

Umbilical-cord blood gas analysis

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The pH, base excess and $p\text{CO}_2$ (acid-base status) of arterial blood flowing through the umbilical cord provides valuable objective evidence of the metabolic condition of neonates at the moment of birth; a notion that has assured a role for the blood gas analyzer in hospital delivery suites in cases of suspected fetal distress/asphyxia.

The intended purpose of this review article is to detail the clinical value of determining acid-base parameters – particularly pH and base excess – of umbilical-cord blood. Important issues surrounding cord blood sampling will also be discussed.

The applicability of cord blood gas analysis is an unresolved controversy that will be addressed: should cord blood gas analysis be reserved for defined high-risk deliveries or should it, as some advise, be more universally applied at all hospital births?

Finally, the potential role of cord-blood lactate

measurement will be discussed. The article begins with some background physiology/anatomy of placental/fetal circulation that highlights the all-important distinction between arterial and venous cord blood for accurate assessment of fetal/neonatal acid-base status.

Background physiology

The growing fetus depends for oxygen and nutrients on maternal blood supply. Fetal and maternal circulation is proximate at the placenta where gas/nutrient exchange between maternal and fetal circulation occurs.

Oxygen and nutrients diffuse across the placental membrane from maternal arterial blood and is transported to the fetus via a single large umbilical vein. Following tissue extraction of oxygen and nutrients, fetal blood returns to the placenta via two small umbilical arteries. This now deoxygenated blood contains the waste products of fetal metabolism, including carbon dioxide ($p\text{CO}_2$), for elimination from maternal circulation via lungs and kidneys.

So, the umbilical cord contains three blood vessels: one large vein carrying oxygenated blood to the fetus and two much smaller arteries carrying deoxygenated blood that is relatively rich in carbon dioxide and other metabolic waste products from the fetus.

Thus venous cord blood reflects the combined effect of maternal acid-base status and placental function, whilst arterial cord blood reflects neonatal acid-base status.

It is vital, therefore, that the acid-base parameters (pH, base excess (BE) and lactate) derived from arterial rather than venous cord blood are used to assess neonatal condition. The normal physiological difference between venous and arterial cord blood gas and acid-base values is described in Table I.

The umbilical-cord blood data contained in the table is derived from a study [1] of all 19,600 live births (>20 weeks gestation) at a tertiary care obstetrics unit during a 3-year period; results are consistent with smaller, earlier studies [2, 3]. This reflects the fact that

it is the umbilical vein that carries oxygenated blood rather than the umbilical artery. After separation from maternal circulation, and throughout life, oxygenated blood is carried in arteries from lungs to the tissues and deoxygenated blood is carried from tissues back to the lungs in veins).

Neonatal hypoxia and resulting acidosis

The clinical value of cord blood gas analysis lies in its ability to provide objective evidence of asphyxia at the moment of birth. It has been shown to be more reliable in this regard than routine clinical assessment at birth using the Apgar scoring system [4].

Asphyxia is reduced tissue oxygen (hypoxia) of sufficient severity and duration to cause metabolic acidosis [5].

Metabolic acidosis develops because when tissue cells are severely depleted of oxygen, aerobic metabolism of glucose is compromised, and cells must depend for their function and survival on less effective anaerobic

	Umbilical artery (n = 12,345)	Umbilical vein (n = 12,345)	Adult arterial (non-cord) blood values (for comparison only)
pH median 5 th -95 th percentile range	7.27 (7.12-7.35)	7.35 (7.23-7.44)	7.40 (7.35-7.45)
pO ₂ median [kPa] 5 th -95 th percentile range	2.2 (0.8-3.7)	3.7 (2.2-5.3)	12.0 (10.6-13.3)
pO ₂ median [mm Hg] 5 th -95 th percentile range	16.3 (6.2-27.6)	27.9 (16.4-40.0)	90 (80-100)
pCO ₂ median [kPa] 5 th -95 th percentile range	7.3 (5.6-9.8)	5.4 (3.8-7.1)	5.3 (4.7-6.0)
pCO ₂ median [mmHg] 5 th -95 th percentile range	55.1 (41.9-73.5)	40.4 (28.8-53.3)	40 (35-45)
Bicarbonate (mmol/L) 5 th -95 th percentile range	24.3 (18.8-28.2)	21.8 (17.2-25.6)	25 (22-28)
Base Excess (mmol/L) 5 th -95 th percentile range	-3.00 (-9.3 to +1.5)	-3.00 (-8.3 to +2.6)	0 (-2.0 to +2.0)
Lactate (mmol/L) 5 th -95 th percentile range	3.7 (2.0-6.7)		1.0 (0.5-1.5)

TABLE I: Median and centile ranges for umbilical-cord blood gas and lactate values [1]. (Note that umbilical venous blood gas values more closely resemble those of adult arterial blood than do those of umbilical arterial blood.

pathways that result in reduced ATP (energy) production and, importantly for this discussion, accumulation of metabolic acids (principally lactic acid) [6].

Normal buffering mechanisms are overwhelmed by this acid influx, and pH falls below normal limits. Cord-blood metabolic acidosis – which is characterized by reduced blood pH and decreased base excess (i.e. increased base deficit) – thus implies that sometime during labour, oxygenation of fetal tissues was severely compromised.

Table II lists some of the factors that may adversely affect fetal oxygenation and contribute to or cause fetal hypoxia and consequent cord-blood metabolic acidosis.

It is important to distinguish cord-blood metabolic acidosis and cord-blood respiratory acidosis; the latter is characterized by reduced pH but normal base excess. The finding of isolated respiratory acidosis (i.e. not associated with metabolic acidosis) at birth is indicative of impaired gas exchange and consequent reduced oxygen delivery to the fetus.

However, the associated hypoxemia is of insufficient severity or duration to cause hypoxia and consequent metabolic acidosis. Cord-blood respiratory acidosis is a relatively common transitory state that resolves soon after birth when the baby starts to breathe; it is of little clinical significance [7, 18].

Cord-blood metabolic acidosis and risk of encephalopathy

Significant metabolic acidosis, widely defined as cord arterial blood pH <7.0 and base excess <-12.0 mmol/L (base deficit >12.0 mmol/L), occurs in around 0.5-1% of deliveries [1]. The severe intrapartum hypoxia that this degree of cord metabolic acidosis reflects is associated with increased risk of hypoxic brain-cell injury and associated hypoxic-ischemic encephalopathy (HIE).

HIE is a condition of brain/neurological dysfunction caused by perinatal asphyxia. Symptoms among affected neonates include hypotonia, poor feeding, respiratory difficulties, seizures and reduced level of consciousness.

Maternal factors	Utero-placental factors	Fetal factors
Maternal hypoxemia due to: <ul style="list-style-type: none"> respiratory disease hypoventilation seizure, trauma smoking 	Excessive uterine activity: <ul style="list-style-type: none"> hyperstimulation by drugs prolonged spontaneous labor placental abruption 	Umbilical cord compression: <ul style="list-style-type: none"> oligohydramnios cord prolapse or entanglement
Maternal reduced oxygen-carrying capability due to: <ul style="list-style-type: none"> anemia carboxy- hemoglobinemia 	Utero-placental dysfunction: <ul style="list-style-type: none"> placental abruption placental infarction/dysfunction marked by intrauterine growth restriction, oligohydramnios or abnormal Doppler studies chorioamnionitis (infection) 	Decreased fetal oxygen-carrying capability: <ul style="list-style-type: none"> significant anemia due to isoimmunization, maternal fetal bleed or vasa previa carboxy- hemoglobinemia (if mother is a smoker)
Decreased uterine blood flow due to: <ul style="list-style-type: none"> hypotension (e.g.shock, sepsis) regional anesthesia maternal positioning 		
Chronic maternal conditions: <ul style="list-style-type: none"> diabetes chronic hypertension SLE antiphospholipid syndrome 		

TABLE II: Factors that may affect fetal oxygenation in labour [7]

Eventual outcome depends on severity/site of brain injury; those with mild HIE survive with usually little or no long-term consequences, but most of those with moderate/severe HIE either die during the neonatal period or survive with severe and permanent neuro/psychological deficit, cerebral palsy is an outcome for some [8, 9].

HIE is thus a significant cause of perinatal death and birth-related permanent disability.

Since the incidence of HIE is much lower (around 1.5/1000 live births [10]) than that of significant metabolic acidosis (0.5-1 % live births [1]), it is clear that HIE is not an inevitable consequence of significant metabolic acidosis. Indeed, most (around 75 %) babies with significant metabolic acidosis (pH <7.0, base excess <-12.0 mmol/L) do not suffer any signs of neurological illness or other adverse effects [7].

However, a diagnosis of HIE depends in part on demonstrating significant cord-blood metabolic acidosis, and a normal arterial cord-blood pH and base excess result usually excludes the possibility of perinatal asphyxia, and thereby that any neurological signs and symptoms (including cerebral palsy) exhibited by the neonate is due to HIE.

This has medico-legal significance for resolving disputes about the cause of brain damage sustained at birth [11]. In short, significant cord metabolic acidosis (pH <7.0 and base excess <-12 mmol/L) is necessary, but not sufficient to confirm that an acute intrapartum hypoxic event was the cause of encephalopathy/cerebral palsy.

Currently, the only effective treatment for HIE is controlled cooling of the baby to a rectal temperature of 34 ± 0.5 °C for 48-72 hours. Efficacy depends on initiating this hypothermic treatment within 6 hours of birth. Significant metabolic acidosis (i.e. cord blood pH <7.0 or base excess <-16 mmol/L) is one of several entry requirements for application of this therapy [12].

Sampling of cord blood

The standard technique of sampling cord blood for gas and acid-base analysis comprises three steps:

- clamping a segment of the cord
- removing the clamped cord segment
- needle aspiration of two blood samples (one venous, one arterial) from the excised clamped cord segment into preheparinized syringes

The purpose of cord blood gas analysis is to determine the acid-base status of the neonate at the moment of delivery. Since acid-base status is in flux during the perinatal period, the timing of isolating a sample for analysis is crucial.

Immediately after birth, ideally before the baby's first breath, an approximate 20-cm segment of cord must be isolated between two sets of two clamps. Delay in clamping by as little as 45 seconds after birth results in significant change in acid-base parameters [13-15]; the longer the delay, the greater is the change [16, 17]. The change is a progressive decrease in pH and base excess, and increase in $p\text{CO}_2$ and lactate.

This so-called "hidden acidosis" phenomenon is thought to be a transient physiological effect of initiation of neonatal breathing [13] and can give a false impression of significant acidosis at birth.

Once isolated from maternal/neonatal circulation, the acid-base parameters of clamped cord blood are stable at room temperature for 60 minutes [14, 15]. To retrieve blood for analysis the cord segment is first cut between the two clamps at each end, so that the clamped segment can be removed from the immediate vicinity of the baby.

Blood is sampled into a preheparinized syringe by needle aspiration. As with any blood sample destined for blood gas analysis it is important to exclude all air bubbles and cap the syringe before mixing the sample. Manor *et al* [18] determined that blood gas values of cord blood stored in a capped heparinized syringe remain sufficiently stable for an hour at room temperature.

Recommendation from the Clinical and Laboratory Standards Institute (CLSI) is that arterial blood specimens should be analyzed within 30 minutes of sampling [19].

As previously discussed, it is vital that arterial blood is sampled for analysis. Unfortunately it is more difficult to sample arterial than venous cord blood because umbilical arteries are much smaller and less visible than umbilical veins [20].

The close juxtaposition of arteries and vein in the umbilical cord makes it quite possible to sample venous blood in the mistaken belief that it is arterial blood [20]. Given these difficulties, it is widely recommended [2, 20-22] that blood from both artery and vein are sampled and analyzed, so that arterial blood results can be validated as truly arterial.

The validation of paired (arterial and venous) samples is based on minimum arterio-venous (A-V) differences for pH and $p\text{CO}_2$ experimentally determined by Westgate *et al* [2]. For pH, the A-V difference should be >0.02 pH units, and for $p\text{CO}_2$ the A-V difference should be >0.5 kPa (3.75 mmHg).

So long as these minimum differences in pH and $p\text{CO}_2$ between the two samples are evident, it can be assumed that the two samples came from different vessels, and that the one with lowest pH and highest $p\text{CO}_2$ came from an artery (Table I).

If the two samples return similar results (i.e. pH difference <0.02 and/or $p\text{CO}_2$ difference <0.5 kPa), then the two samples almost certainly came from the same vessel, either a vein or an artery. Under these circumstances it cannot be assumed that the results relate to arterial blood; indeed, it is most probable, given the relative ease of sampling venous blood, that they relate to venous blood.

The problem of delayed cord clamping

For many years it has been standard obstetric practice to clamp the umbilical cord within seconds of birth,

a policy that is, as discussed above, coincidentally fortuitous for the most accurate assessment of neonatal acid-base status.

In recent years there has been increasing acceptance of the notion that delaying cord clamping by 2-3 minutes after birth is beneficial to the baby because of the placental blood transfusion it permits.

A recent Cochrane review of study in this area concluded that the benefit to the baby associated with delayed clamping (higher birth weight, increased haemoglobin concentration and iron reserves) outweighs the small increased risk of jaundice, stating that a more liberal approach to delayed clamping is warranted [23].

The policy of delayed cord clamping clearly poses a potential problem for accurate assessment of neonatal acid-base status at birth, because of the “hidden acidosis” phenomenon. A solution to this problem has been validated by the results of two recent clinical studies [24, 25].

The solution, which is standard practice in some units, is to sample blood within seconds of birth directly from the still pulsating unclamped umbilical cord, rather than from a separated clamped cord segment.

Should cord-blood testing be performed at selected births or at all births?

National clinical guidelines in the UK [26], endorsed by the Royal College of Obstetricians and Gynaecologists, suggest a selective approach, in stating that “Paired cord blood gases do not need to be taken routinely. They should be taken when there has been concern about the baby either in labour or immediately following birth.”

The American College of Obstetricians and Gynaecologists (ACOG) also favor a selective approach, stating that cord-blood testing should be applied in the following situations [22]:

- Cesarean delivery for fetal compromise
- Low 5-minute Apgar score

- Severe intrauterine growth restriction
- Abnormal fetal heart rate tracing
- Maternal thyroid disease
- Intrapartum fever
- Multifetal gestations

The Society of Obstetricians and Gynaecologists of Canada (SOGC), by contrast, recommend that cord blood gas analysis be performed at all births [7].

The lack of consensus on this issue among national expert bodies is reflected in obstetric practice around the world; some obstetric units having a selective policy, whilst others are routinely performing cord blood gas analysis at all births. The pros and cons of selective versus routine cord blood gas analyses were discussed by Thorp *et al* [20]; their views are summarized below.

Advantages of routine (non-selective) cord blood gas testing:

- All “damaged babies” will have a cord-blood pH on record (important for medico-legal disputes because a normal cord-blood pH usually excludes perinatal asphyxia as the cause of brain injury)
- Staff become more proficient in obtaining cord-blood samples
- Process becomes habitual, so less chance of “forgetting” to perform in emergency situations
- Result may assist with newborn care, should unforeseen problems develop after birth
- Helps clinicians gain insight into interpretation of electronic fetal monitoring for safe and effective intervention strategies – has educative value

Disadvantages of routine (non-selective) cord blood gas testing:

- More costly than selective policy
- Requires increased staff resources that might simply not be available in some units
- Occasional finding of reduced cord-blood pH in a normally healthy “vigorous” newborn might pose a potential medico-legal concern because it falsely suggests birth asphyxia

Proponents of routine cord blood gas analysis also argue that it can be used as an audit of the effectiveness of the fetal monitoring and intervention strategies used in the unit to prevent significant metabolic acidosis and associated neonatal morbidity and mortality.

The prevalence of metabolic acidosis at an obstetric unit, which can only be determined by performing cord-blood testing at all births, is thus a valuable safety audit measure. This potential safety audit function of universal cord blood gas testing is addressed by a recent study [1] that suggests adoption of a universal testing policy resulted in improved perinatal outcomes.

The prevalence of metabolic acidosis can be used as an outcome measure for testing the efficacy of novel fetal monitoring strategies. In one study [27], for example, the introduction of ST waveform analysis as an adjunct to fetal ECG monitoring resulted in a remarkable reduction in the prevalence of significant metabolic acidosis (0.72 % of all live births to 0.06 %).

The design of this study depended on the policy of universal cord blood gas testing that had been adopted in the obstetric unit where the study was conducted.

Does cord-blood lactate measurement have a role?

Techniques for rapid and convenient measurement of lactate concentration on very small blood volumes (<5 µL) became available around 20 years ago, allowing the feasibility of cord-blood lactate measurement [28].

Lactic acid is the principal metabolic acid responsible for the fall in cord-blood pH and base excess that is associated with cord-blood metabolic acidosis and birth asphyxia [28]. It follows, theoretically at least, that arterial cord-blood lactate concentration should be as reliable an indicator of birth asphyxia and risk of HIE as the more established tests, arterial cord-blood pH and base excess.

A limited number of studies [29-32] have been conducted to test this proposition and thereby validate

the clinical use of cord-blood lactate measurement. In summary, these studies have confirmed that cord-blood lactate concentration is a good predictor of cord-blood pH and base excess, and that it is at least as good as pH and base excess in predicting outcome.

Wiberg *et al* [31] argue that lactate may be superior to base excess because the former is a direct measure of metabolic acidosis, whereas base excess is an indirect estimated (calculated) value derived from measured pH and $p\text{CO}_2$. This is important because there is little consensus on which of several algorithms should be used for this calculation. The effect of this inconsistency in determining cord-blood base excess has recently been demonstrated [33].

Two unresolved issues militate against the routine use of cord-blood lactate alone, at the current time. First, the A-V difference of lactate in cord blood has not been sufficiently clearly defined, so there is no way of reliably confirming that a lactate result relates to cord arterial blood. Second, there remains no consensus on the cut-off lactate value that should be used to define significant cord metabolic acidosis, as there is for pH and base excess (pH <7.0, base excess <-12.0 mmol/L).

However, there is an apparent consensus among those who have studied the issue that measurement of cord-blood lactate measurement has potential that should be further investigated.

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