J. Perinat. Med.
10 (1982) 266

Plasma hypoxanthine levels in newborn infants: A specific indicator of hypoxia*

O. D. Saugstad, L. Gluck

Division of Neonatal and Perinatal Medicine. Dept. of Pediatrics, School of Medicine, University of California, San Diego

1 Introduction

Since we introduced hypoxanthine measurements in plasma for evaluating hypoxia [18], several other investigators have documented that plasma hypoxanthine levels in humans reflect hypoxia [4, 6, 11, 29, 30]. It has further been established in a series of animal experiments that the hypoxanthine concentration of plasma sensitively reflects the degree and duration of hypoxia [21, 22, 26, 31, 34].

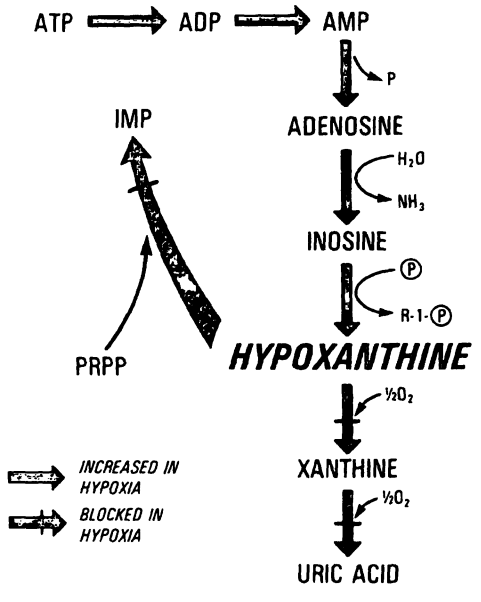

Fig. 1. Schematic outline of adenine nucleotide metabolism. AMP is degraded to hypoxanthine and accumulated in hypoxia. Salvage of hypoxanthine to IMP is reduced as is the further catabolism to uric acid when lack of oxygen. PRPP = phosphoribosylpyrophosphate.

Curriculum vitae

OLA DIDRIK SAUGSTAD, *MD, PhD. was born in Oslo 1947. He received his MD from University of Oslo 1973. From 1973–1974 he was research fellow at the Perinatal Research Unit in Uppsala. In 1974 he was research fellow at the Institute for Surgical Research, National Hospital of Norway. 1977 he defended his PhD thesis: Hypoxanthine as an indicator of hypoxia. 1980–81 he held an International Research Fellowship (Fogarty) from NIH at the Neonatal Intensive Care Unit, Department of Pediatrics, University of California San Diego. In 1979 he started his training in general pediatrics at the Oslo City Hospital, University of Oslo. Special interests: Purine metabolism and perinatal hypoxia, Neonatal lung failure.*

Hypoxanthine is the breakdown product of energy rich nucleotides such as ATP. In Fig. 1 we have outlined some aspects of purine metabolism and how we believe this to be affected by hypoxia. During hypoxia there is an accelerated catabolism of AMP to hypoxanthine, which is one way the cells restore their intracellular energy charge [2, 14]. Furthermore, the salvage of hypoxanthine to inosine monophosphate (IMP) is blocked since this

* This study was supported by USPHS grants: F05 TW02934, HD 10622, and HD 04380. The American-Scandinavian foundation (Crown princess Märthas friendship fund) and the Norwegian Research Council for Science and the Humanities. ODS is an International Research Fellow (Fogarty).

0300-5577/82/0010-0266$02.00

process is ATP dependant for the formation of phosphoribosylpyrophosphate (PRPP) [27]. The further catabolism of hypoxanthine to urate via xanthine is also slowed down, or even stopped during hypoxia, since xanthine oxidase is oxygen dependant [5]. Thus there are at least three reasons why hypoxanthine accumulates in hypoxia.

There is a need for a specific biochemical indicator of hypoxia, since lactate and base deficit (BD) are elevated in a number of conditions not associated with hypoxia [7]. Hypoxanthine is a more specific indicator of hypoxia than these other metabolites. It has recently been shown by THIRINGER [30], that umbilical cord plasma hypoxanthine values are a better indicator of intrauterine hypoxia than BD, pH, lactate, or APGAR score. Preliminary data from this author suggest that hypoxanthine levels of umbilical cord plasma are better predictors of neurological sequelae than these other parameters [30].

Elevated plasma hypoxanthine concentrations have been found in cancer patients [23, 33], however for all practical reasons elevated plasma hypoxanthine concentrations indicate hypoxia.

Very little data are available concerning plasma hypoxanthine in the newborn period. In the present study, the aim has been to compare plasma hypoxanthine levels with BD, pH and paO_2, and further to see whether hypoxanthine levels can serve as a prognostic guide in hypoxic newborn infants.

2 Methods and materials

2.1 Patients

Thirty two infants in our neonatal intensive care unit (ICU) were studied. All but one were less than one week old. One patient was 5 months old and was readmitted because of an infected ventriculo-peritoneal shunt. The gestational age of the neonates ranged from 25–44 weeks (mean 32.2±5 weeks). The birthweights ranged from 730–4130 gram, with mean and SD 1850 ± 1000 gram. Most of the patients suffered from respiratory distress syndrome (RDS) (n = 21). Other diagnoses were: Sepsis (n = 5), pneumonia (n = 3), aspiration (n = 2) and transient tachypnea (n = 1).

2.2 Blood sampling

Fifty samples of arterial blood were drawn from indwelling arterial umbilical catheters (mean 1.5, range 1–4 blood samples from each baby). The first sample (n = 32) was taken as soon as possible after the infant was admitted to the unit. Thus most of the first samples (n = 24) were taken in the first 24 hours of life. In six neonates, the first sample was obtained on the second day of life, while in one neonate the first sample was obtained on the third day of life. When more than one sample was drawn, these were taken on consecutive days. Thus all samples from the neonates (n = 49) were obtained during the first week of life. However, blood was not taken from patients treated with alkali; i.e. $NaHCO_3$ or THAM. Neither were samples taken immediately after infusion of colloids, since such treatment can affect hypoxanthine values by washing out phenomenon [1, 6]. 0.6 ml of blood was taken for hypoxanthine analysis simultaneously with a blood gas and acid base determination for the routine care. The blood for hypoxanthine analysis was collected in heparinized tubes. The erythrocytes were spun down immediately and the plasma stored at −20 °C until analysis. Hypoxanthine concentrations in frozen plasma have been proven stable for at least four months [4].

2.3 Analysis

Blood gases and acid base status were determined with a CORNING 175 automatic blood gas analysis system. Hypoxanthine was measured as previously described [19]. The equipment included IL 113 blood gas equipment linked to a PERKIN ELMER 690 recorder with paper speed of 20 mm/min. The method is based on the principle that oxygen is consumed when hypoxanthine is converted to urate in the presence of xanthine oxidase. By measuring the oxygen consumption, a quantitative measure of the hypoxanthine present is obtained. The method does not distinguish between hypoxanthine and xanthine, since half of the xanthine present is measured as well. Since the fraction of xanthine/hypoxanthine is relatively small

– especially in hypoxia – an error of no potential significance is introduced when the results are given as "hypoxanthine". The method has been used by a series of groups [4, 6, 11, 13, 17, 31, 32] and when compared with high pressure liquid chromatography there is an excellent correlation (r = 0.99) between the two methods in the concentration range from 0–187 μmol/l, with a line of identity of 0.94 [25]. With the present method, 0.2 ml of plasma is required and one analysis is performed in 3–4 minutes.

The project was approved by the hospitals ethical committee, and written informed consent was obtained from the mothers.

3 Results

Hypoxanthine values in the 50 samples ranged from 0–59 μmol/l. The pH ranged from 7.45 to 6.62, BD from – 3 to 31 mmol/l), and paO_2 from 470 to 16 mm Hg (62.7 –2.1 kPa).

In Fig. 2 are shown the correlations between hypoxanthine and pH (2A), hypoxanthine and BD (2B), and hypoxanthine and paO_2 (2C) in the first blood sample taken (n = 32). As can be seen, there is a negative linear correlation between hypoxanthine and pH:pH = 7.44 – 0.0123x Hypoxanthine, r = –0.80, $p < 0.001$). The relation between hypoxanthine and BD is described by the curve: BD = 0.51x Hypoxanthine –1.6, r = 0.84, $p < 0.001$). The relation between hypoxanthine (Hx) and PaO_2 (mm Hg) fitted best to an exponential curve: $PaO_2 = 137 \times 10^{-0.0159\,Hx}$, r = –0.64, $p < 0.001$).

Sequential studies of the relation between hypoxanthine, BD and pH were performed in some patients without giving more information. (Data not shown).

3.1 Survival

Nine patients died. When the highest hypoxanthine value in each of these patients was compared with the highest hypoxanthine value in the survivors, there was a statistical significant difference between these two groups. Those who died had a mean maximal hypoxanthine value of 28.3 ± 14.6 μmol/l, compared to survivors whose mean maximal hypoxanthine value was 15.6 ± 8.4 μmol/l ($p < 0.0005$, t-test). One baby who died of cardiac arrythmia was excluded from this calculation (hypoxanthine = 10 μmol/l).

Four out of six infants with hypoxanthine levels greater than 25 μmol/l died, while six out of 25 babies with levels lower than or equal to 25 μmol/l died ($p < 0.02$, Chi square test).

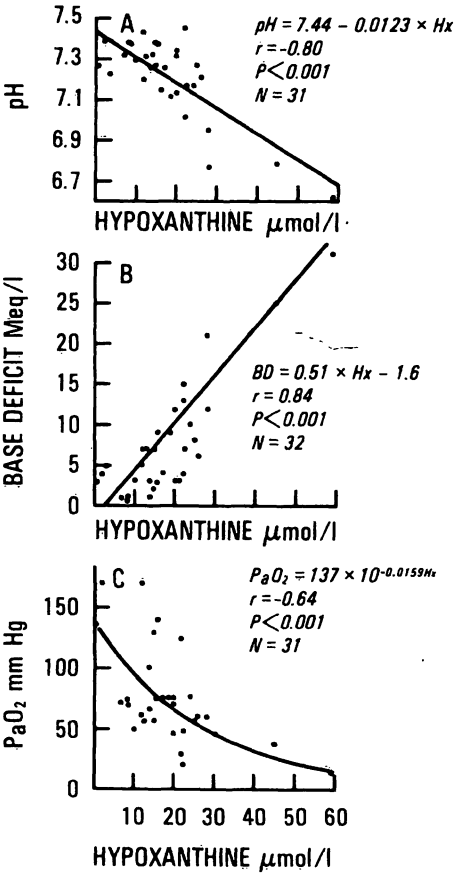

Fig. 2. Linear correlation between arterial pH and plasma hypoxanthine (A), and between BD and hypoxanthine (B). The correlation between PaO_2 and hypoxanthine (Hx) was best fit to an exponential curve (C).

3.2 Complications

Nine patients developed intracranial hemorrhage evaluated by real time ultrasound [3]. Their mean maximal hypoxanthine value was 21.6 ± 8.0 μmol/l; the surviving patients without intraventricular hemorrhage had a mean maximal hypoxanthine value of 13.3 ± 12.8 μmol/l ($p < 0.01$,

t-test). The first hypoxanthine values in patients with intraventricular hemorrhages also were significantly higher than those in patients without ($p < 0.025$, t-test).

Four patients developed bronchopulmonary dysplasia. Their mean maximal hypoxanthine value was 19.3 ± 12.8 μmol/l compared to a mean level of 12.8 ± 7.5 μmol/l in survivors without complications (NS).

3.3 Hypoxanthine and artificial ventilation

There was no significant correlation between hypoxanthine values and mean airway pressure (MAP)*, peak inspiratory pressure (PIP), or FiO_2. Patients requiring high MAP i.e. 11 cmH_2O or more, had higher mean hypoxanthine concentration in first blood sample (23.8 ± 10.6 μmol/l) than babies with MAP lower than 11 cmH_2O (15.9 ± 12.5 μmol/l, $p < 0.05$, t-test).

4 Discussion

These data demonstrate a very good correlation between hypoxanthine and established measurements of hypoxia such as pH and BD. In the study described, the metabolic acidosis was caused by hypoxia, since babies with acidosis from other causes (e.g. renal problems) were not included. The data are in good accordance with the results from animal experiments [21, 22, 26, 31] and show that hypoxanthine can be useful in the hypoxia diagnosis. This will be especially useful when acidosis is present from other causes than hypoxia. Even if a baby is treated with alkali, the hypoxanthine level will still give information about the degree of hypoxia, whilst BD will not. From a theoretical point of view, hypoxanthine is a more "correct" measure of hypoxia, since this metabolite gives more direct information on the intracellular energy level than, for instance, lactate or BD. Since hypoxanthine is measured easily and rapidly by the method we have described [19, 25], this metabolite could well be measured routinely e.g. in the ICU.

Hypoxanthine in body fluids other than plasma also are of interest. Hypoxanthine is elevated in the CSF of hypoxic babies [4, 9, 13, 15]. Elevated hypoxanthine levels also are found in CSF after seizures [13, 15] and meningitis [4, 15]. Care must therefore be exercised when interpreting hypoxanthine values in CSF. High hypoxanthine values have been found in meconium stained amniotic fluid as well and this has been interpreted as a sign of intrauterine hypoxia [16]. Elevated oxypurine excretion in the urine by newborns after intrauterine hypoxia has been reported [12], although in another study on hypoxic newborns no such elevation in urine was found [10]. However, in the latter investigation, it is doubtful whether the investigators actually studied hypoxic babies, since these authors considered all babies with RDS to be hypoxic. In addition, they collected 24 hour samples. However, to detect elevated oxypurines in the urine after hypoxia, the urine would have to be sampled at much closer intervals, probably every 2–4 hours. In dogs, there was a many fold increase in urinary hypoxanthine excretion after hemorrhagic hypotension was relieved. The output of elevated hypoxanthine lasted only about 90 minutes. (SAUGSTAD unpublished data). By considering the time factor, the measurement of the total purine pool (except urate) in urine could be of interest in evaluating a past hypoxic insult.

Thus, the plasma hypoxanthine concentration can serve as a prognostic indicator, both for survival as for complications such as intraventricular hemorrhage. This is in accordance with animal studies, where it was found that the rate of plasma hypoxanthine elevation can serve as an indicator of survival time in hypoxic pigs [20]. In the present study it was found that there was a greater risk for non-survival when plasma hypoxanthine levels exceeded 25 μmol/l. In another study it was found that 50% of the babies with plasma hypoxanthine concentration more than 50 μmol/l died, compared with 33% mortality in the group with levels lower than 50 μmol/l [4].

---

* MAP: $\frac{R \times IT \times PIP + (60 - R \times IT) \times PEEP}{60}$

R: ventilatory rate, IT: inspiration time, PEEP: Positive end expiratory pressure.

There is an exponential relationship between PaO_2 and hypoxanthine, although we anticipated that the hypoxanthine level would start to increase at a certain level of PaO_2, e.g. around 40 mm Hg. Instead it seems that the hypoxanthine level starts to increase as soon as PaO_2 decreases. This finding probably reflects an accumulation of hypoxanthine in the cells, as explained in the introduction, as soon as oxygen delivery to the cells is decreased. Therefore, there may not be a definite limit for PaO_2 at which the cells may be considered hypoxic; i.e. there may be a transition between hypoxic and non-hypoxic states. When the PaO_2 reaches a certain level, e.g. 40 mm Hg, the hypoxanthine level increases more rapidly. A drop in PaO_2 from 100 to 90 mm Hg corresponds to a hypoxanthine rise in plasma of 2.9 μmol/l, while a drop in PaO_2 from 40 to 30 mm Hg elicite hypoxanthine rise in plasma of 7.9 μmol/l according to the present data. The correspondence between the PaO_2 values and the intracellular PO_2 values are, of course, not known, but would be of great interest to establish.

It recently was shown in vitro that hypoxanthine or xanthine, with xanthine oxidase and oxygen, forms free oxygen radicals [8]. These free radicals have the ability to destroy cell membranes by lipid peroxidation. They can attack granulocytes, so that proteolytic enzymes such as elastase are released. The combination of hypoxanthine and 100% O_2 appeared to have a damaging effect on the rat lung [24].

It has been reported that xanthine oxidase is liberated from the liver and is found in plasma in several diseases [28]. In sich newborns, xanthine oxidase could well be found in plasma, although this has never been measured. It is possible that the combination of elevated hypoxanthine levels, high O_2 levels plus xanthine oxidase in plasma are factors which, in combination partly or fully are responsible for conditions such as intraventricular hemorrhage, retrolental fibroplasia, the acute lung damage often seen in premature infants, and the chronic bronchpulmonary dysplasia. Free radical oxygen production theoretically could explain the pathogenesis of a wide variety of conditions in medicine. If our speculations are correct, which could be tested by further animal experiments, hypoxanthine measurements could be of value not only as an indicator of hypoxia, but also as an indicator for the prognosis and as a guideline for the success of treatment.

Summary

Plasma hypoxanthine concentrations have been determined in 50 samples from 32 newborn babies suffering of hypoxia of different degree and etiology. When the hypoxanthine level of the first sample was correlated with pH, base deficit or paO_2, high correlation coefficients were found. A linear relation between hypoxanthine and pH was found according to the equation: $pH = 7.44 - 0.0123x$ Hypoxanthine, $r = -0.80$, $p < 0.001$. The relation between hypoxanthine and base deficit was described by the curve: BD = 0.51x Hypoxanthine − 1.6. $r = 0.84$, $p < 0.001$. The relation between hypoxanthine and paO_2 (mm Hg) fitted best to an exponential curve: $paO_2 = 137 \times 10^{-0.0159Hx}$, $r = -0.64$, $p < 0.001$).

The patients who survived had significantly lower hypoxanthine levels (15.6 μmol/l) than non survivors (28.3 μmol/l) ($p < 0.0005$), when the maximal hypoxanthine levels were compared. Babies with hypoxanthine levels higher than 25 μmol/l had higher risk for dying than when the level was less than 25 μmol/l ($p < 0.02$).

In babies with intracranial hemorrhage there was as well higher hypoxanthine levels than in survivors without hemorrhage. (21.6 vs 13.3 μmol/l, $p < 0.01$). Babies requiring high mean airway pressures (11 cmH_2O or more) had higher hypoxanthine levels in the first blood sample (23.8 μmol/l) when compared with babies with mean airway pressure lower than this level (15.9 μmol/l), $p < 0.05$). It is concluded that **hypoxanthine is a good indicator of hypoxia in the neonate** and this metabolite could be a valuable supplement to the routine diagnostic tools for hypoxia. This metabolite is probably a more specific hypoxia measure than other established hypoxia indicators as lactate, pH or base deficit. In addition hypoxanthine from a theoretical point of view is a reflection of the level of energyrich nucleotides as ATP since it is a direct breakdown product of these.

It could be especially important to measure the hypoxanthine levels since it recently has been shown that hypoxanthine plus xanthine oxidase and oxygen creates oxygen free radicals which have damaging effects to the cell. Thus the combination of hypoxanthine and oxygen in the resuscitated asphyxiated newborn could have adverse effects damaging the cells. We speculate whether this creation of free radicals is responsible for several conditions in neonatology with unknown pathogenesis as intraventricular hemorrhage, retrolental fibroplasia, acute lung damage and bronchopulmonary dysplasia etc.

Keywords: Free radicals, hypoxia, hypoxanthine, neonates, pH.

Zusammenfassung

Plasmahypoxanthinspiegel bei Neugeborenen: Ein spezifisches Anzeichen für Hypoxie

Wir bestimmten in 50 Blutproben von 32 Neugeborenen, die an einer Hypoxie unterschiedlichen Ausmaßes und unterschiedlicher Genese litten, die Plasmahypoxanthinkonzentrationen. Wenn man den Hypoxanthinspiegel der ersten Probe zum pH, Basenmangel oder arteriellem pO_2 setzte, ergab sich ein hoher Korrelationskoeffizient. Die lineare Beziehung zwischen Hypoxanthin und pH wurde durch die folgende Gleichung beschrieben: pH = 7.44 − 0.0123 x Hypoxanthin, r = − 0.80; $p < 0.001$. Die Beziehung zwischen Hypoxanthin und Basenmangel ließ sich beschreiben durch die Kurve: BM = 0.51 x Hypoxanthin − 1.6, r = 0.84; $p < 0.001$. Die Beziehung zwischen Hypoxanthin und arteriellem pO_2 (mmHg) wurde am besten durch die exponentielle Kurve beschrieben: $paO_2 = 137 \times 10^{-0,0159Hx}$, r = − 0.64; $p < 0.001$.

Die überlebenden Neugeborenen hatten signifikant niedrigere Hypoxanthinspiegel (15.6 µmol/l) als die Nichtüberlebenden (28.3 µmol/l) ($p < 0.0005$), wenn man die Höchstspiegel miteinander verglich. Neugeborene mit Hypoxanthinkonzentrationen, die über 25 µmol/l lagen, hatten ein höheres Sterberisiko, als unterhalb dieses Wertes ($p < 0.02$).

Bei Neugeborenen mit intrakraniellen Blutungen fanden sich ebenfalls höhere Hypoxanthinspiegel, als bei überlebenden Kindern ohne Blutungen (21.6 versus 13.3 µmol/l, $p < 0.01$). Neugeborene, die mit mittleren Drukken (11 cm H_2O oder mehr) beatmet wurden, hatten höhere Hypoxanthinkonzentrationen in der ersten Blutprobe (23.8 µmol/l) im Vergleich mit Kindern, die mit niedrigeren Drucken beatmet wurden (15.9 µmol/l, $p < 0.05$).

Wir schließen daraus, daß **der Hypoxanthinspiegel ein guter Indikator für Hypoxie bei Neugeborenen** ist und dieser Metabolit als ein ergänzender Parameter in der Routinediagnostik vermerkt werden kann. Dieser Metabolit ist wahrscheinlich ein spezifischer Parameter für Hypoxie, als andere bisher verwendete Indikatoren wie Laktat, pH oder Basenmangel. Darüber hinaus spiegelt Hypoxanthin von einem theoretischen Gesichtspunkt aus den Metabolismus energiereicher Nukleotide wie ATP wider, weil es ein direktes Abbauprodukt ist.

Es könnte von besonderer Bedeutung sein, die Hypoxanthinkonzentration zu messen, weil erst kürzlich gezeigt wurde, daß Hypoxanthin und Xanthinoxidase und Sauerstoff freie Radikale bilden, die schädigende Effekte auf die Zelle haben. So könnte die Kombination von Hypoxanthin und Sauerstoff zellschädigende Effekte bei wiederbelebten, asphyktischen Neugeborenen haben. Wir erwägen, ob diese Bildung von freien Radikalen für einige Erscheinungen in der Neonatologie mit unbekannter Pathogenese wie intraventrikuläre Blutungen, retrolentale Fibroplasien, akute Lungenschädigung und bronchopulmonale Dysplasie verantwortlich gemacht werden können.

Schlüsselwörter: Freie Radikale, Hypoxanthin, Hypoxie, Neugeborene, pH.

Résumé

Taux d'hypoxanthine plasmatique chez les nouveaux-nés: Un indicateur spécifique d'hypoxie

Les auteurs ont déterminé les concentrations plasmatiques d'hypoxanthine sur 50 échantillons en provenance de 32 nouveaux-nés en hypoxie plus ou moins grave et d'étiologies variées. Des coefficients de haute corrélation ont été trouvés lorsque le taux d'hypoxanthine du premier échantillon correspond au pH, au déficit basique ou à la paO_2. Une relation linéaire entre hypoxanthine et pH a été mise en évidence conformément à l'équation: pH = 7,44 − 0,0123 x hypoxanthine, r = −0,80; $p < 0,001$. La relation entre hypoxanthine et déficit basique est décrite par la courbe: BD = 0,51 x hypoxanthine − 1,6, r = 0,84; $p < 0,001$. La relation entre hypoxanthine et paO_2 (en mm de Hg) s'accorde au mieux avec une courve exponentielle: $paO_2 = 137 \times 10^{-0,0159Hx}$, r = − 0,64; $p < 0,001$.

Les patients ayant survécu avaient des taux d'hypoxanthine significativement plus bas (15,6 µmol/l) que les autres (28,3 µmol/l) ($p < 0,0005$), si l'on compare les résultats les plus élevés. Les nouveaux-nés ayant des taux d'hypoxanthine supérieurs à 25 µmol/l ont un risque de mortalité plus élévé que ceux dont le taux est inférieur à 25 µmol/l ($p < 0,02$). De même les taux d'hypoxanthine sont plus élévés chez les nourissons avec hémorragie intracranienne que chez les autres (21,6 contre 13,3 µmol/l, $p < 0,01$). Les enfants nécessitant des pressions ventilatoires élevées (11 cm H_2O ou plus) ont des taux d'hypoxanthine plus élevés dans le premier échantillon sanguin (23,8 µmol/l) que ceux des enfants nécessitant des pressions inférieures à ce niveau (15,9 µmol/l), $p < 0,05$.

On peut conclure **que l'hypoxanthine est un bon indicateur d'hypoxie chez le nouveau-né** et que ce métabolite peut êntre un complément valable pour le diagnostic d'hypoxie, en routine. Ce métabolite mesure probablement l'hypoxie de façon plus spécifique que les autres indicateurs tels que lactate, pH ou déficit basique. En outre, d'un point de vue théorique, l'hypoxanthine est le reflet du niveau des nucléotides riches en énergie tels que l'ATP puisqu'il représente un produit direct de leur dégradation.

Il pourrait être tout particulièrement important de déterminer les taux d'hypoxanthine puisqu'il a été récemment mis en évidence que l'hypoxanthine en présence de xanthine oxydase et d'oxygène provoque la formation de radicaux libres d'oxygène qui ont des effets nuisibles pour la cellule. C'est pourquoi l'association d'hypoxanthine et d'oxygène chez les nouveaux-nés asphyxiques réanimés peut avoir des effets nuisibles lésant les cellules. Les auteurs soulèvent la question de savoir si cette formation de radicaux libres n'est pas responsable d'un certain numbre de troubles néonataux de pathogénie inconnue tels que Hémorragie intraventriculaire, fibrodysplasie retrolentale, lésions pulmonaires aigües et dysplasie bronchopulmonaire etc.

Mots-cles: Hypoxanthine, hypoxie, nouveaux-nés, pH, radicaux libres.

Bibliography

[1] AASEN, A. O., O. D. SAUGSTAD: Hypoxanthine in lethal canine endotoxin shock. Circ. Shock 6 (1979) 158

[2] ATKINSON, D. E.: Cellular energy metabolism and its regulation. Academic Press, New York 1977

[3] BEJAR, R., V. CURBELO, R. COEN, G. LEOPOLD, H. JAMES, L. GLUCK: Diagnosis and follow-up of intraventicular and intracerebral hemorrhages by ultrasound studies of infants brain through the fontanelles and sutures. Pediatrics 66 (1980) 661

[4] BERTHOLD, F.: Hypoxanthinbestimmung im Plasma neugeborener und junger Säuglinge als Maß für die Gewebehypoxia. Medical Dissert. Medizinische Akademie Carl Gustaf Carus, Dresden 1977

[5] BOOTH, V. H.: The specificity of xanthine oxidase. Biochem. J. 32 (1938) 494

[6] BRATTEBY, L. E., S. SWANSTRÖM: Hypoxanthine concentration in plasma during the first two hours after birth in normal and asphyxiated infants. Pediatr. Res. 16 (1982) 152

[7] COHEN, R. D., H. F. WOODS: Clinical and biochemical aspects of lactic acidosis. Blackwell Scientific Publications, Boston 1976

[8] FRIDOVICH, I.: The biology of oxygen radicals. Science 201 (1978) 875

[9] HARKNESS, R. A., R. J. SIMMOND, M. C. O'CONNOR: Hypoxic effects on purine metabolism studied with high pressure liquid chromatography. In: ARPADO, A., R. W. E. WATTS, C. H. M. M. DE BRUYN (Eds.): Purine metabolism 111. Plenum press, New York 1980

[10] JENSEN, M. H., M. M. BRINKLØV, K. LILLQUIST: Urinary loss of oxypurines in hypoxic premature neonates. Biol. Neonate 38 (1980) 123

[11] LUN, A., R. POHLE, A. HARTWIG, W. IHLE, J. GROSS: Verhalten der Hypoxanthinkonzentration im Plasma bei Neugeborenen und Kindern mit Herzfehlern. Dtsch. Gesundh.wes. 35 (1980) 1006

[12] MANZKE, H., K. DÖRNER, J. GRÜNITZ: Urinary hypoxanthine, xanthine, and uric acid excretion in newborn infants with perinatal complications. Acta Paed. Scand. 66 (1977) 713

[13] MANZKE, H., W. STAEMMLER, K. DÖRNER, H. DOOSE: Erhöhte Hypoxanthinkonzentration im Liquor nach zerebralen Anfällen. In: DOOSE, H., G. GROSS-SELBEKK (Eds.): Epilepsie 1978. Thieme, Stuttgart 1979

[14] MATSUMOTO, S. S., K. O. RAIVIO, J. E. SEEGMILLER: Adenine nucleotide degradation during energy depletion in human lymphoblasts. J. Biol. Chem. 254 (1979) 8956

[15] MEBERG, A., O. D. SAUGSTAD: Hypoxanthine in cerebrospinal fluid in children. Scand. J. clin. Lab. Invest. 57 (1978) 281

[16] O'CONNOR, M. C., R. A. HARKNESS, R. J. SIMMOND, F. E. HYTTEN: Raised hypoxanthine, xanthine, and uridine concentrations in meconium stained amniotic fluid during labour. Brit. J. Obstet. Gynaec. 88 (1981) 375

[17] O'CONNOR, M. C., R. A. HARKNESS, R. J. SIMMOND, F. E. HYTTEN: The measurement of hypoxanthine, xanthine, inosine, and uridine in umbilical cord blood and fetal scalp blood samples as a measure of fetal hypoxia. Brit. J. Obstet. Gynaec. 88 (1981) 381

[18] SAUGSTAD, O. D.: Hypoxanthine as a measurement of hypoxia. Pediat. Res. 9 (1975) 158

[19] SAUGSTAD, O. D.: The determination of hypoxanthine and xanthine with a PO_2-electrode. Pediat. Res. 9 (1975) 575

[20] SAUGSTAD, O. D., A. O. AASEN: Plasma hypoxanthine levels as a prognostic aid of tissue hypoxia. Europ. Surg. Res. 12 (1980) 123

[21] SAUGSTAD, O. D., A. O. AASEN, Ø. HETLAND: Plasma hypoxanthine levels in pigs during acute hypoxemia. Europ. Surg. Res. 10 (1978) 314

[22] SAUGSTAD, O. D., G. BØ, T. ØSTREM, A. O. AASEN: Hypoxanthine levels of plasma during hypoxemia in dogs. Europ. Surg. Res. 9 (1977) 23

[23] SAUGSTAD, O. D., S. GUNDERSEN, A. FLOKKMANN: Elevation of plasma hypoxanthine in patients with malignant lymphomas. Submitted

[24] SAUGSTAD, O. D., M. HALLMAN, J. L. ABRAHAM, C. COCHRANE, L. GLUCK: Hypoxanthine and O_2 induced lung damage. A basic mechanism mediated by free-radicals@ Pediat. Res. 16 (1982) 316

[25] SAUGSTAD, O. D., W. E. WUNG, S. B. HOWELL, L. GLUCK: Determination of plasma hypoxanthine: A comparison of high pressure liquid chromatographic and oxygen consumption methods. Analyt. Biochem. 122 (1982) 159

[126] SAUGSTAD, O. D., T. ØSTREM: Hypoxanthine and urate levels of plasma during and after hemorrhagic hypotension. Europ. Surg. Res. 9 (1977) 48

[27] SEEGMILLER, J. E.: Purine metabolism. Arthr. Rheum. (Suppl.) 18 (1975) 681

[28] SHAMMAA, M. H., S. M. NASHRULLAH, U. A. S. AL-KHALIDI: Serum xanthine oxidase. Amer. J. Digest. Dis. 18 (1973) 15

[29] SWANSTRÖM, S., L. E. BRATTEBY: Hypoxanthine as a test of perinatal hypoxia as compared to lactate, base deficit, and pH. Pediat. Res. 16 (1982) 156

[30] THIRINGER, K.: Cord plasma hypoxanthine as a measure of foetal asphyxia. Comparison with clinical assessment and laboratory measures of asphyxia in newborn infants. Acta Paed. Scand. In press

[31] THIRINGER, K., O. D. SAUGSTAD, I. KJELLMER: Plasma hypoxanthine in exteriorized acutely asphyxiated fetal lambs. Pediat. Res. 14 (1980) 905

[32] TUCHSCHMID, P. E., U. BOUTELLIER, E. A. KOLLER, G. V. DUC: Comparison of hypoxanthine, lactate, and ECG signs as indicators of hypoxia. Pediat. Res. 15 (1981) 28

[33] WUNG, W. E., S. B. HOWELL: Hypoxanthine concentrations in human biological fluids and their significance for purine antimetabolic activity. Canc. Res. In press

[34] YOSHINO, M., R. HAYASHI, Y. KATSUMATA, S. MORI, G. MITARAI: Blood oxypurines and erythrocyte 2,3-diphosphoglycerate levels at high altitude hypoxia. Life Sci. 27 (1980) 1265

Received May 14, 1982. Accepted August 11, 1982.

O. D. Saugstad, M.D.
Department of Paediatrics (17)
Ulleval Sykehus
Oslo 1
Norway