Comparison of Hypoxanthine, Lactate, and ECG Signs as Indicators of Hypoxia

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Summary

High altitude-induced hypoxemia in 26 young adults was used to compare hypoxia parameters such as blood lactate, hypoxia-induced electrocardiogram signs, and the recently proposed plasma hypoxanthine concentration. At a PaO_2 of 30 mm Hg, no elevation in hypoxanthine and small increase in lactate was observed. Minimal leg exercise was added to further increase hypoxia during hypoxemia. A significant increase in lactate and considerable ST-T depression in electrocardiogram indicated hypoxia, but no change in plasma hypoxanthine was found. Work-dependent hyperventilation as a main cause of lactate elevation was excluded. Blockade of hypoxanthine breakdown by allopurinol *in vivo* increased plasma hypoxanthine levels, but hypoxemia with or without leg exercise failed to consistently increase this level further. Elevations of blood lactate above the normal range were found at a PaO_2 of 30 mm Hg and below.

Speculation

The increased plasma hypoxanthine concentration in newborns after delivery may result from other factors, additional to hypoxia, because in mild hypoxemic hypoxia in healthy adults hypoxanthine was not elevated, although blood lactate was already increased. Cellular hypoxia is indicated by beginning of lactate elevation at a threshold level of PaO_2 of 30 mm Hg.

Hypoxia has been recognized as the main cause of brain damage in the perinatal period. Because in clinical situations lack of cellular oxygen cannot be directly measured, indirect parameters to detect this condition have been studied. Three types of signals have been used in clinical perinatology: blood oxygen transport variables, cellular activity, and metabolic products.

Parameters of oxygen transport (arterial or transcutaneous PO_2 and oxygen saturation) are useful if hypoxia is caused by hypoxemia (for definitions, see Ref. 4). They are unable to detect hypoxia due to reduced perfusion and cannot be used as markers of past hypoxia. Parameters of cellular activity which are clinically available such as variations in heart rate and respiratory patterns are accepted as screening parameters, but they are influenced by a number of other factors, and the interpretation of their variations is difficult. The relation of electroencephalogram to brain hypoxia is now beginning to be documented, but not yet introduced in routine (9).

Changes in metabolic products, particularly elevation of blood lactate, represent a useful signal of anaerobic glycolysis. Because blood lactate disappears quickly after correction of hypoxia and may also be elevated in the absence of hypoxia (8, 10, 24), obstetricians and neonatologists are still in search of other indicators.

Hypoxanthine, a purine metabolite, was found to be elevated in severe hypoxic conditions in animal models (21, 22) and newborns (18), but no clear correlation between plasma hypoxanthine levels

and severity of intrauterine hypoxia could be found (15). Because these situations cannot be considered to be pure hypoxia, we looked for a model of well-defined and isolated hypoxia in man. We studied the following parameters of hypoxia: hypoxanthine, lactate, and electrocardiogram (ECG) alterations in adults exposed to an altitude of 6000 m in a low-pressure chamber.

MATERIALS AND METHODS

SUBJECTS

Twenty-six young male adults were asked to participate in the experiment. Their state of health was checked by clinical examinations and ECG during exercise of 150 W or more. The informed consent of all participants was obtained.

LOW-PRESSURE CHAMBER

The system described in detail by Laciga and Koller (13) was used. The test person was supine for about 1 hr before and during the experiment (2 to 3 hr) and was controlled by a physician present in the chamber. No experiment had to be terminated because of subjective inconvenience or deterioration as was noted at 7000 m (14).

EXPERIMENTAL PROCEDURE

A standardized procedure was followed, and major deviations are mentioned in "Results." Ascent and descent were carried out at a rate of 750 m/min and were interrupted every 1000 m for 6 to 8 min. The stay at maximal altitude, however, lasted 20 to 30 min. ECG and circulatory and respiratory parameters were registered at each altitude level and twice at 6000 m. Blood samples were obtained from a cubital vein catheter which was placed before the beginning of the experiment. In nine experiments, the test person performed an exercise consisting of leg movements (20 watts, 4 min) at ground level as well as at 6000 m.

RESPIRATION

Respired air was analyzed during one min at each altitude level by a mass spectrometer (M-3, MAT; Varian). Alveolar PaO_2 and PaCO_2 were calculated from the corresponding endexpiratory values. Ventilation was recorded by a Fleisch-pneumotachograph.

CIRCULATION AND ELECTROCARDIOGRAPHY

Blood pressure was measured at each altitude level, and heart rate was followed continuously. The electrocardiogram was obtained as described elsewhere (13). Standard bipolar limb leads (Einthoven) and unipolar precordial leads (Wilson) were recorded; V_2 , V_4 , and V_6 were monitored as a control of the test person. ST-T changes were analyzed by dividing the segment in four equal intervals, yielding five regularly distributed points. Amplitudes of corresponding points were compared by paired *t* tests and aver-

aged to visualize changes of a group of probands during ascent to 6000 m.

BLOOD SAMPLING

Blood was collected from the permanent vein catheter in a heparinized syringe. One part of the sample was used for blood gas measurements (AVL; Schaffhausen, Switzerland), the other was immediately deproteinized for lactate determination or centrifuged, and the plasma was frozen for hypoxanthine measurements.

CHEMICAL ANALYSIS

Lactate. Supernatants of the deproteinized duplicate blood samples (1 volume of blood in 2 volumes of ice-cold 0.6 M perchloric acid) were obtained within 4 hr after collection by centrifugation and were stored frozen at -20°C until lactate was determined with a commercially available kit (Böhringer, Mannheim, West Germany).

Hypoxanthine. Two methods were used. During eight preliminary experiments, hypoxanthine was determined by the Po_2 method introduced by Saugstad (19) with the following modifications shown to have no influence on the accuracy of the original technique. The micro- pO_2 electrode (E 5021 a; Radiometer, Copenhagen, Denmark) was operated at 25°C rather than at 37°C and only one-half of catalase activity and only one-fifth of xanthine oxidase activity was used. Plasma samples stored at -20°C for up to 2 wk were centrifuged ($8000 \times g$ for 30 sec) before the determination. Differences in Po_2 before and after addition of xanthine oxidase were calculated from the recorded Po_2 traces to correct for drifting baselines. The electrode was calibrated with water-saturated atmospheric air at a known barometric pressure. Calibration curves with standard hypoxanthine solutions were obtained daily.

The plasma concentration of hypoxanthine in the remaining 18 subjects was determined by a newly developed method. Figure 1 depicts the combination of hydrogen peroxide-producing oxidation of hypoxanthine with the detection of the former (6) by the enzyme aldehyde dehydrogenase (EC 1.2.1.5). An assay mixture containing 10% (w/v) of ethanol, 13 IU/ml of catalase, 6 IU/ml of aldehyde dehydrogenase, 10 mM of NADP, 50 mM of sodium pyrophosphate and 50 mM of potassium chloride, adjusted to a final pH of 7.4, was prepared daily and kept on ice. Eight-tenths ml of this assay mixture and 0.2 ml of plasma (or 0.9% sodium chloride as blank or 5 to $50 \mu\text{M}$ hypoxanthine standard solution) was placed in a 1 cm path cuvette. The absorbance at 340 nm was recorded in a spectrophotometer thermostated to 37°C . After warming up, $5 \mu\text{l}$ of xanthine oxidase solution (4 IU/ml in 50 mM sodium pyrophosphate, 50 mM potassium chloride, pH 7.4) were added, and the increase in the absorbance was followed to the end

point of the reaction (within 5 min). Hypoxanthine concentration was calculated from the change in absorbance at 340 nm, corrected for the blank reading, and read on a daily prepared calibration curve.

Chemicals. All reagents were of analytical grade. Xanthine oxidase (EC 1.2.3.2), 0.4 IU/mg, and catalase (EC 1.11.1.6), 65,000 IU/mg, were obtained as crystal suspensions, and aldehyde dehydrogenase (EC 1.2.1.5), 15 IU/mg, was obtained as lyophilized powder from Böhringer (Mannheim, West Germany). The crystallized enzymes were centrifuged, and the sediments were made up to the initial volume with the appropriate buffer before their use. Hypoxanthine was obtained from Merck (Darmstadt, West Germany), dissolved in 0.1 M sodium-carbonate, and then adjusted to pH 8.0 and used as standard stock solution for not longer than one day.

Statistical Analyses. Paired two-tailed *t* test was used to determine the significance of the data obtained (17).

RESULTS

COMPARISON OF THE TWO METHODS TO DETERMINE HYPOXANTHINE

The detection limit of Po_2 method (19) turned out to be 4 to 6 μM in hypoxanthine, corresponding to a change in Po_2 of 3 to 4 mm Hg of the initial Po_2 of 145 mm Hg (water-saturated room air at 25°C). We were unable to detect changes of plasma hypoxanthine concentrations within the normal range of 0 to $5 \mu\text{M}$ by this technique, which is suitable to determine rapidly and easily elevations above the normal range. With the aldehyde dehydrogenase method, the detection limit was less than $2 \mu\text{M}$ of hypoxanthine, corresponding to a change in absorbance of 0.002 (ΔE).

The normal values for hypoxanthine determined by this method in plasma of adults were $3.2 \pm 2.5 \mu\text{M}$; range, 0.4 to $9.9 \mu\text{M}$ ($n = 13$) in agreement with the earlier reported values (11, 19) but slightly higher than those found by Kugler (12) ($1.3 \pm 1.0 \mu\text{M}$) and by Remme *et al.* (16) ($1.2 \pm 0.2 \mu\text{M}$).

EFFECT OF HYPOXEMIA ON PLASMA LACTATE, HYPOXANTHINE, AND ECG

Fifteen healthy volunteers exposed to an altitude of 6000 m during 27 ± 3 min showed a decrease in PaO_2 from 94.5 ± 3.3 mm Hg at ground level to 30.9 ± 2.9 mm Hg. No change of plasma hypoxanthine was observed in seven subjects where it was determined by the Po_2 technique. Figure 2 summarizes the findings in the further eight experiments. No increase in plasma hypoxanthine, determined by the aldehyde dehydrogenase method could be observed throughout the experiments. Blood lactate was not elevated at the time of minimal Po_2 but some 10 to 20 min later during descent (4000 m) when compared to the initial value at 450 m ($P < 0.05$). No elevation above the normal range of 1.11 to 1.33 mM (5) was detectable. The ST-T segments of the ECG of both groups of the above mentioned experiments ($n = 15$) at ground level were compared with those at 6000 m. The S-T segment was significantly depressed ($P < 0.01$) in the left precordial leads (Fig. 3, V_5), in contrast to the right precordial leads (Fig. 3, V_2). The voltage of the T-wave was decreased in all leads, the flattening, however being more pronounced in V_5 ($P < 0.001$) than in V_2 ($P < 0.01$). The Q-T interval was shortened in absolute terms at 6000 m, but relatively prolonged with regard to the increased heart rate.

EFFECT OF EXERCISE AND HYPOXEMIA ON PLASMA HYPOXANTHINE AND LACTATE

Influence of minimal work load on hypoxia parameters was studied in five experiments. Figure 4 shows the absence of a hypoxanthine elevation due to work at both altitudes, whereas lactate increases significantly at 6000 m ($P < 0.05$) but not at 450 m after work. Table 1 summarizes the changes due to exercise at both altitudes and includes respiratory data inasmuch as they are

Fig. 1. Reaction pathway used for the modified determination of hypoxanthine (see "Materials and Methods").

Fig. 2. PaO_2 (---), blood lactate (—), and plasma hypoxanthine (—) (mean values ± 1 S.D.) during exposure of eight healthy adults to reduced atmospheric pressure.

Fig. 3. Comparison of ST-T segments of ECG leads V_2 and V_5 at ground level (mean ± 1 S.D.) (—) and at 6000 m (mean, -1 S.D.) (---) of 15 healthy adults exposed to reduced atmospheric pressure.

essential in the interpretation of lactate concentration because alkalosis can cause an elevation of lactate (24). In one case, given separately in Table 1 and excluded from Figure 4, marked hyperventilation (see $\dot{V}$, PaCO_2 , pH) occurred during exercise resulting in excessive increase in lactate. In the other cases, a further increase in ventilation was excluded considering pH and PaCO_2 . Heart rates increased significantly ($P < 0.001$) during ascent to 6000 m, and blood pressure showed only small decrease of the diastolic values.

EFFECT OF EXERCISE AND HYPOXEMIA ON PLASMA HYPOXANTHINE AND LACTATE AFTER *IN VIVO* INHIBITION OF HYPOXANTHINE BREAKDOWN

To distinguish hypoxanthine production from its steady state concentration in the plasma, the purine breakdown was inhibited at the enzymatic conversion of hypoxanthine to xanthine and to urate by the xanthine oxidase inhibitor allopurinol. Thus the subjects were given 3×100 mg Zyloric (Wellcome) during 3 days

preceding the exposure to high altitude. This caused a significant elevation ($P < 0.001$) of plasma hypoxanthine from $3.2 \pm 2.5 \mu\text{M}$ ($n = 13$) to $10.9 \pm 4.9 \mu\text{M}$ ($n = 6$). Figure 5 demonstrates that leg exercise as stated in the preceding paragraph causes no change in plasma hypoxanthine at either altitude, whereas lactate is consistently elevated by work at 6000 m but not at ground level. Table 2 summarizes the work-induced changes including blood gas values. Data on PaCO_2 changes and respiratory minute volumes exclude an augmented ventilation caused by exercise in these experiments. A significant increase in heart rates ($P < 0.05$) and only minimal changes of blood pressure were noted during ascent to 6000 m. To rule out inhibitory effects of plasma of allopurinol-treated persons on xanthine oxidase used to quantitate hypoxanthine, the recovery of an added hypoxanthine standard was checked. In Figure 6, lactate concentrations of six experiments with exercise were plotted against the corresponding PaO_2 and mean lactate values were calculated in PaO_2 groups of 10 mm Hg. The significance of the changes in mean lactate were tested against the mean lactate in the group of PaO_2 of 90 to 100 mm Hg using the t test for small samples with unequal variance (17).

DISCUSSION

No clinical parameter to detect past hypoxia is available at present. Only concomitant or very recent hypoxic events can be detected by heart rate monitoring during delivery (7) or by blood lactate measurement (3). An extension of the lag between time of hypoxia and moment of its detection as well as a more sensitive factor would be of interest for perinatologists concerned with the problem of intrauterine hypoxia. Reports that plasma concentration of the purine metabolite hypoxanthine depends on the oxygen supply to tissue in animal models (21) as well as in newborns (18) were of special interest because it might be the factor looked for. The sensitivity in detecting hypoxia of this newly found parameter is compared in this study with the classical ones, like increase in blood lactate and depression of the ST-T segment of the ECG. Because QT changes depend on heart-rate, their interpretation is more difficult than those of ST-T changes, and only the latter are further analyzed. Because of the complexity of changes in metabolism, respiration, and circulation at birth, newborns are not good models of pure hypoxemic hypoxia, particularly because cellular breakdown in ischemia and severe acidosis are a source of purine metabolites independent of hypoxia (2, 25) (see Fig. 7). We considered that hypoxemia in healthy adults provides a better condition for differentiating between hypoxemic hypoxia and other situations possibly increasing production of hypoxanthine in man.

Table 1. Influence of exercise at 450 and 6000 m on plasma hypoxanthine, blood lactate, and respiratory and circulatory data in four healthy adults¹

Altitude (m) (work load of 20 W, 4 min)	Paco ₂ (mm Hg)	Hypoxanthine (μ M)	Lactate (mM)	V (l/min)	pH (venous)	Paco ₂ (mm Hg)	Heart rate (min ⁻¹)	Blood pressure (systolic/ diastolic) (mm Hg)
450								
Before work	96.4 $\pm$ 7.0 ² (95.6) ³	3.3 $\pm$ 2.3 (1.0)	1.00 $\pm$ 0.30 (1.48)	8.1 $\pm$ 1.5 (9.2)	7.30 $\pm$ 0.04 (7.26)	37.1 $\pm$ 2.8 (40.6)	59 $\pm$ 8 (61)	124/65 $\pm$ 6/9 (110/60)
After work	98.1 $\pm$ 5.3 (95.1)	4.7 $\pm$ 1.6 (0.8)	0.91 $\pm$ 0.26 (1.34)	8.5 $\pm$ 1.4 (9.2)	7.29 $\pm$ 0.04 (7.26)	36.8 $\pm$ 2.1 (40.6)	63 $\pm$ 11 (58)	123/58 $\pm$ 5/13 (110/60)
6000								
Before work	34.5 $\pm$ 2.5 (39.1)	3.1 $\pm$ 2.4 (0.9)	1.08 $\pm$ 0.24 (1.12)	11.2 $\pm$ 1.5 (15.7)	7.36 $\pm$ 0.02 (7.27)	29.3 $\pm$ 0.7 (28.2)	86 $\pm$ 11 (82)	130/50 $\pm$ 8/9 (130/55)
After work	30.7 $\pm$ 1.5 (52.0)	2.8 $\pm$ 2.7 (0.5)	1.41 $\pm$ 0.42 ² (2.00)	9.5 $\pm$ 1.2 (32.7)	7.36 $\pm$ 0.03 (7.36)	28.7 $\pm$ 1.0 (13.5)	87 $\pm$ 9 (83)	139/39 $\pm$ 28/6 (125/55)

¹ Significance of change during work is estimated by paired *t* test.² Mean $\pm$ S.D. [*n* = 4].³ Numbers in parentheses, values at one additional subject hyperventilating upon work at 6000 m.⁴ *P* < 0.05.

In the experiments reported here, mean minimal PaO₂ of 30.9 mm Hg can be considered as mild hypoxia (23), but it should be pointed out that further decrease in PaO₂ leads to signs of serious deterioration as unconsciousness, ectopic heart beats, or cardiac arrest (14). With the exception of two occasions, no elevation of plasma hypoxanthine was found in the 26 reported experiments.

In two cases, hypoxanthine increased upon work at 6000 m in individuals with allopurinol-blocked hypoxanthine breakdown, but the same effect was missing in the other two subjects of the same experimental group. Lack of increase of hypoxanthine during exposition to hypoxemia could have the following reasons: (1) insensitivity of the detection of hypoxanthine; (2) insufficient hypoxia; and (3) prevention of accumulation of hypoxanthine by too rapid degradation *in vivo*.

(1) Normal values of hypoxanthine are near the detection limit of the Po₂ method (see "Materials and Methods"), and changes not exceeding the normal range can not be ruled out. Two- to three-fold increase in sensitivity was achieved by the newly developed method, and no differences between the normal values obtained with the two alternative methods were observed. Even with increased sensitivity, no elevation of hypoxanthine levels was noted during hypoxemia. Inasmuch as only elevations larger than the considerable variations of the normal values are of diagnostic interest, a further increase in sensitivity of the hypoxanthine detection would be of limited value.

(2) To test whether the experimental hypoxemia led to hypoxia, two classical parameters, increase in lactate and depression of ST-T segment of the ECG, were concomitantly analyzed. Small but significant changes of lactate concentration and considerable hypoxia-induced ECG changes particularly in the left precordial leads indicated the presence of hypoxia. In experiments with additional slight work, hypoxanthine remained unchanged although a further increase in lactate occurred. This additional work did not cause changes either in lactate or in the ECG at normal altitude. No lactate/pyruvate ratios were measured to exclude that hyperventilation was the cause of rise in lactate during work. The statistically significant increase in blood-pH during work at 6000 m (Table 2) is too small to be of biologic relevance and is contrasted by unchanged Paco₂ and V, thus strongly suggesting that augmentation of lactate was independent of hyperventilation. Duration of maximal hypoxemia was in the order of 30 min. Separate analyses of two experiments with a prolonged stay (60 min) at 6000 m showed no difference to the normal experiments in respect to hypoxanthine concentrations. Conclusion drawn from these data are therefore limited to mild, acute hypoxia. Similarly, Kugler (12) did not find significant elevations of coronary sinus hypoxanthine concentrations, but did find considerable elevations of inosine and lactate during pacing-induced angina pectoris. Remme *et al.* (16) found in analogous pacing experiments small but significant elevations of coronary sinus hypoxanthine, but none in the arterial blood, indicating that hypoxanthine release of the ischemic heart muscle is too small to be detected systemically. It was further shown that lactate occurred earlier in gradual pacing, which supports our findings.

(3) Increased production of hypoxanthine may remain undetected if its degradation is rapid enough to prevent its accumulation in spite of increased production. Among the breakdown products of ADP (Figure 7), hypoxanthine can be considered as a good parameter of hypoxia because the xanthine oxidase reaction is oxygen dependent. If, on the other hand, the latter reaction is less sensitive to hypoxia than the degradation of ATP, elevation of hypoxanthine would be less than expected or even absent. Blockade of the enzyme xanthine oxidase *in vivo* would therefore increase the sensitivity of the plasma hypoxanthine concentration as a hypoxia parameter. Pharmacologic inhibition of the enzyme by allopurinol increased hypoxanthine levels in the absence of hypoxia, confirming its predicted action *in vivo*. No elevation of hypoxanthine levels caused by hypoxia was observed in four experiments with allopurinol blockade, whereas changes were consistently found for lactate and ECG parameters. No conclu-

Fig. 4. P_{aO_2} (----), blood lactate (—), and plasma hypoxanthine (—) (mean values $\pm$ 1 S.D.) during hypoxemia and exercise (20 W during 4 min: shaded areas) in four healthy adults exposed to reduced atmospheric pressure.

Fig. 5. P_{aO_2} (----), (mean values $\pm$ 1 S.D.), blood lactate (—), (mean values, $\pm$ 1 S.D.) and plasma hypoxanthine (—) (mean values $\pm$ 1 S.D.) during hypoxemia and exercise (20 W during 4 min: shaded areas) in four healthy adults with allopurinol-blocked hypoxanthine breakdown exposed to reduced atmospheric pressure.

Table 2. Influence of exercise at 450 and at 6000 m on plasma hypoxanthine, blood lactate, and respiratory and circulatory data in four healthy adults with allopurinol-blocked hypoxanthine breakdown¹

Altitude (m) (work load of 20 W, 4 min)	P_{aCO_2} (mm Hg)	Hypo- xanthine (μ M)	Lactate (mM)	$\dot{V}$ (l/min)	pH (venous)	P_{aO_2} (mm Hg)	Heart rate (min^{-1})	Blood pressure (systolic/ diastolic) (mm Hg)
450								
Before work	92.5 ± 4.7^2	11.7 ± 4.9	0.87 ± 0.14	6.8 ± 0.9	7.30 ± 0.05	37.1 ± 1.9	62 ± 7	$121/59 \pm 9/3$
After work	94.5 ± 5.9	9.2 ± 5.4	0.83 ± 0.10	7.0 ± 1.2	7.29 ± 0.04	37.6 ± 2.1	60 ± 7^3	$116/56 \pm 8/3$
6000								
Before work	35.8 ± 7.0	11.0 ± 5.9	0.92 ± 0.07	11.4 ± 3.4	7.36 ± 0.07	26.7 ± 4.9	81 ± 18	$116/61 \pm 21/9$
After work	28.8 ± 3.3	11.0 ± 5.6	1.29 ± 0.21^3	10.5 ± 1.7	7.38 ± 0.07^4	26.0 ± 3.4	80 ± 8	$120/46 \pm 7/10$

¹ Significance of change during work is estimated by paired *t* test.

² Mean $\pm$ S.D. ($n = 4$).

³ $P < 0.05$.

⁴ $P < 0.01$.

sions concerning half-life of hypoxanthine can be made from our data, but differences in arteriovenous concentrations of the metabolite in dogs (21) suggest that its rapid breakdown is possibly caused by xanthine oxidase activity. Even in pigs which possess

no xanthine oxidase in their lung tissue (1), the half-life of hypoxanthine was found to be 40 min and, in the same experiment, less than the half-life of the lactate elevation (20). The presence of a measurable arteriovenous difference of hypoxanthine concentra-

Fig. 6. Correlation of blood lactate concentrations with P_{aO_2} in healthy adults exposed to reduced atmospheric pressure. Mean lactate concentrations (± 1 S.D.) were calculated in P_{aO_2} groups of 10 mm Hg. *, $P < 0.05$; **, $P < 0.01$ as compared to the 90 to 100 mm Hg mean value.

Fig. 7. Schematic pathway of purine catabolism including breakdown of nucleic acids.

tion in human cord blood (15) indicates its rapid clearance from the fetal circulation.

Plasma lactate concentrations in our experiments indicated the beginning of hypoxia. Figure 6 correlates P_{aO_2} with corresponding lactate levels. Beginning lack of cellular oxygen is signaled by this parameter in the range of 50 to 40 mm Hg. Lack of significance of lactate elevation in the group of 20 to 30 mm Hg is due to small number of measurements ($n = 4$). No comparable increase of hypoxanthine with decreasing P_{aO_2} was noted.

From our experiments, we conclude that hypoxanthine in isolated, acute hypoxemic hypoxia in young adults is a less sensitive parameter than lactate and ST and T changes of the ECG. Elevations of hypoxanthine in newborns as reported by Saugstad (18) and confirmed later (15) may be in part due to hypoxia but are probably influenced by other factors, like acidosis or cellular destruction, leading to an increase in purine breakdown.

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