Gynécologie Obstétrique & Fertilité 44 (2016) 357–362

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EM|consulte
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Clinical expert series

Neonatal metabolic acidosis at birth: In search of a reliable marker☆

Acidose métabolique néonatale à la naissance : à la recherche d'un marqueur pertinent

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ARTICLE INFO

Article history:
Received 18 March 2016
Accepted 11 April 2016
Available online 20 May 2016

Keywords:
Neonate
Respiratory acidosis
Metabolic acidosis
Birth-related eucapnic neonatal pH

ABSTRACT

Objective. – A newborn may present acidemia on the umbilical artery blood which can result from respiratory acidosis or metabolic acidosis or be of mixed origin. Currently, in the absence of a satisfactory definition, the challenge is to determine the most accurate marker for metabolic acidosis, which can be deleterious for the neonate.
Methods. – We reviewed the methodological and physiological aspects of the perinatal literature to search for the best marker of NMA.
Results. – Base deficit and pH have been criticized as the standard criteria to predict outcome. The proposed threshold of pathogenicity is not based on convincing studies. The algorithms of various blood gas analyzers differ and do not take into account the specific neonatal acid–base profile.
Conclusion. – Birth-related neonatal eucapnic pH is described as the most pertinent marker of NMA at birth. The various means of calculating this value and the level below which it seems to play a possible pathogenic role are presented.

Mots clés :
Nouveau-né
Acidose respiratoire
Acidose métabolique
PH eucapnique néonatal à la naissance

RÉSUMÉ

Objectif. – Un nouveau-né peut présenter une acidémie dans le sang cordonal, résultant d'une acidose respiratoire ou d'une acidose métabolique (ANM) ou bien d'une acidose mixte. Devant l'utilisation persistante de définitions non satisfaisantes, il paraît nécessaire de déterminer quel est le meilleur marqueur d'une ANM, car celle-ci peut se révéler pathogène pour le nouveau-né.
Méthode. – Nous avons revu les aspects méthodologiques et les bases physiologiques de la littérature périnatale pour construire un marqueur fiable de l'ANM.
Résultats. – Le déficit de base et le pH ne sont pas des marqueurs fiables du pronostic néonatal. Le seuil proposé pour les valeurs pathogènes ne repose pas sur des études convaincantes. Les algorithmes utilisés par les divers analyseurs de gaz du sang diffèrent et ne prennent pas en compte le profil spécifique acido-basique du nouveau-né.
Conclusion. – Le pH eucapnique néonatal à la naissance est décrit comme le marqueur le plus pertinent de l'AMN. Les diverses méthodes de calcul et le niveau au-dessous duquel il paraît pouvoir jouer un rôle pathogène sont présentés.

DOI of original article: http://dx.doi.org/10.1016/j.gyobfe.2016.04.011

☆ Voir, dans ce même numéro de *Gynécologie Obstérique & Fertilité*, l'avant-propos signé par E. Simon : Interprétation du pH au cordon à la naissance : le piège de l'hypercapnie [Interpretation of umbilical cord pH at birth: the trap of hypercapnia]. Gynecol Obstet Fertil 2016;44. http://dx.doi.org/10.1016/j.gyobfe.2016.04.011.

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http://dx.doi.org/10.1016/j.gyobfe.2016.04.005
1297-9589/

1. Introduction

The pathophysiology of fetal asphyxia ultimately leads to neonatal metabolic acidosis (NMA), measured in umbilical artery blood in the neonate, who may have survived the stress of acute or even chronic asphyxia *in utero*. NMA is considered to be an indirect measurement of fetal hypoxia [1].

The presence of NMA at birth is the necessary but not the only biochemical criterion to support an increasing probability that a peripartum hypoxic-ischemic event may be a causal pathway of neonatal encephalopathy preceding cerebral palsy (CP) [2,3]. Conversely, the presence or absence of NMA takes on a broader medical-legal dimension because of the significant compensation allowed for CP [4]. NMA could also be an argument for initiating cerebral hypothermia as a preventive measure [5].

2. Methodology

Among the diagnostic criteria for NMA, pH and mainly base deficit (BD) should be challenged because various nomenclatures are used to express BD and it is calculated with different algorithms. We analyzed the most relevant publications on NMA that included pH and gazometry, in order to choose a reliable marker for clinical purposes at the bedside.

3. Results

3.1. Acid–base criteria of NMA diagnosis

According to the consensus of the Task Force on Cerebral Palsy [2] and the 2003 consensus of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (ACOG-AAP) revised in 2014 [3], umbilical artery blood acid–base criteria are defined by:

- pH < 7.0;
- or BD ≥ 12 mmol/L (or > 16 mmol/L for therapeutic hypothermia [5]);
- or both.

Given that respiratory acidosis related to hypercapnia can explain a low pH and significant BD, the latter criterion, which is intended to measure the severity of NMA, appears imprecise and poorly adapted to the objective targeted in this high-risk period for asphyxia. It also appears that the defined threshold of pathogenicity is based on a methodology that calls for review.

3.1.1. What is the pH threshold value for severe acidosis?

According to the ACOG-AAP, the threshold for severe umbilical artery acidemia has evolved from $pH_{ua} \leq 7.00$ in 2003 to $pH_{ua} < 7.0$ in 2014 (pH_{ua}, pH in umbilical artery). This second value appears to be more restrictive than the first one because it does not take into account values at 7.0.

Moreover, for the ACOG-AAP, the threshold of severe acidemia changes from its original status as an "essential criterion" (supporting the notion that acute intrapartum asphyxia may have been sufficient to create CP) to a secondary criterion where it only increases the likelihood that neonatal encephalopathy has an intrapartum hypoxic component. However, in 2015, McLennan considered that the ACOG-AAP 2014's report chose to focus on neonatal encephalopathy rather than discuss CP causation specifically and addressed the ramifications of litigation following a diagnosis of CP. For this purpose, he recommended keeping the 2003 essential criteria, which had disappeared in 2014 [6].

3.1.2. The "base deficit" criterion should be more precise: in vitro vs. in vivo BD

BD is usually used as an indicator of metabolic acidosis, especially if it is high and ventilation is normal, as is the case in the older child. However, in the newborn it is particularly important to know whether acidemia has a metabolic, hypercapnic, or mixed origin.

BD is calculated from measurements of pH, PCO_2, and bicarbonate ion, the latter being calculated with the Henderson-Hasselbalch (HH) equation as follows:

$$pH = 6.1 + \log(HCO_3/0.03PCO_2)$$

In fact, two forms of BD are known: *in vitro* and *in vivo*. Failure to specify which form of BD is used can misguide the interpretation. None of the two consensus statements [2,3] specifies which BD is used in the diagnostic criteria of NMA.

The algorithms used to calculate blood gas parameters stem from the recommendations devised by the Clinical Laboratory Standards Institute (CLSI) [7]. Accordingly, the two forms of BD are calculated based on the following reasoning.

In vitro BD (whole blood) is calculated from pH, HCO_3, and total hemoglobin. It evaluates the quantity of base needed to titrate 1 L of blood to a pH of 7.40, without mentioning simultaneous titration to a referent PCO_2.

In vivo BD (extracellular fluid) is calculated from pH and PCO_2. Modeling extracellular fluid using a mixture containing one part blood and two parts plasma is considered a good approximation of the composition of the whole body internal environment. This *in vivo* BD evaluates the quantity of base needed to titrate the extracellular fluid to a pH of 7.40, at a PCO_2 of 40 mmHg. *In vivo* BD is meant to reflect only the metabolic component, but with reference to normal adult values. According to the CLSI, the *in vivo* BD is calculated by applying the following sequences:

$$\textit{Invivo}\,BD = 24.8 - HCO_3 - (16.2 \times (pH - 7.40))$$

where: pH = actual pH.

HCO_3 is calculated from PCO_2 and pH as follows: $\log(HCO_3) = pH + \log(PCO_2) - 7.608$.

Under acid–base balance conditions (pH = 7.40 for adults), the values of these two forms of BD are very close, but they grow farther apart with increasing acidemia, a condition that is relatively frequent at birth. Accordingly, *in vivo* BD may demonstrate a value below the accepted threshold of pathogenicity of 12 mmol/L, whereas *in vitro* BD may be higher than *in vivo* BD. The choice of one or the other of the BDs adds to the uncertainty of clinical interpretation.

3.1.3. Elimination of the respiratory component in calculating in vivo BD

The CLSI recommends calculating *in vivo* BD with a PCO_2 to a classic value of 40 mmHg obtained after regular ventilation [7]. In fact, it seems implicit that the actual pH value should also be replaced by a pH value free of the influence of hypercapnia, which is referred to as standard or eucapnic pH. On several analyzers we have noted that this recommendation is not always applied, thus inducing different results for the same sample. We have taken the well-founded position of introducing eucapnic pH into this algorithm, instead conserving the measured value of pH.

With reference to Saling's experimental demonstration [1] and keeping in mind the theoretical objective of the CLSI, the *in vivo* BD, which we suggest calling birth-related neonatal eucapnic BD (to clearly specify that it measures acidity at normal newborn PCO_2, as demonstrated in the next section), is always lower than the BD initially calculated from the measured data.