venepuncture was performed. The blood was collected on ice and separated, as described. Extraction of AVP from plasma was performed immediately so that routine biochemistry results were available to the clinicians without delay.

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Table 1 Details of groups median (range)

	Ventilated unstable (n=14)	Ventilated stable (n=11)	Non-ventilated stable (n=10)
Gestational age (weeks)	28 (25–31)	29 (24–34)	28 (28–33)
Birth weight (g)	1057 (740–1605)	1170 (505–2015)	1105 (665–1704)
Age at time of study (h)	49 (36–120)	46 (24–120)	44 (24–72)

## MODIFICATION OF AVP EXTRACTION

This modification of the method of Rooke and Baylis<sup>9</sup> involved reusing rather than discarding plasma after Florisil extraction of AVP, for subsequent measurement of electrolytes and creatinine. It enabled pAVP to be measured with only a requirement of 100–150 µl of extra blood. To validate the modification, blood from the umbilical cord artery of five fresh placentas and venous blood from five normal adult volunteers was taken. Samples were drawn into pre-cooled syringes, transferred to chilled plastic tubes containing lithium heparin, rapidly cooled in ice and centrifuged at 3000 rpm at 4°C within 10 minutes, and the plasma was aspirated and immediately frozen and stored at -40°C. After thawing plasma samples were divided and biochemistry measurements were performed before and after Florisil extraction of AVP. Plasma sodium and potassium were measured using an ion selective electrode, urea using spectrophotometric diacetyl monoxime, and creatinine using a modified Jaffe reaction, all with an SMAC II analyser (Technicon Instruments, Tarry Town, NY, USA). Magnesium was measured by atomic absorption (Perkin Elmer 2380 spectrophotometer, Perkin Elmer Instruments, Norwalk, CT, USA).

To extract the AVP, 500 µl of plasma was mixed with about 20 mg of “activated” Florisil (magnesium silicate, 100–200 mesh, Sigma F7752) for 20 minutes at room temperature in a silicon coated glass tube. The Florisil was allowed to settle at the bottom of the tube, and the plasma was carefully aspirated for biochemical analysis instead of being discarded (as in the original method). More than 80% of the initial plasma volume was recoverable. The Florisil was then washed using distilled water, followed by 0.2 molar hydrochloric acid. The AVP was then eluted from the Florisil with 90% acetone and separated using diethyl ether, and dried under a stream of nitrogen. The double antibody radioimmunoassay for AVP described by Rooke and Baylis<sup>9</sup> was subsequently used.

The results showed that the plasma concentrations of sodium, potassium, urea and creatinine were unaffected by the extraction process (table 2), but plasma magnesium concentration was higher after extraction (paired *t* test; *p*<0.005).

Standard curves plotted using extractions from cord plasma ran parallel to those using normal adult volunteer plasma. Recovery of AVP added to cord plasma was 96% at 5 pmol/l and 90% at 10 pmol/l, using the modified extraction method. Using cord plasma the intra-assay coefficient of variation (CV) was

Table 2 Mean (SD) plasma biochemistry results pre and post mixing with Florisil using adult and cord plasma

Units	Adult (5 samples)		Cord (5 samples)		
	pre	post	pre	post	
Sodium	mmol/l	139 (1.6)	139 (1.5)	137 (1.6)	138 (1.9)
Potassium	mmol/l	4.0 (0.19)	4.0 (0.1)	4.0 (0.3)	4.1 (0.4)
Urea	mmol/l	4.3 (0.7)	4.3 (0.8)	4.4 (0.8)	4.3 (0.7)
Creatinine	umol/l	77 (10.9)	78 (10.8)	88 (5.5)	88 (3.7)
Magnesium	mmol/l	0.8 (0.05)	1.2 (0.10)	0.8 (0.03)	1.1 (0.09)

Table 3 Plasma AVP concentration sampled via different routes

Patient	Plasma AVP in pmol/l from	
	Arterial line	Venepuncture
1	1.9	2.2
2	2.6	2.0
3	1.5	1.4
4	0.8	1.1
5	≤0.5	≤0.5
6	2.8	2.4

(limit of detection 0.5 pmol/l)

5.4% (n=10) and the interassay CV was 11.5%. (n=20) at 2 pmol/l.

Thus, plasma was “reused” after extraction of AVP with Florisil for measurement of plasma sodium, potassium, urea and creatinine, therefore reducing the extra volume of plasma required solely for study purposes by at least fivefold. Physiological validation of the method by hyperosmolar saline infusion or lowering of blood pressure in neonates was not considered ethically justifiable and was therefore not performed.

## VALIDATION OF BLOOD SAMPLING METHOD

This comparison was performed as it was recognised that not all babies in neonatal units have arterial or other blood sampling lines in situ, and because AVP may be released in response to the pain of venepuncture.

Six babies were studied who were not part of the main study. They were selected because they were well and had arterial lines in situ but also required a venepuncture for a clinical indication (insertion of intravenous cannula or blood sampling for clotting studies). A blood sample was taken from the arterial line immediately before venepuncture. All samplings were performed by one researcher (HJL) and were completed within 5 minutes, with minimal disturbance to the baby. The pair of samples were processed identically and the pAVP measured in the same assay. Verbal

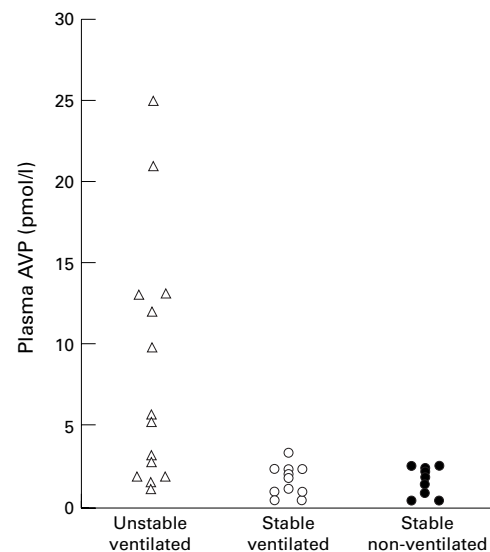


Figure 1 Plasma AVP concentration in three groups of preterm neonates: unstable ventilated; stable ventilated; and stable non-ventilated.

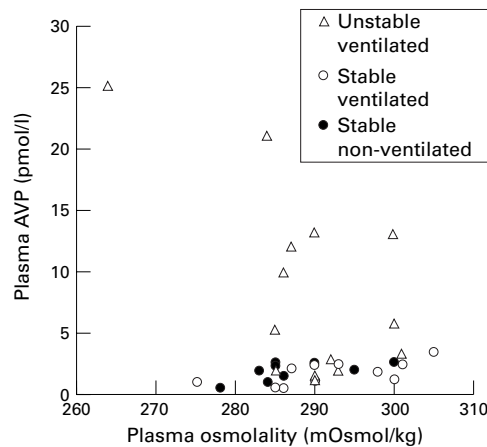


Figure 2 Relation between plasma AVP concentration and plasma osmolality.

parental consent was obtained for the extra blood volume (about 2 ml) taken.

There was no statistical difference shown (paired *t* test;  $p=0.6$ ) nor trend observed between the two sets of results, and differences were within the variation of the methods used (table 3).

#### OTHER MEASUREMENTS

Urine samples were collected by placing the baby on an upturned nappy at the time of blood sampling and collecting the urine in a syringe as soon as the baby had voided. Plasma and urine osmolality were measured by depression of freezing point (Camlab MOD200), the CV being 0.5% at 300 mOsm/kg.

Systolic blood pressure was measured directly using an arterial line transducer in all of the unstable ventilated, stable ventilated babies and some of the non-ventilated babies; and with an automatic BP machine (Dynamap) in those stable non-ventilated babies without arterial lines. Details of the babies' ventilation requirements and blood gases were also noted at the time of blood sampling and classification into stable and unstable made at that time.

Non-parametric tests were used for statistical analysis of the main study. Approval for the studies was obtained from the Newcastle District Health Authority/University Joint Ethics Committee.

#### Results

Plasma AVP values for the babies in the three groups are shown in fig 1. The median (range) pAVP concentration in the unstable ventilated group was 5.7 (1.1 to 25), in the stable ventilated group 1.85 (0.5 to 3.4), and in the stable non-ventilated group 2.0 (0.5 to 2.6) pmol/l. There was no significant difference in pAVP between the stable ventilated and stable non-ventilated babies (Mann-Whitney U test;  $p = 0.8$ ), but pAVP was higher in the unstable group than in either of the stable groups ( $p < 0.01$ ).

There was no significant relation between plasma AVP concentration and either plasma or urine osmolality (figs 2 and 3).

All the stable babies had systolic blood pressure within the expected range from published data as this was part of the criteria for their

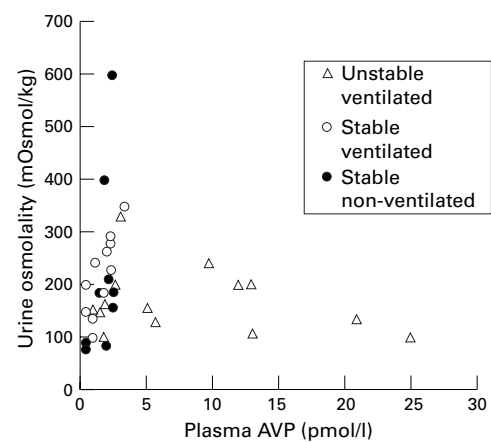


Figure 3 Relation between urine osmolality and plasma AVP concentration.

selection as "stable." Within this group there was no relation between systolic blood pressure and pAVP. There was a negative correlation between pAVP and systolic blood pressure when all the babies were considered together (Spearman rank correlation coefficient  $-0.69$ ;  $p < 0.01$ ), and when the unstable group was considered separately (Spearman rank correlation coefficient  $-0.65$ ;  $p < 0.01$ ) (fig 4).

As expected, the babies in the unstable group had lower systolic blood pressure than those in the ventilated and non-ventilated stable groups (Mann-Whitney U test;  $p < 0.005$ ). There was no difference in systolic blood pressure between ventilated and non-ventilated babies ( $p = 0.13$ ) within the stable groups.

The median (range) peak/minimum ventilator pressure in the unstable group was 30/3 (18 to 36/2 to 5), and 25/3 (11 to 30/2 to 4) cm water in the stable ventilated group. There was no relation between ventilator pressures and pAVP.

#### Discussion

This study shows that babies classified clinically as unstable have higher concentrations of pAVP and a wider range of values than babies classified as stable, and that babies classified as stable had similar values of pAVP whether or not they were receiving IPPV. If the data from the present study were analysed by grouping

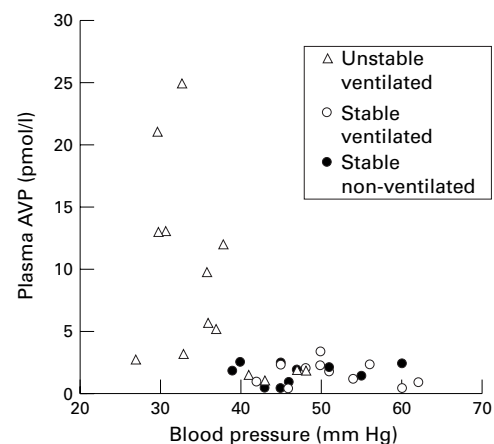


Figure 4 Relation between plasma AVP concentration and systolic blood pressure.

the results from all the ventilated babies together (unstable and stable) and comparing the results in that group with those obtained in non-ventilated babies, then it could be concluded that ventilated babies have higher pAVP than non-ventilated babies. However, when pAVP values are compared between stable babies receiving IPPV and stable babies not receiving ventilatory support, no difference is found. Thus IPPV itself does not seem to be a cause of raised pAVP. Our criteria for classifying babies are empirical and the unstable group particularly were somewhat heterogeneous, but if this group contained some babies who were less severely ill than others it further supports our findings that IPPV is not a cause of raised pAVP. Previous studies reporting an increase in AVP in ventilated babies have only studied very sick infants<sup>7</sup> or babies with additional problems such as pneumothorax<sup>5</sup> or intracranial injury.<sup>13</sup> Our study shows that results from babies with differing clinical conditions can substantially skew the data and alter conclusions.

It is commonly believed that pAVP is increased or that SIADH occurs in patients receiving IPPV.<sup>14-16</sup> This is based on data from animal experiments<sup>17, 18</sup> and adult clinical studies.<sup>2</sup> In animal experiments well animals are ventilated electively and may receive anaesthetic agents or sedation which could affect release of AVP. Ventilator pressures, which may be very different from those used clinically, may also affect haemodynamic status and AVP release, and thus conclusions of studies.<sup>17, 19</sup> In adult clinical studies the patients may have other complicating medical conditions; they may or may not have intrinsic lung disease, but they do *not* have RDS secondary to surfactant deficiency, this being the major indication for assisted ventilation of preterm babies. Babies with RDS have poor lung compliance and thus the effect on intrathoracic pressures and the haemodynamic consequences will be different than in experimental animals and adults.

Higher urinary AVP excretion has been reported in very low birthweight babies receiving assisted ventilation compared with those with spontaneous respiration on postnatal day 1 but not on day 2.<sup>20</sup> Increased urinary AVP concentration and decreased urine output have been reported in neonates during treatment with continuous positive airways pressure (CPAP) at high pressures (8 cm water).<sup>21</sup> In neither study was pAVP measured. In a study of adults ventilated for neurological disease no evidence of increased AVP release was shown during positive end expiratory pressure (PEEP) of 15 cm water compared with zero PEEP, although reduced urine output was observed.<sup>22</sup> In the present study babies receiving CPAP were not studied, and the PEEP was normally between 2 and 4 cm water. There was no relation between peak inspiratory pressure or PEEP and pAVP. Further studies on neonates involving assessment of transthoracic pressure—for example, by means of intraoesophageal pressure transducer—together with assessment of cardiac output, might be informative.

This study found no correlation between pAVP and plasma osmolality under these clinical circumstances, which agrees with other reports of a minimal or absent correlation.<sup>8, 23, 24</sup> Thus it must be concluded that AVP is released in babies in response, at least in part, to non-osmotic stimuli. Release of AVP in response to non-osmotic stimulation has been well described in adults and experimental animals. Most studies in adults showing the relation between increased plasma osmolality and release of AVP have subjected individuals to an experimental increase in plasma osmolality (for example, by dehydration or infusion of hypertonic saline). It is not possible, because of practical and ethical considerations, to repeat such studies in neonates, thus making the contribution of changes in plasma osmolality to AVP release difficult to assess.

A poor urinary concentrating response to plasma AVP was shown in this study, with some of the babies that had the highest plasma AVP values still producing hypo-osmolar urine; there was no correlation between urine osmolality and plasma AVP concentration. This finding agrees with other studies which show no relation or a poor urinary concentrating response to AVP in some preterm neonates.<sup>8, 23, 25, 26</sup> The explanation for this finding is unclear. It is well established that neonates are unable maximally to concentrate their urine in relation to healthy adults and this is thought to be related to the newborn's less effective intrarenal concentrating gradient and a relatively poorer end organ responsiveness to AVP. It may also be explained by methodological problems relating to the timing of the pAVP measurement in relation to the urine collection; or it may be that a single measurement does not reflect the rapid changes in pAVP that can take place over a short period of time.

It was not the intention of this study to compare different methods of blood pressure measurement and therefore the method already in use clinically on the babies during the study was continued. All of the babies who were ventilated had blood pressure measured by arterial line transducer. These were the babies most likely to have "abnormal" blood pressure. Although it can be argued that there are no true "normal" ranges for blood pressure in preterm babies, there are data on ranges found in preterm neonates<sup>10-12</sup> and these show that blood pressure increases with gestational and postnatal age. It is not surprising that in those babies with blood pressure within the expected ranges, no relation was seen between systolic blood pressure and pAVP. There was a significant negative correlation between systolic blood pressure and pAVP, overall, and in the unstable group, and this agrees with the data from many animal and adult studies, which show a release of AVP with hypotension. Some of the unstable babies seemed to be hypotensive but did not have high plasma AVP concentrations. Although these babies might have been unable to produce high concentrations of AVP, it is perhaps more likely that our

assessment of what is a "normal" blood pressure for a particular baby is limited.

In conclusion, this study shows that in preterm newborns pAVP is affected by the clinical condition and systolic blood pressure, but not by treatment with IPPV.

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