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Cerebrospinal fluid lactate, pyruvate concentration and lactate/pyruvate ratio in newborn infants with perinatal hypoxia and oxygen dependency*

by

M. FEKETE, Maria VINCELLÉR and L. KLUJBER

Department of Paediatrics, University Medical School, Pécs, Hungary

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CSF lactate concentration and the lactate/pyruvate (L/P) ratio were measured in two groups of newborn infants suffering from RDS of various severity and with different final outcome. In newborns who died of RDS complicated with subependymal or intraventricular haemorrhage, significantly higher mean CSF lactate level and L/P ratio were found than in those who survived or in the control patients. As for the individual values, wide variations were found in all groups of newborn infants studied. It is concluded that increased CSF lactate concentration and L/P ratio indicate cerebral hypoxia in general, but the possibility of individual variations of multifactorial origin should also be considered when using these parameters as an indicator of brain hypoxia.

CSF is known to be produced by the choroid plexus and a considerable part of it to originate from the brain's extracellular fluid [5, 8, 12, 13]. Consequently, the CSF can to some extent be taken as a representative of cerebral interstitial fluid, and metabolic alteration of the brain must therefore be reflected in changes in the composition of CSF.

Clinical studies in man and animal experiments proved that the CSF lactate level rises in various pathological conditions of the brain. Increased lactate concentration was observed in case of traumatic brain oedema [6], intracranial hypertension [18], cerebral haemorrhage [7], purulent meningitis [2, 3, 9] and post-anoxic episodes [11, 17]. In principle, increased CSF lactate concentration can be expected in every pathological condition associated with reduced oxygenation and increased anaerobic metabolism of the brain.

Perinatal hypoxia is one of the most serious consequences of disorders of neonatal cardiorespiratory adaptation. Since cerebral hypoxia has a decisive role in survival and/or later quality of life of surviving newborn infants, a direct indicator of brain hypoxia would be needed, which is simple and reliable enough for clinical

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use. CSF lactate concentraton and/or the L/P ratio seem to meet this requirement, but relevant data in hypoxic human neonates are rather scanty.

The present study was undertaken to investigate the CSF lactate and pyruvate levels and the L/P ratio in newborn infants with perinatal hypoxia of various severity. Furthermore, an attempt was made to look for associations between CSF lactate, pyruvate, L/P ratio and various clinical and biochemical parameters in hypoxic newborn infants.

Patients and Methods

A total of 51 newborn infants was studied. They were classified in three groups.

Group I (D): 20 newborn infants, of whom 4 suffered from intrauterine pneumonia and 16 from respiratory distress syndrome. Each neonate died in this group. At postmortem examination, subependymal or intraventricular haemorrhage was found in the 16 patients with IRDS. All patients in this group needed oxygen therapy throughout the time from admission until death. Oxygen was supplied via head-box in 4 cases, CPAP and/or IPPV ventilation was necessary in 16 patients. Mean ($\pm$SD) birthweight and gestational age of the neonates was 1515 ± 452 g and 31 ± 3 week, respectively (Table I).

Group II (SO) consisted of 16 newborns, all of whom survived. IRDS was diagnosed in 5, RDS-II in 11 patients, on the basis of generally accepted clinical and X-ray criteria. All babies in this group required oxygen therapy. In 11 cases oxygen was supplied via head-box and only 5 patients needed CPAP ventilation. Birthweight and gestational age of patients in this group were 2133 ± 726 g and 34 ± 3 week (Table I).

Group III (S): 15 neonates admitted for prematurity or intrauterine growth retardation or some other neonatal condition, but none of them experienced perinatal hypoxia. Birthweight of these patients was 2516 ± 848 g and their gestational age was 36 ± 3 week. All babies survived without requiring oxygen therapy.

Lumbar puncture was performed and CSF obtained from each newborn infant in order to detect intracranial haemorrhage in Groups I and II, and to exclude infection in Group III. Postnatal age of infants at the time of the lumbar tap was calculated in hours. On culturing, all CSF specimens proved to be sterile. If blood stained CSF was obtained and it was due to artificial trauma, the specimen was excluded from further study.

Concentration of lactate [10], pyruvate [10], glucose [16] and protein [10] was measured and the L/P ratio calculated in each sample.

In order to estimate the severity of RDS and oxygen dependency in Groups I and II, the extremes of arterial pH, negative base excess and PCO_2, measured during treatment, were evaluated and compared. Besides, the total amount of bicarbonate infused was calculated as it was supposed that the amount required might to a certain extent reflect the severity of hypoxia and the associated metabolic acidosis. Since neither the onset of hypoxia, nor its exact duration and severity could reliably be estimated, it was assumed that the clinical course and the final outcome together with some characteristic biochemical parameters would reflect the persistent or intermittent hypoxaemia experienced by the patients.

CSF lactate, pyruvate, glucose, protein concentration and L/P ratio of newborns in the three study groups were analysed. Correlation analysis was performed between all CSF parameters measured and gestational age, birthweight, postnatal age at the time of lumbar puncture. In

TABLE I

Some clinical data and biochemical parameters of the three groups of newborn infants studied

	No	Mean	±SD	±SEM	Range
Gestational age, nk					
D	20	31	3	0.6	26—39
SO	16	34	3	0.9	29—42
S	15	36	3	0.7	31—40
Birthweight, g					
D	20	1515	452	101	700—2480
SO	16	2133	726	181	1100—3650
S	15	2516	848	219	1300—4000
Postnatal age at lumbar puncture, h					
D	20	31	28	6	2— 90
SO	16	21	19	5	4— 84
S	15	32	33	8	1— 102
Total amount of bicarbonate infused (mEq/kg)					
D	20	9.8	3.2	0.7	3.4—18.7
SO	16	4.3	3.4	0.8	0.0 —10.4
S	15	0.2	0.5	0.1	0.0 — 2.0
Extreme of pH, -BE and pCO_2 during treatment					
Arterial pH					
D	20	7.17	0.07	0.01	7.00— 7.28
SO	16	7.24	0.07	0.01	7.11— 7.41
S	15	7.32	0.06	0.01	7.14— 7.40
Negative base excess (mEq/l)					
D	20	10.3	4.9	1.0	5.2 —20.0
SO	16	8.7	4.7	1.1	1.0 —18.5
S	15	7.3	3.7	0.9	1.0 —14.3
Plasma CO_2 (mm Hg)					
D	20	66	20	4	37— 102
SO	16	52	15	3	26— 76
S	15	37	7	1	29— 50

Abbreviations: D = newborn infants who died
SO = infants who survived but oxygen therapy was needed
S = infants who survived without oxygen therapy

addition, the significance of correlation between lactate-pyruvate, lactate-L/P ratio, lactate-bicarbonate, lactate-glucose, lactate-protein, pyruvate-glucose, pyruvate-protein, protein-L/P ratio, glucose-L/P ratio and bicarbonate-L/P ratio was tested.

For statistical analysis, standard methods were used.

Results

Table I shows the clinical data of patients in the three groups and some biochemical parameters such as bicarbonate requirement and the least compensated acidotic state throughout treatment. Gestational age and birthweight of newborns who died (Group-I(D) was significantly less than those of the survivors, either with oxygen therapy (Group-II(SO), $p < 0.05$) or without it (Group-III(S), $p < 0.001$). Mean postnatal age of infants at the time of lumbar puncture was similar ($p < 0.05$), i.e. 21—32 hours, but individual values scattered widely, due to the different clinical course and the indications for CSF analysis. Neither gestational age nor birthweight correlated significantly with either parameter studied, but between postnatal age and CSF glucose level, a significant positive relation was found ($r = 0.380$, $p < 0.02$). It

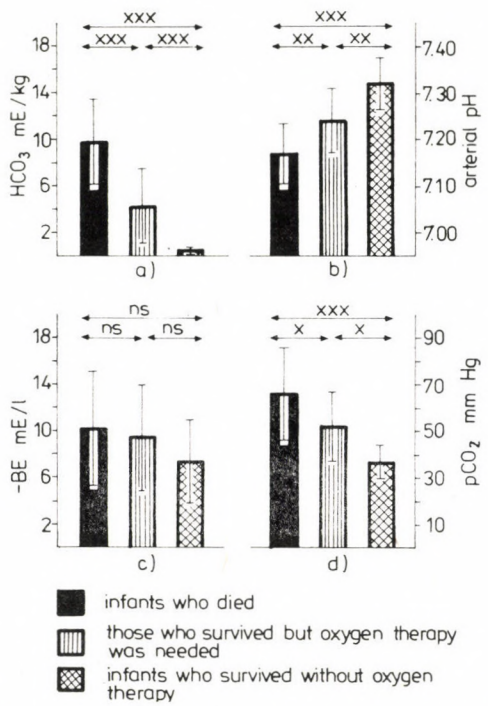

Fig. 1. Total amount of bicarbonate infused to the patients during treatment (A), and extremes of arterial pH (B), negative base excess (C) and pCO_2 (D) observed in the three groups of newborn infants (mean $\pm$ SD). xxx = $p < 0.001$, xx = $p < 0.01$, x = $p < 0.05$

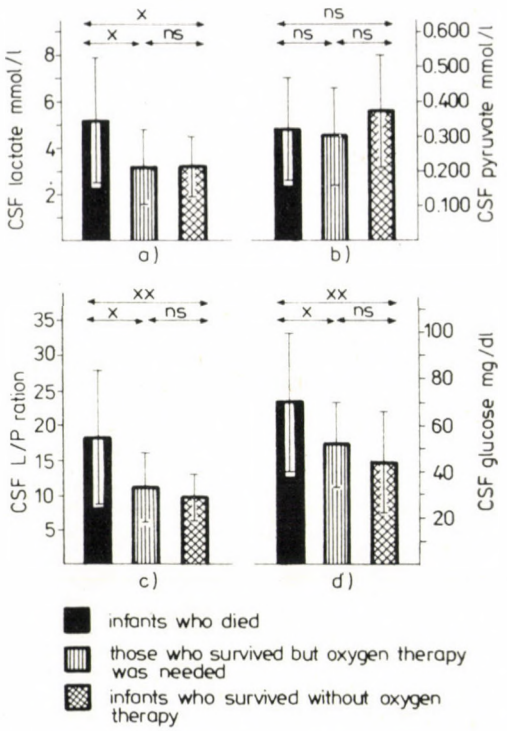

FIG. 2. CSF lactate (A), pyruvate (B), lactate/pyruvate ratio (C) and glucose (D) in the three groups (mean $\pm$SD). xxx = $p < 0.001$, xx = $p < 0.01$, x = $p < 0.05$

is also seen that group-I(D) babies required much more bicarbonate than the patients in group-II(SO) (9.8 ± 3.2 vs 4.3 ± 3.4 mE/kg, $p < 0.001$) or group-III(S) (0.2 ± 0.5 mE/kg, $p < 0.001$). In spite of this, the mean value for extreme arterial pH and pCO_2 was the worst in group-I(D) (7.17 ± 0.07 and 66 ± 20 mm Hg) which differed significantly ($p < 0.001$) from that of patients in group-III(S), (7.32 ± 0.06 and 37 ± 7 mm Hg) and group-II(SO), (7.24 ± 0.07 and 52 ± 15 mm Hg, $p < 0.05$). H^+ concentration and pCO_2 were significantly lower in the patients who survived without oxygen therapy than in those who needed it ($p < 0.01$ and $p < 0.05$, respectively). The mean negative base excess was similar in the three groups (Table I and Fig. 1).

As it is shown in Fig. 2 and detailed in Table II, the mean ($\pm$SD) CSF lactate was 5.14 ± 2.96 mmol/l whilst the L/P ratio was 18.33 ± 10.23 in group-I(D), both being significantly higher ($p < 0.05$ and $p < 0.01$) than in group-II(S), i.e. 3.21 ± 1.30 mmol/l and 9.64 ± 4.94, or in group-III(SO), (3.16 ± 1.67 mmol/l, $p < 0.05$ and 11.30 ± 5.42, $p < 0.05$). The two parameters were, however, closely similar in the survivors. Interestingly enough, mean CSF glucose concentration var-

TABLE II

Cerebrospinal fluid lactate, pyruvate, lactate/pyruvate ratio, glucose and protein concentration in the three groups of newborn infants studied

	No	Mean	±SD	±SEM	Range
Lactate, mmol/l					
D	20	5.14	2.96	0.66	2.06 – 12.80
SO	16	3.16	1.67	0.41	1.59 – 7.91
S	15	3.21	1.30	0.33	1.69 – 6.20
Pyruvate, mmol/l					
D	20	0.325	0.144	0.032	0.120 – 0.633
SO	16	0.295	0.154	0.038	0.096 – 0.624
S	15	0.375	0.174	0.045	0.184 – 0.880
Lactate/pyruvate ratio					
D	20	18.33	10.23	2.29	3.49 – 38.09
SO	16	11.30	5.42	1.35	4.28 – 28.54
S	15	9.69	4.94	1.27	3.38 – 21.08
Glucose, mg/dl					
D	20	70	29	6	27 – 158
SO	16	52	18	4	15 – 88
S	15	44	22	5	11 – 103
Protein, mg/dl					
D	20	121	54	12	62 – 260
SO	16	174	67	16	88 – 310
S	15	90	43	11	39 – 215

Abbreviations: D = newborn infants who died
SO = infants who survived but oxygen therapy was needed
S = infants who survived without oxygen therapy

ied nearly parallel with the lactate levels. 70 ± 29 mg/dl, the highest concentration, was found in the newborns who died, 52 ± 18 mg/dl and 44 ± 22 mg/dl in the survivors with and without oxygen therapy, respectively, both being significantly ($p < 0.05$ and $p < 0.01$) lower than in group-I(D), (Fig. 2). No difference was observed in pyruvate concentration in spite of similar trends in variation of the lactate levels and L/P ratios.

CSF lactate and glucose concentration correlated positively and significantly (Fig. 3) in all the newborns studied and a statistically significant relation was observed between the

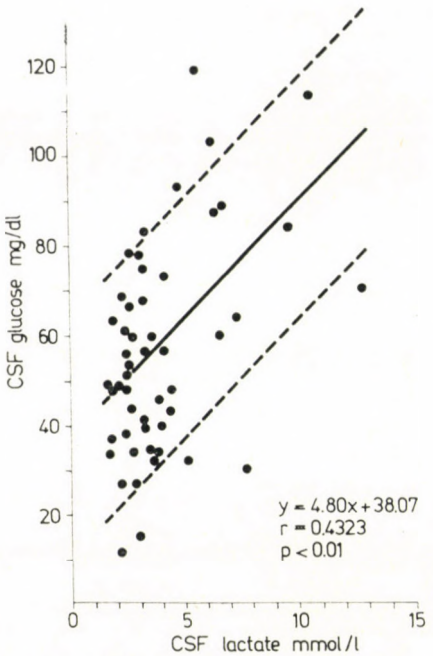

FIG. 3. Correlation between CSF lactate and glucose level in 51 newborn infants

lactate level and the total amount of bicarbonate infused ($r = 0.2807$, $p < 0.05$). Correlation between all the other parameter-pairs was not significant statistically.

DISCUSSION

Various disorders of neonatal cardio-respiratory adaptation associated with arterial hypoxaemia, hypercarbia and acidosis may cause brain hypoxia, the severity of which determines the ultimate prognosis, and should, therefore, guide the therapeutic measures. Since arterial hypoxia in the systemic circulation does not necessarily reflect the degree of brain hypoxia, a more direct indicator has long been sought for. The rise in CSF lactate concentration and increased L/P ratio was reported [6, 7, 11, 15, 17] to meet this requirement, but data on human newborns are so far fragmentary.

In the present study the CSF lactate level and L/P ratio were measured in two groups of newborn infants with perinatal hypoxia of various severity and duration and also in control patients who did not suffer from hypoxia. In accordance with previous observations [17] it was found that in newborns with severe and prolonged hypoxia and oxygen dependency, mean CSF lactate concentration and L/P ratio were remarkably higher than either in those with less definite hypoxia or in the control

patients. CSF lactate level and L/P ratio were similar in the two groups of survivors which means that a rise of these two parameters can be expected only in the case of severe and/or durable hypoxia of the brain. The mean lactate concentration measured by us in the CSF of survivors corresponded fairly well to that found normal by others [1, 2, 9, 17], i.e. < 3.33 mmol/l. It should, however, be emphasized, that individual lactate concentrations scattered widely in all groups. Since birthweight, gestational age and postnatal age did not correlate significantly with CSF lactate and L/P ratio, the remarkable individual variations of the latter parameters were not due to the inhomogeneity of the patient material in regard of birthweight, gestational age and postnatal age. It seems that variations in the lactate level and the L/P ratio are related to factors influencing the CSF lactate content independently of the increased anaerobic metabolism of brain tissue. CSF is well known to be produced by the brain tissue, but cellular elements also contribute to lactate production, and a certain amount of it originates from the blood via the blood-CSF barrier [14, 16]. Although all specimens proved to be sterile on culture and had a normal cell content, alterations of barriers may have occurred as also changes in lactate clearance mechanisms, such as retrodiffusion or bulk flow resorption.

Despite all these uncertainties, increased CSF lactate concentration and L/P ratio seem to indicate cerebral hypoxia, and have some prognostic significance in pathological newborn infants. CSF lactate and L/P ratio were found to be > 3.33 mmol/l and > 10.00, respectively, in 13/20 of the newborns who died with RDS or neonatal pneumonia, associated with intraventricular or subependymal haemorrhage in 16 of them. On the contrary, the lactate level was < 3.33 mmol/l and the L/P ratio < 10.00 in 13/16 and 9/16, respectively, of the patients who recovered from RDS, but needed oxygen therapy. In the control group, CSF lactate was less than 3.33 mmol/l in 10/15 and the L/P ratio below 10.00 in 9/15 of the patients.

The time interval elapsed from the brain hypoxia to the time of the spinal tap may have varied greatly from patient to patient. This fact offers another possible explanation for the wide individual variations in the lactate level and L/P ratio. If the interval in term, which in fact had not been known, is too short or too long, CSF lactate concentration and L/P ratio may well be still or already normal.

From amongst the various parameters thought to reflect the severity of hypoxia and acidosis of the patients, only the total amount of bicarbonate infused correlated significantly with the CSF lactate level. This association is certainly an indirect one, since the total amount what the patients received all over their treatment was used for calculations. This finding seems to prove that bicarbonate requirement may perhaps be used as an

indicator of the severity of pathological conditions associated with hypoxia and combined respiratory and metabolic acidosis. The cause of the significant positive correlation between CSF lactate and glucose concentration remains obscure and needs further investigation. Alterations in glucose transport from blood or clearence of glucose from CSF, associated with brain hypoxia and increased lactate production, might have been operative.

In conclusion, it is suggested that CSF lactate level and L/P ratio increase significantly in most newborn infants with severe and persistent hypoxia, due to RDS with intracranial haemorrhage and fatal outcome. In the case of a less serious clinical course and survival, CSF lactate level and L/P ratio remain normal in most of the cases, that is < 3.33 mmol/l and < 10.00. The wide individual differences of these parameters in pathological and control newborn infants are certainly of multifactorial origin, and should be taken into account when using lactate concentration and/or L/P ratio as an indicator of brain hypoxia.

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M. Fekete, M. D.
József A. u. 7.
H-7623 Pécs, Hungary