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NEONATOLOGY

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Myocardial ischaemia in neonates with perinatal asphyxia

Electrocardiographic, echocardiographic and enzymatic correlations

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Abstract In asphyxiated neonates, hypoxia is often responsible for myocardial ischaemia. To evaluate cardiac involvement in neonates with respiratory distress, ECG and echocardiographic recordings were performed, and cardiac enzymes determined. These data were related to clinical presentation and patient outcome. Three groups of neonates were studied: 22 healthy newborn infants (group I) with 5 min Apgar scores >9 and pH >7.3; 15 neonates with moderate respiratory distress (group II) which had Apgar scores ranging between 7 and 9, and pH between 7.2 and 7.3; and 13 neonates with severe asphyxia, Apgar scores <7, and pH <7.2 (group III). The ECGs were evaluated according to the 4-grade classification proposed by Jedeikin et al. [8]. On the echocardiograms, fractional shortening and aortic flow curve parameters were taken into account. Serum creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB) and lactate dehydrogenase were determined. All of groups I and II survived, but 5 out of 13 in group III died within the 1st week. Grade 3 or 4 ECG changes were observed only in group III patients, while all group II and 3 patients of group I showed grade 2 ECG changes. Fractional shortening, peak aortic velocity and mean acceleration were significantly reduced in group III, whereas the only abnormality found in group II was a reduced fractional shortening. CK, CK-MB, CK-MB/CK ratio and lactate dehydrogenase were all increased in group III, while in group II only CK-MB and the CK-MB/CK ratio were abnormal.

Conclusion Severely asphyxiated newborn infants reflect relevant ischaemic electrocardiographic changes, depressed left ventricular function and marked cardiac enzyme increase. These alterations are far less pronounced in neonates with mild respiratory distress.

Key words Myocardial ischaemia · Electrocardiogram · Echocardiogram · Myocardial enzymes

Abbreviations *AT* acceleration time · *CK* creatine kinase · *CK-MB* creatine kinase MB isoenzyme · *FS* fractional shortening · *LDH* lactate dehydrogenase · *LVET* left ventricular ejection time

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Introduction

Myocardial damage of ischaemic origin is easily diagnosed in adults. Apart from the clinical presentation, the ECG, echocardiogram and determination of cardiac enzymes are useful tools to detect myocardial involvement [10]. In contrast, recognition of myocardial ischaemia is far more difficult in neonates than in adults. A few investigations have stressed the value of the ECG, echocardiogram and enzyme increase to detect the ischaemic insult to the neonatal heart [3, 7, 8, 13, 14, 16, 18]. The aim of this study was to evaluate the presence and extent of cardiac involvement in asphyxiated newborn infants in order to establish which clinical and laboratory parameters represented the most reliable markers of cardiac damage in these patients.

Methods

Patients

A total of 50 newborn infants free of congenital heart disease were included in the study. They were subdivided into three groups according to their Apgar score and pH in cord arterial blood, sampled on admission as part of routine management of neonates admitted in the intensive care unit.

Group I consisted of 22 neonates (10 full-term, 12 preterm) who had 5 min Apgar scores >9 and pH >7.3.

Group II comprised 15 neonates (5 full-term, 10 preterm) with moderate respiratory distress. They had mild symptoms, a 5 min Apgar score ranging between 7 and 9, and pH between 7.2 and 7.3.

Group III included 13 symptomatic neonates (6 full-term, 7 preterm) with severe asphyxia with 5 min Apgar scores <7 and pH <7.2. All the neonates in the latter group required conventional mechanical ventilation for a mean of 3.1 ± 1.7 days.

Brain involvement was graded according to a simplified Amiel-Tison and Ellison score [1], as suggested by Martin Ancel et al. [11]: stage 1 consisted of hyperexcitability or hypotonia; stage 2 was diagnosed in the presence of lethargy, hypotonia and marked reduction of reflexes and stage 3 was characterized by severe tonus abnormalities, seizures, and coma or stupor.

The three groups did not differ from each other with respect to gestational age or weight at birth. The mean gestational age was 34.3 ± 4.6 weeks, 35.1 ± 2.5 weeks, 34.5 ± 5.2 for groups I, II and III respectively. The mean birth-weight was 2.359 ± 0.921 kg, 2.365 ± 0.814 kg, 2.429 ± 1.093 kg in the same groups. None of the newborn infants received cardio-active drugs at the time of examination. On the 2nd day of life (between 24 and 36 h), all the neonates had an ECG, echocardiogram and venous blood sampling.

Electrocardiogram

The ECGs were evaluated by two independent observers, unaware of the clinical condition of the patients. Tracings were analysed for signs of myocardial involvement, according to the criteria proposed by Jedeikin et al. [8]. Every 12-lead ECG was classified as follows: – grade 1: the presence of T wave flat or inverted in one or two leads (except aVR); – grade 2: T wave flat or inverted in three or more leads (except aVR); – grade 3: T wave flat or inverted in three or more leads and either ST depression or elevation >2 mm in at least two chest leads or >1 mm in at least two standard leads, or Q wave abnormality defined as duration >0.02 s or amplitude $>25\%$ of the R wave, in one anterior or three related chest leads; – grade 4: classical segmental infarction with abnormal Q waves and markedly elevated ST segment or complete left bundle branch block.

Echocardiogram

Echocardiographic evaluation was performed on the neonatal intensive care unit with an Aloka Ultrasound Imaging System (model SSD 830), using a 5 MHz transducer for mono- and two-dimensional imaging; the length of the sample volume for PW Doppler examination was 5 mm. All the investigations were performed by the same author (MPC), whereas the measurements were made by two other cardiologists who were not informed about the clinical condition of the patients. On M-mode images of the left ventricle, the fractional shortening (FS) was determined by the formula $FS = (LVED - LVES)/LVED$, where LVED is left ventricular end-diastolic diameter and LVES is left ventricular end-systolic diameter. The aortic flow curve was obtained using the five chamber apical view, by positioning the sample volume on the tip of the aortic leaflets. The following parameters of cardiac function were determined on each curve: peak velocity, mean acceleration, acceleration time (AT), left ventricular ejection time (LVET) and stroke distance, namely the area under the velocity curve, also known as the velocity time integral [6].

All measurements were performed on three consecutive cardiac cycles and the results averaged. In addition, an accurate search for tricuspid regurgitation was done; in positive cases, the pulmonary artery systolic pressure was estimated using conventional methodology [2].

Enzyme determination

Creatine kinase (CK), MB isoenzyme (CK-MB), LDH were determined in serum from each sample of venous blood. CK and CK-MB activities were measured by the Cardio REP procedure (Helena Laboratories, Beaumont, TX) according to their electrophoretic mobility on agarose gel. LDH activity was measured with LDH-P test (Instrumentation Laboratory, Lixington, Mass.). Values were expressed in IU/l at 15°–30°.

Statistical analysis

For echocardiographic parameters and enzyme values the average and standard deviation was calculated for each group. Comparison of groups was performed by Kruskall-Wallis non parametric analysis. Moreover, the Mann-Whitney test was used to verify multiple comparison between groups (group I vs. II; I vs. III; II vs. III). One-way variance analysis was also used to compare patients who survived to those who died in group III.

Results

All the neonates in groups I and II survived and were discharged from the hospital, while 5 out of the 13 patients in group III (38%) died during the 1st week. Table 1 shows the incidence of ECG alterations attributable to myocardial damage in the three groups of patients. Changes of grade 3 or 4 were present only in group III infants, with an incidence of 61.5%. The three patients with grade 4 changes (23%) died within the 1st week of life. Two other group III neonates, both premature, died; one of them had grade 3 ECG changes, the other grade 2 alterations.

All group II infants showed mild ECG alterations, classified as grade 2. Among group I neonates the ECG

Table 1 ECG Score in the 3 groups

Group	Normal ECG	ECG changes			
		Grade 1	Grade 2	Grade 3	Grade 4
I	10 (45.4%) 6[a]–4[b]	9 (41%) 3[a]–6[b]	3 (13.6%) 1[a]–2[b]	–	–
II	–	–	15 (100%) 5[a]–10[b]	–	–
III	–	–	5 (38.5%) 2[a]–3[b]	5 (38.5%) 3[a]–2[b]	3 (23%) 1[a]–2[b]

[a] Full-term
[b] Preterm

was normal in 45.4% of cases, whereas grade 1 changes were present in 41%, and grade 2 changes in 13.6%. Figure 1 shows the ECG recorded from the newborn infant with the highest CK-MB value and the lowest FS. The tracing reflects a pattern of acute inferior myocardial infarction with deep Q waves and elevated ST segment in the inferior leads; ventricular extrasystoles in trigeminal rhythm are also present, as well as an episode of non-sustained ventricular tachycardia.

Table 2 shows data of group III patients, in particular the presence and severity of extracardiac damage related to perinatal asphyxia. Five neonates (38%) died and eight (62%) survived in group III. Comparison of those subgroups (died and survivors) revealed no statistically significant differences in FS (18.8 ± 2.4 vs. 21.4 ± 3.4). In contrast, the CK-MB level was significantly higher in patients whose outcome was unfavourable than in those who survived (504.8 ± 293.6 vs. 228.9 ± 90.3; $P < 0.05$). In addition, multiorgan extracardiac failure was present only in neonates who died.

The results of echocardiographic analysis are shown in Table 3. FS decreased progressively from group I to group III ($P < 0.001$). The peak aortic flow velocity behaved similarly, the difference between groups I and III as well as between groups II and III was significant, but no significant distinction was present between groups I and II. Concerning aortic flow acceleration, the only significant difference was between groups I and III. In contrast, analysis of stroke distance and AT/LVET ratio did not reveal any statistically significant difference among the groups. Tricuspid regurgitation was observed in six neonates in group I (27%), seven in group II (47%), and seven in group III (54%). Pulmonary hypertension was present in three and four infants of groups II and III respectively, whereas pulmonary pressure was normal in all group I subjects with tricuspid regurgitation.

Table 4 shows the results of enzyme determination. It is evident that all three enzymes considered were higher in group III than in the other two groups. The only significant difference between group I and II concerned the CK-MB, which was higher in group II than in group I. In contrast, total CK and LDH did not differ significantly in the first two groups. When CK-MB was expressed as a percentage of the total CK activity, the ratio CK-MB/CK was markedly increased in groups II and III with respect to group I.

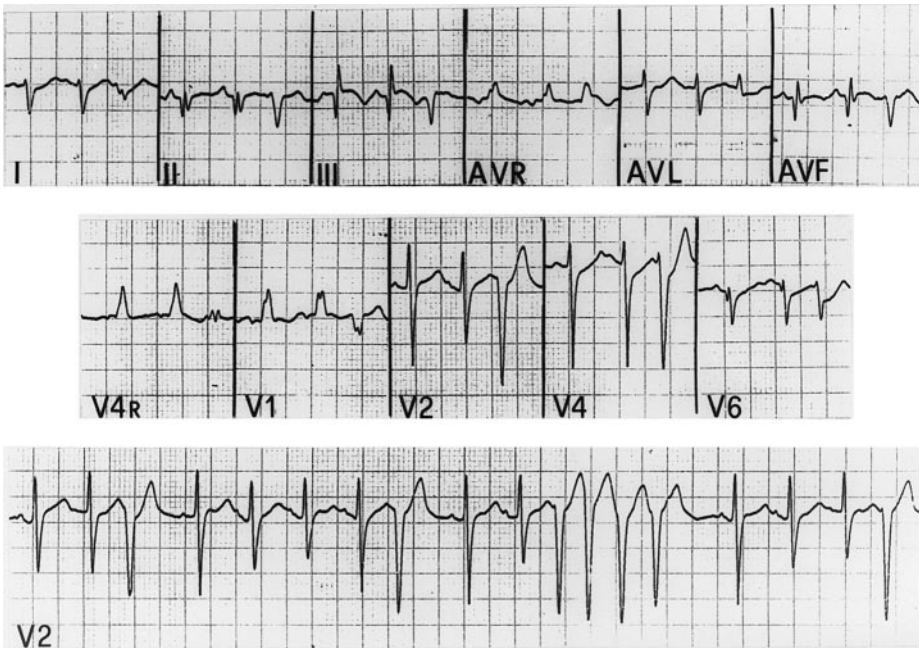

Fig. 1 ECG recorded from a group III patient. See text

Table 2 Group III neonates – clinical data. *B* brain *HIE* hypoxic-ischaemic encephalopathy *K* kidney *L* liver

	Gestational Age (weeks)	Weight (g)	CK-MB (IU/ECG 1)		Fractional shortening (%)	Outcome	Extracardiac involvement
1	40	4070	723	IV	21	D	B (HIE stage3), K, L
2	26	925	259	II	20	D	B (HIE stage3), K
3	37	3600	839	IV	15	D	B (HIE stage3), K, L
4	26	1010	154	III	20	D	B (HIE stage2)
5	31	2030	549	IV	18	D	K
6	33	2740	206	II	28	A	B (HIE stage1)
7	33	2190	253	III	18	A	B (HIE stage2)
8	39	3290	96	III	23	A	B (HIE stage1)
9	39	3300	227	II	18	A	K
10	38	3400	192	III	22	A	K
11	41	3650	414	II	19	A	B (HIE stage2),K
12	31	1380	257	III	20	A	–
13	40	3120	186	II	23	A	–

Table 3 Echocardiographic parameters in the 3 groups of neonates. (*NS* not significant)

Group	FS (%)	Peak velocity (cm/s)	Mean acceleration (cm/s^2)	Stroke distance (cm)	AT/LVET
I	37 ± 5 (28–44)	78.8 ± 12.6 (58.9–95.8)	1386.9 ± 315.6 (809.8–1767.3)	10.5 ± 2.01 (7.5–13.5)	0.28 ± 0.04 (0.17–0.35)
II	26 ± 5 (19–35)	75.9 ± 13.5 (52.0–98.1)	1212.8 ± 357.9 (699.0–1909.3)	10.8 ± 1.76 (8.6–13.8)	0.29 ± 0.05 (0.21–0.42)
III	20 ± 3 (15–28)	63.2 ± 14.3 (42.7–97.8)	1083.6 ± 382.5 (687.1–1924.1)	9.44 ± 2.25 (6.5–12.7)	0.29 ± 0.06 (0.20–0.42)
(Mean ± SD. Range in parentheses)					
I vs II	$P < 0.001$	NS	NS	NS	NS
II vs III	$P < 0.001$	$P < 0.05$	NS	NS	NS
I vs III	$P < 0.001$	$P < 0.001$	$P < 0.05$	NS	NS

Table 4 Serum CK, CKMB and LDH in the 3 groups

Group	CK (IU/1)	CKMB (IU/1)	$\frac{CKMB}{CK}$ (%)	LDH (IU/1)
I	629.7 ± 370.1 (219–1089)	12.5 ± 6.7 (2–21)	1.9	529 ± 176 (295–1050)
II	774.1 ± 460.4 (253–1736)	127 ± 94.2 (19.6–260)	16.4	682 ± 305 (324–1249)
III	2.210 ± 2.121 (471–17.401)	334 ± 239 (96–723)	15.1	1775 ± 1604 (543–2276)
(Mean ± SD. Range in parentheses)				
I vs II	NS	$P < 0.001$	$P < 0.001$	NS
II vs III	$P < 0.05$	$P < 0.001$	NS	$P < 0.05$
I vs III	$P < 0.05$	$P < 0.001$	$P < 0.001$	$P < 0.05$

Discussion

In this study there is a clear relationship between clinical pattern of asphyxiated newborn infants and alterations of ECG, echocardiographic and enzymatic parameters. Patients showing the most severe hypoxic damage (group III) also reflected the most striking changes: in particular, grade 3 or 4 ECG alterations and a highly reduced FS, indicating severe myocardial involvement, only occurred in group III neonates. Most of such patients died early, presumably not only as a result of cardiac deterioration, but also due to multiorgan failure (Table 2).

The degree of ECG, echocardiogram and enzymes alterations was minor in group II with respect to group III, as a manifestation of mild myocardial involvement consequent to moderate hypoxia. Finally, group I infants, who were free of respiratory symptoms, did not show any sign of cardiac disease.

We found some degree of myocardial involvement, expressed by enzyme rise, ECG changes or echocardiographic abnormalities, in all neonates with severe asphyxia (group III). In several patients (cases 2, 6, 9, 11, 13 in Table 2), the ECG signs of myocardial damage were mild and would have been underscored in the absence of extensive heart investigation. This may explain the reason why some previous studies [11] on neonatal

asphyxia, not specifically focused on the heart, reported a relatively low incidence of myocardial involvement, on the basis of ECG and clinical data only.

Myocardial ischaemia of newborns is a well known syndrome and is usually related to perinatal asphyxia. Transient neonatal myocardial ischaemia was originally described in full-term infants [16] and later also recognized in preterm neonates [5, 9, 17]. Hypoxia is responsible for multiorgan lesions, but particularly results in myocardial damage despite "preferential" myocardial perfusion.

The diagnosis of neonatal myocardial involvement is simple in severe clinical conditions but is less definite in the presence of moderate respiratory disease. Unfortunately, no single parameter helps to identify myocardial damage, especially when hypoxia is mild. During the 1st day of life, ECG ST-T changes are at times non-specific or related to electrolyte imbalance [14]; moreover, enzyme increase is not necessarily an expression of myocardial damage in newborns.

In the present study, the interplay of information provided by ECG, echocardiogram and serum enzymes results in a reliable detection and grading of myocardial damage. The specificity of ECG changes is expected to be higher on the 2nd day than on the 1st day of life, according to the presence of several "innocent" repolarization changes during the first 24 h [8]. This is the reason why we preferred to record the ECGs on the 2nd day of life. Moreover, in asphyxiated newborn infants, the absolute CK-MB value is higher throughout the first 24 h than during the 2nd day, but the ratio CK-MB/total CK is significantly increased in these patients only starting from the 27th hour [14]. Accordingly, we determined the cardiac enzymes on the 2nd day to rule out the possibility of a normal CK-MB/total CK ratio despite myocardial necrosis.

An important role is played by the echocardiogram which may show two basic patterns representative of myocardial damage: 1) a depressed left ventricular function [4], expressed by reduction of both the FS and peak aortic velocity; and 2) tricuspid regurgitation, eventually associated with pulmonary hypertension [12, 15, 19]. Although a mild tricuspid regurgitation is relatively common in normal newborn infants, a moderate to severe valve insufficiency is often associated with pulmonary hypertension, as in some of our group II and group III patients.

Our results suggest that severe ECG changes (grade 3 or 4) are present only in very sick neonates, and should be considered as a specific marker of severe myocardial involvement. Mild T wave changes (grade 1 or 2), in contrast, may be at times observed in normal newborns; their presence, thus, is not diagnostic when in isolation. On the other hand, a CK-MB elevation and a reduced FS should be regarded as the most reliable markers of myocardial ischaemia, since they are detectable even in mildly compromised infants.

This study suggests that observation of simple clinical data may result in recognition of myocardial ischaemia: the co-existence of Apgar 5 min score <7 and arterial blood pH <7.2 heralds a very high risk of hypoxic heart involvement, thereby dictating the need for ECG, echocardiogram and CK-MB determination. Finally, asphyxiated newborns with grade 3 or 4 ECG changes, depressed left ventricular function and CK-MB >154 IU/l have a very poor prognosis due to both extensive myocardial damage and concomitant multiorgan involvement.

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ANNOUNCEMENTS

9th International conference of the International Society for Research in Human Milk and Lactation (ISRHML) on "Short and long term effects of breast feeding on child health"

October 2–6, 1999
Kloster Irsee Manstery, Kaufbeuren (near Munich), Germany

Scientific organizers:
Prof. B. Koletzko, Munich (Germany)
Prof. O. Hernell, Umea (Sweden)
Prof. K.F. Michaelsen, Copenhagen (Danmark)

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7th Salzburg Weekend Seminar Oral Diseases in Children

October 23–24, 1999

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