Use of umbilical cord blood gas analysis in the assessment of the newborn

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Analysis of paired arterial and venous specimens can give insights into the aetiology of acidosis in the newborn

In 1958, James *et al* recognised that umbilical cord blood gas analysis can give an indication of preceding fetal hypoxic stress.[1] It has since become widely accepted that umbilical cord blood gas analysis can provide important information about the past, present and possibly the future condition of the infant. Umbilical cord blood gas analysis is now recommended in all high-risk deliveries by both the British and American Colleges of Obstetrics and Gynaecology,[2 3] and in some centres it is practised routinely following all deliveries. It is therefore of increasing clinical and medicolegal importance that clinicians caring for newborn infants are familiar with the principles and practice of obtaining and interpreting cord blood gas values, and with the underlying evidence base.

SAMPLING PROCEDURE

Umbilical cord blood analysis is assumed to give a picture of the acid–base balance of the infant at the moment of birth when the umbilical circulation was arrested by clamping of the cord. However, from this moment onwards the umbilical cord blood, if it remains in continuity with placenta, will demonstrate progressive change in acid–base status due to ongoing placental metabolism and gas exchange. Small changes in umbilical pH occur within 60 s of delivery,[4] and over 60 min cord arterial or venous pH can fall by more than 0.2 pH units.[5] Similar changes occur in blood sampled from placental surface vessels except that they are larger and less predictable.[6] These changes are not observed if the cord is doubly clamped at birth, isolating a segment of cord blood from both the placenta and the environment.[4] The pH of the blood then remains relatively constant at room temperature for an hour.[5 7–9]

When there is considerable delay in sampling, it is essential to know whether the sample was taken from isolated cord blood or whether ongoing placental metabolism may have altered the results, rendering them uninterpretable. It is also important to recognise that the umbilical cord can become obstructed before birth. Restriction of umbilical blood flow causes a progressive widening of the difference between umbilical arterial and venous blood gas values. Martin *et al* showed that term infants with nuchal cords have larger differences in umbilical venous and arterial pH, P_{CO_2} and P_{O_2} than those without evidence of cord compression.[10] In contrast, arterial to venous differences are small where there is impairment of the maternal perfusion of the placenta, such as in cases of abruption.[11] In a comparative study between infants born after cord prolapse and those born after placental abruption, Johnson *et al* observed veno-arterial differences in pH of up to 0.3 units, and showed that a difference greater than 0.15 units could be used to differentiate reliably between the two.[11] Belai *et al* showed that in severe cases, where the cord arterial pH is less than 7.0, the magnitude of the difference in P_{CO_2} between the umbilical artery and vein predicts the risk of the infant developing encephalopathy.[12] Because of this it is imperative to sample both arterial and venous blood, especially if an infant is depressed at birth. In the presence of cord obstruction, a normal umbilical cord venous blood gas could conceal severe mixed umbilical arterial acidosis in an infant with a high risk of adverse outcome. If the obstruction to the umbilical vessels was sudden and complete and this persisted until the moment of delivery or until fetal death then the cord gases sampled at birth would give a snapshot of the fetal acid–base balance prior to the obstruction. Both umbilical arterial and venous gases could then be normal despite severe intrapartum asphyxia.[13 14] Fetal death with normal cord gases could also occur with fetal cardiac arrest.[13] In cases of intrapartum stillbirth and in infants who are in very poor condition at birth and who require considerable resuscitation, normal cord venous and arterial pH do not therefore exclude acute intrapartum asphyxia. A blood gas sample taken from the infant soon after birth would be expected to show marked acidosis if there had been cord obstruction.[14]

The umbilical vein is larger and easier to sample from than the umbilical artery, and when only a single sample can be obtained because of sampling difficulties it is likely to be venous. Even when paired samples are obtained it cannot always be assumed that one is from an artery and one from the vein. Because fetal carbon dioxide is removed from the umbilical arterial blood in the placenta, umbilical venous blood should have a slightly higher pH and lower P_{CO_2} than umbilical arterial blood. Westgate *et al*[15] reported on 1798 supposedly paired umbilical arterial and venous blood samples. They found that in 350 (19.5%) cases the paired samples were unreliable. In 169 (9.4%) cases the umbilical venous pH was lower or P_{CO_2} was higher than the corresponding arterial value, suggesting that the samples had been mixed up. In 181 (10.1%) cases, where the difference in pH between the two samples was <0.02 units (5th centile) or the difference in P_{CO_2} was less than 0.5 kPa (10th centile) they considered the two samples to be so similar that they must have been taken from the same vessel. In the remaining 1448 validated pairs, the median (range) arteriovenous difference in pH was 0.09 (0.02–0.49) units, and in P_{CO_2} was 1.9 (0.5–9.9) kPa. Tong *et al* had similar findings.[16]

When paired cord blood gas samples produce results that are so similar that it is physiologically implausible and statistically unlikely that they came from an artery and a vein they should therefore be interpreted in the same way if they were a single vessel sample,[17] and it is most likely that they came from the umbilical vein. They do not then exclude the possibility of notable umbilical arterial acidosis, particularly if the rest of the clinical picture points towards this.

WHAT IS A NORMAL CORD pH?

Many authors have studied normal umbilical blood biochemistry and acid–base status. Most available data relate to infants born at full term. Parity,[18] breech presentation,[19] mode of delivery[20] and many other factors influence cord gas values. Reference ranges for term and preterm infants are summarised in table 1.

In a study of more than 15 000 vigorous newborn infants, Helwig *et al* showed a stepwise reduction in mean umbilical arterial pH for infants born preterm, term and post term, respectively.[22] They hypothesised that this trend could be explained by the prevalence of a shorter duration of labour in preterm

Table 1 Studies reporting umbilical cord values for term and preterm infants

Author	Umbilical artery				Umbilical vein				Number	Population studied
	pH	Base excess (mmol/l)	P_{CO_2} (kPa)	P_{O_2} (kPa)	pH	Base excess (mmol/l)	P_{CO_2} (kPa)	P_{O_2} (kPa)		
Victory *et al*[21] 2004	7.24 (0.07)	−5.6 (3.0)			7.33 (0.06)	−4.5 (2.4)			20 456	Term non-anomalous singletons
Helwig *et al*[22] 1996	7.26 (0.07)	−4.0 (3.0)	7.05 (1.33)	2.26 (0.8)	7.34 (0.06)	−3.0 (3.0)	5.45 (0.93)	3.86 (0.93)	15 073	All gestations, all delivery types, Apgar >7[5]
Thorp *et al*[18] 1989	7.24 (0.07)	−3.6 (2.7)	7.49 (1.14)	2.38 (0.92)	7.32 (0.06)	−2.9 (2.4)	5.83 (0.89)	3.82 (0.97)	1694a 1820v	Term, nulliparous, SOL, all delivery types
Riley and Johnson[20] 1993	7.27 (0.07)	−2.7 (2.8)	6.69 (1.48)	2.45 (1.09)	7.34 (0.06)	−2.4 (2.0)	5.41 (1.05)	3.79 (1.02)	3522	Term singleton infants, vaginal delivery
Dickinson *et al*[23] 1992	7.26 (0.08)	−3.2 (2.9)	7.05 (1.33)	2.53 (1.05)	7.33 (0.07)	−2.6 (2.5)	5.77 (1.1)	3.88 (1.29)	1393a 1526v	Preterm (24–36 weeks), normal CTG

Data are presented as mean (SD). Arterial (a) and venous (v) sample numbers are given separately where available.
CTG, cardiotocogram; SOL, spontaneous onset of labour; SVD, spontaneous vertex delivery.

infants. However data by Nicolaides *et al*[24] and Weiner *et al*[25] demonstrated a similar trend in premature infants who had not undergone labour. They hypothesised that this may reflect increased placental oxygen consumption with advancing gestational age.

OTHER FACTORS WHICH INFLUENCE CORD BLOOD VALUES

Infants born by elective caesarean section without labour[20] have results which are closer to normal adult values (higher pH, P_{O_2}, base excess and bicarbonate, and lower P_{CO_2}), as do infants born of multiparous mothers.[18] The repeated uterine contractions of normal labour exert appreciable metabolic stress on the fetus. This effect is exaggerated in twin labour at full term, where the time-related deterioration of arterial cord pH is more precipitous in the second twin.[26] Regional anaesthesia, particularly spinal anaesthesia is associated with increased incidence of cord blood acidosis.[27] Sympathetic blockade reduces uteroplacental perfusion. The resultant carbon dioxide retention is manifest by predominantly respiratory acidosis, but there is no evidence that this affects clinical outcome.[27] Although there seems to be a weakly positive correlation between cord pH and umbilical cord length, number of coils and number of vascular coils per centimetre,[28] umbilical cord morphology is of uncertain clinical importance. The presence of true knotting of the cord seldom seems to cause a problem.[29]

Chorioamnionitis, with or without funisitis does not appear to influence cord blood pH or base excess.[30] Although placental infection is associated with cerebral palsy in both term and preterm infants, the mechanism appears to be largely independent of hypoxia-ischaemia.[31]

Evaluation of fetal acidosis

The pH of umbilical cord blood is determined by presence of respiratory and metabolic acids. Carbon dioxide diffuses readily across the placenta. Fixed acids such as lactic acid and β-hydroxybutyrate, which account for the majority of the metabolic load, have a relatively slow passage across the placenta.[32]

It is important to evaluate both the respiratory and metabolic components of each sample. Isolated fetal respiratory acidosis is usually the result of short-lived impairment of the uteroplacental or fetoplacental circulation and is seldom associated with adverse outcome.[33] Ongoing impairment results in progressive metabolic acidosis due to anaerobic glycolysis. Consequently most severe fetal acidosis is mixed.[34 35] Although it is the most commonly quoted figure, pH is not an ideal parameter for estimating the cumulative exposure to hypoxia. Because it is a logarithmic term it does not give a linear measure of acid accumulation. The change in hydrogen ion concentration associated with a fall in pH from 7.0 to 6.9 is almost twice that which is associated with a fall in pH from 7.3 to 7.2. The base excess provides a more linear measure of the degree of accumulation of metabolic acid and is adjusted for variation in P_{CO_2}.[36]

Uterine contraction during the second stage of labour may impair placental flow, although periodic relaxation usually allows restitution of gas exchange unless placental function is already poor. In cases of excessive contraction such as during uterine hyperstimulation or prolonged second stage, incomplete restitution may result in cumulative acidosis. Interrupted placental perfusion also occurs during maternal hypotension, as seen in acute blood loss, regional anaesthesia and systemic illness, as well as during placental abruption and acute cord compression.[32]

Uncomplicated labour changes base excess by around 3 mmol/l overall.[36] A normal second stage of labour changes it by around 1 mmol/l per h.[37] In contrast, base excess changes by around 1 mmol/l per 30 min during prolonged periods when there are repeated fetal heart rate decelerations.[38] The most profound fetal compromise, such as that associated with terminal bradycardia following acute uterine rupture, changes base excess by 1 mmol/l per 2–3 min.[36]

CORD BLOOD P_{O_2} AND P_{CO_2}

The blood gas analyser measures pH, P_{CO_2} and P_{O_2} and then calculates base excess after normalising P_{CO_2}. The P_{O_2} and P_{CO_2} values can provide further clues to the interpretation of the clinical picture and helps to exclude rogue results. From the data series in table 1, the upper 95% confidence level (mean + 2 SD) for umbilical arterial P_{O_2} is 4.2 kPa and for umbilical venous P_{O_2} is 5.8 kPa.[39] In mothers breathing 60% mask oxygen during uncomplicated delivery the upper 95% confidence levels for P_{O_2} were 5.0 kPa (umbilical artery) and 6.8 kPa (umbilical vein).[40] In mothers ventilated with 100% oxygen during caesarean section the upper 95% confidence level for umbilical arterial P_{O_2} was 4.9 kPa.[41] These data indicate that cord arterial samples with P_{O_2} greater than 5.0 kPa are likely to have been affected by the presence of an air bubble in the specimen. Because the carbon dioxide content of air is very low, this can be accompanied by a substantial lowering of the P_{CO_2} of the sample

followed by a large rise in pH, with consequent risk of misinterpretation.[42] These changes are likely to begin within a few minutes of exposure of the sample to a bubble.[43] The base excess should still provide a reliable measure of metabolic acidosis in the specimen but it may not be possible to determine whether the specimen is arterial or venous.

The lower limit of carbon dioxide is less informative because mothers can spontaneously hyperventilate to low P_{CO_2}. In the absence of compromise to the placental perfusion by mother and fetus there is a linear relationship between maternal and fetal P_{CO_2}.[44] However the changes in fetal pH associated with brief hyperventilation are small. Maternal hyperventilation lowers fetal P_{O_2}.[44 45]

WHAT IS PATHOLOGICAL ACIDOSIS?

It is unhelpful to define pathological acidosis statistically, using deviation from the normal population values. This is because acidosis is generally tolerated by the fetus without sequelae until it becomes very severe. It is more clinically relevant to define pathological acidosis as the threshold at which the incidence of adverse clinical events starts to correlate strongly.

Serious adverse sequelae in the newborn period are rare after birth with umbilical cord pH greater than 7.0 or base excess less acidotic than minus 12 mmol/l.[34 35 46] Follow up of infants with cord pH above 7.0 suggests no adverse effect of acidosis on cognitive outcome.[47] Even at pH below 7.0 most infants will still recover fully without remarkable illness.[48–50] In this respect cord pH or base excess alone are poor predictors of outcome.[48 51 52] Most infants with evidence of intrapartum asphyxia do not develop serious long-term sequelae. In a series of around 14 000 newborn infants with routine cord blood gas analysis, King *et al* identified pH <7.0 in 58 (0.4%) infants who were born at 35 weeks' gestation or more.[49] On the basis that they had birth weight >2100 g, 5-mim Apgar score ⩾7 and an absence of cardiopulmonary disturbance, 37 of these 58 infants were triaged after birth to the routine postnatal nursery. They were followed closely and none developed clinical manifestations of hypoxic-ischaemic injury. Two of the infants were admitted to the neonatal unit because of hypoglycaemia. This suggests that infants who are in good clinical condition at birth and are free of cardiopulmonary disturbance do not require neonatal unit admission or detailed investigation purely on the basis of low cord pH.

In contrast, the combination of low pH at birth with other abnormal clinical patterns becomes very strongly predictive of adverse sequelae. Perlman and Risser showed that a combination of cord pH <7.0, a requirement for intubation and a 5-min Apgar score of ⩽5 had an 80% positive predictive value for the development of seizures.[53] Portman *et al* developed and validated a scoring system for predicting multiorgan impairment following perinatal asphyxia.[54] They found that a score combining a measure of cardiotocographic abnormality, umbilical arterial base excess, and low 5-min Apgar score was much more strongly associated with morbidity than any individual factor. In a separate study the score showed a positive predictive value of 73% and negative predictive value of 99% for predicting impairment of three or more organ systems.[55]

Goldaber *et al* studied the association between umbilical arterial acidosis and adverse neurological events among 3506 term, singleton infants with cord arterial pH<7.20.[56] Neonatal death was much more likely at pH <7.00. The cut-off at which seizures became more likely was pH <7.05, and for unexplained seizures was pH <7.00. They recommended that a realistic value for defining pathological acidaemia was pH <7.00. Williams *et al* also found that a threshold of pH <7.00 was the best independent predictor of neonatal seizures when compared with other indices.[57] Low and colleagues studied the association between metabolic acidosis and multiorgan impairment. Using a scoring system for renal, central nervous system, respiratory and cardiovascular morbidity they showed that both the presence and magnitude of metabolic disturbance was a good predictor of multiorgan involvement in both term and preterm infants.[33 58] They found that the threshold of metabolic acidosis associated with increased risk of newborn complications in term infants was a base excess of minus 12 mmol/l or worse.[46]

Once severe acidosis is present, the likelihood of adverse sequelae rises sharply with worsening acidosis. Goodwin *et al* found that hypoxic-ischaemic encephalopathy occurred in 12% of infants with cord pH <7.0, 33% with cord pH <6.9, 60% with cord pH <6.8, and 80% with cord pH <6.7.[35] In a study of 69 000 term deliveries with cord blood gas measurements, no infant was live born with pH <6.6.[35] Increasing morbidity with worsening acidosis, once severe acidosis is present, has also been noted in several other studies.[59–61] Collectively these data suggest that permanent neurologic injury from intrapartum asphyxia occurs late in the course of the asphyxial insult in most of the cases, once the fetus is close to death.

Whereas cord blood analysis provides a static measurement, longitudinal measurement of acid–base status after birth may be useful in prognosis. Casey *et al* found that infants in whom acidosis (pH <7.20) persisted 2 h beyond delivery had a poorer outcome than those in whom acidosis had resolved.[62] Recent data suggest that persisting lactic acidosis is associated with severe encephalopathy and may be a reflection of the presence and severity of seizures.[63]

PRETERM INFANTS

The value of umbilical cord blood for predicting morbidity and mortality in preterm infants is less clear. As in term infants, Victory *et al* demonstrated a relationship between increasing metabolic acidosis and adverse outcomes in a large cohort of preterm and very preterm infants (32–36 weeks and 25–32 weeks, respectively).[64] Hibbard *et al* found that very low birthweight infants who survived had higher umbilical arterial pH than those who did not survive.[65] Tejani and Verma demonstrated similar findings in low birthweight infants (<2000 g) for mortality, and also found a weak inverse association between umbilical artery pH and risk of respiratory distress syndrome.[66] Beeby *et al* found that any association between umbilical artery pH and neonatal morbidity was negated when adjusting for other risk factors such as gestation and birthweight.[67]

In a retrospective study of extremely low birthweight infants, Gaudier *et al* showed that condition of the neonate at birth, evaluated by a low 1-min or 5-min Apgar score (<4 and <7, respectively) was a better predictor of survival, adjusted for gestation, than any individual cord blood measurement.[68] This is perhaps not surprising, as the Apgar scores are substantially influenced by whether or not any resuscitative measures are implemented and whether these are performed effectively. However, in an earlier study involving essentially the same cohort, the same authors demonstrated that in those who survived, the risk of neurosensory impairment was independently predicted by cord arterial metabolic acidosis, when adjusted for gestation, weight and other confounding variables. The odds ratio (95% CI) of major neurosensory impairment for pH <7.05 was 6.48 (1.1 to 37.4) and for bicarbonate ⩽14 mEq/l was 14.2 (1.8 to 112.8).[69]

LACTIC ACID MEASUREMENT

Lactate is now routinely measured by many blood gas analysers. Because it only sparingly crosses the placenta lactate measured in umbilical cord blood samples is almost entirely fetal in origin.[70] Umbilical cord lactate has been shown to correlate with both pH and base

excess.[71] In a study of 4045 cord samples, Westgren *et al* showed that lactate was similar to both pH and base excess in its ability to predict low Apgar scores, and other selected short-term morbidities.[72] A cut-off of the 95th centile (value not given) predicted mortality with a sensitivity of 43% and specificity of 95%. Chou *et al* studied the additional benefits of using pyruvate in combination with lactate to predict outcomes.[73] Lactate is oxidised to pyruvate once adequate cellular oxygenation is restored. In a study of high-risk infants born at term and preterm, they demonstrated that a combination of high lactate (>4.1 mmol/l) and high lactate/pyruvate ratio (>22) predicted neonatal encephalopathy with a sensitivity of 100% and specificity of 95.4%. The ability to predict long-term outcomes correctly, such as abnormal development and death was below 50%. Since most mild and moderate encephalopathy resolves without sequelae, very large studies would be needed to examine these outcomes meaningfully.

SUMMARY

Umbilical cord blood gas analysis is recommended in all high-risk deliveries and is performed after all deliveries in some centres. For optimal interpretation paired umbilical arterial and venous samples should be taken soon after birth from a segment of cord that has been doubly clamped to isolate it from the placenta. Low cord pH in infants who are vigorous at birth and free of cardiopulmonary compromise does not indicate an increased risk of adverse outcome. Infants with pH <7.0 at birth who are not vigorous are at high risk of adverse outcome. Identification of infants at risk of encephalopathy is especially important now that early intervention is being considered. Analysis of paired arterial and venous specimens can give insights into the aetiology of the acidosis. In combination with other clinical information, normal paired arterial and venous cord blood gas results can usually provide a robust defence against a suggestion that an infant had an intrapartum hypoxic-ischaemic event.

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