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Serum Concentration of Myosin Light Chain I and Left Ventricular Shortening Fraction in Neonates

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We compared the serum concentrations of myosin light chain I (MLC-I) and left ventricular shortening fraction (LVSF) measured by echocardiography of 13 normal neonates with those of 38 neonates with fetal distress, neonatal asphyxia, or cardiovascular/respiratory diseases not associated with structural abnormalities. The diseased group included 9 neonates with elevated MLC-I concentrations and 18 with low LVSF. Elevated MLC-I concentrations were frequently noted in neonates with transient myocardial ischemia and persistent pulmonary hypertension of the newborn, suggesting a high specificity of MLC-I elevation in these diseases. Although echocardiographically determined LVSF identifies the affected sections of the myocardium, it did not allow rating of the severity of the disorder. There was no correlation between MLC-I and LVSF probably due to therapeutic interventions and pulmonary hypertension. Our results suggest that MLC-I is a useful marker of neonatal myocardial diseases.

Key words: acute myocardial infarction; heart failure; persistent pulmonary hypertension of the newborn; transient myocardial ischemia of the newborn infant

Myocardial myosin light chain I (MLC-I), a component of the myocardial structural protein, plays a key role in myocardial constriction as well as echocardiographically left ventricular shortening fraction (LVSF). Previous studies showed increased blood levels of MLC-I in myocyte disorders, and indicated that MLC-I is a good marker of myocardial necrosis and is useful in the diagnosis and follow-up of myocardial infarction (Trahern et al., 1978; Yazaki et al., 1980). In neonates, asphyxia and various other pathologic conditions may cause heart failure. In this regard, MLC-I may potentially be a useful marker for the assessment of the severity of heart failure. To explore the usefulness of MLC-I for this purpose in the pediatric population, we compared the LVSF, determined by echocardiography, with serum concentrations of MLC-I, as an index of myocardial ischemia and myocyte necrosis, in neonates with fetal distress, neonatal asphyxia, and those with circulatory/respiratory diseases not associated with cardiac structural abnormalities, and compared these parameters with those of normal neonates.

Subjects and Methods

Subjects

We studied 13 newborn children with no physical abnormalities weighing more than 2,500 g who were delivered normally at full-term at our hospital (normal neonates). The group consisted of 9 boys and 4 girls, with a mean gestational

Abbreviations: AMI, acute myocardial infarction; AST, aspartate aminotransferase; CK, creatine phosphokinase; EFE, endocardial fibroelastosis; FD, fetal distress; MAS, meconium aspiration syndrome; MLC-I, myosin light chain I; LVSF, left ventricular shortening fraction; NA, neonatal asphyxia; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; TMI, transient myocardial ischemia of the newborn infant; TTN, transient tachypnea of the newborn

period and mean birth weight of 38 weeks and 6 days (range: 37 weeks and 0 day–40 weeks and 6 days) and 2,986 g (range: 2,500–3,392 g), respectively. We also examined 38 newborns at our hospital or affiliated facilities, with a history of fetal distress (FD), neonatal asphyxia (NA), or circulatory/respiratory diseases not associated with anatomical abnormalities. We defined all cases using the biophysical profile score (Manning et al., 1985) with less than 6 points as FD. The group consisted of 27 boys and 11 girls, with a mean gestational period and mean birth weight of 34 weeks and 1 day (range: 27 weeks and 4 days–42 weeks and 2 days) and 2,107 g (range: 782–3,504 g), respectively. The diseased group consisted of the following: i) The FD group comprised 6 patients, including 5 with complications—2 with transient tachypnea of the newborn (TTN), 1 with meconium aspiration syndrome (MAS) and 2 with transient myocardial ischemia of the newborn infant (TMI); ii) The FD + NA group consisted of 12 patients, including 7 with complications—2 with respiratory distress syndrome (RDS), 4 with TMI and 1 with MAS/persistent pulmonary hypertension of the newborn (PPHN); iii) The NA group consisted of 9 patients, including 8 with complications—2 with TTN, 3 with RDS and 3 with TMI; iv) The remaining newborns had the following underlying diseases—TTN in 4 patients, PPHN with TTN in 1, RDS in 2, TMI in 1, left ventricular dilation disease similar to endocardial fibroelastosis (EFE-like disease) in 1, shock caused by anencephaly in 1, and latent FD with reduced LVSF without heart failure in 1. Severe NA, defined by a 1-min Apgar score of 0 to 4 points, was noted in 13 patients. Of the circulatory/respiratory diseases there was TTN in 9 patients, RDS in 7, MAS in 2, PPHN in 2, and TMI in 10. There were 3 infants in 2 pairs, all with twin-to-twin transfusion syndrome (Table 1). Definite criteria are available for the diagnosis of TMI and PPHN; these 2 are often viewed together as one pathological condition (Riemenschneider et al., 1976; Levin et al., 1979). The diagnosis of PPHN was established in patients with marked pulmonary hypertension irrespective of the cause and the remaining fetal circulation, and TMI in patients with heart failure symptoms, and without underlying respiratory diseases, congenital heart diseases or metabolic diseases (Rowe, 1977; Daga et al., 1983).

Methods

Measurement of MLC-I

Serum concentrations of MLC-I were measured using the Yamaha EIA myosin L-1 kit (Yamasa Shoyu Co., Choshi, Japan). Briefly, the inner walls of a tube were first coated with an anti-human ventricular myocardial MLC-I mouse antibody (MLM-544; solid phase antibody, Yamasa Shoyu). To this tube, we added 200 μL of a peroxidase-labeled anti-human ventricular myocardial MLC-I mouse antibody (MLM-508; enzyme antibody, Yamasa Shoyu), and a 50-μL sample (antigen), followed by incubation for 1 h. After triplicate washing with 2,000 μL of 0.9% NaCl, we added 500 μL of a color-developing substrate (liquid A: tetramethylbenzidine; liquid B: hydrogen peroxide), followed by incubation at 15 to 30˚C for 30 min. Finally, 1,000 μL of a reaction stopper (2 N H_2SO_4) was added and mixed, followed by determination of absorbance at a 450 nm wavelength using a spectrophotometer. Serum concentrations of MLC-I were determined by a working curve constructed using the kit component standard myosin solution.

Determination of LVSF

All ultrasonographic studies were performed by the same operator with an SSD-875 (Aloka, Tokyo, Japan) with a 5.0 MHz transducer. Left ventricular internal dimensions at end-diastole and -systole were measured by a thoracic near-sternal procedure using the method of Sahn and coworkers (1978) , while the child was in a supine position. Data from 3 runs obtained on recording paper were averaged. LVSF was then calculated using the following equation:

$$LVSF = (LVIDd - LVIDs) / LVIDd$$

where LVIDd = left ventricular internal dimension at end-diastole, LVIDs = left ventricular internal dimension at end-systole.

Protocol

In the normal neonates, a 1-mL blood sample was collected from the dorsal vein of the hand on day 2 (3rd day of life) and used for the determination of MLC-I. In addition, we also determined LVSF on day 0 (1st day of life). Both procedures were repeated on day 5. In the diseased group, a 1-mL blood sample was collected from the dorsal vein of the hand or radial artery and assayed for MLC-I during hospitalization (within 24 h after delivery). We also determined LVSF at the same time. In 25 of the 38 patients, MLC-I and LVSF were also determined on days 2 through 10, more specifically in 6 patients on days 0 and 2, in 3 on days 0 and 3, in 2 on days 0 and 5, in 3 on days 0 and 6, in 7 on days 0 and 10, in 2 on days 0, 2 and 6, and in 2 on days 0, 5 and 8 (Table 1). In addition, patients with reduced LVSF were also examined over several days.

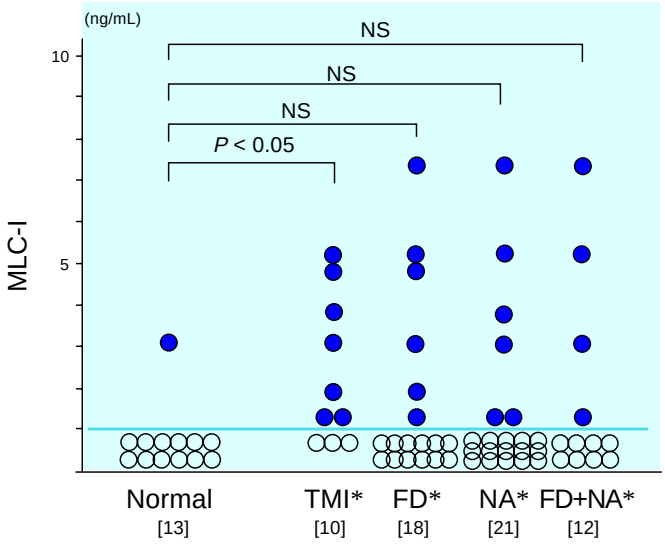

Fig. 1. Comparison of MLC-I between normal and diseased groups. *Groups have duplicate cases. ○, MLC-I < 1.0 ng/mL; ●, MLC-I ≥ 1.0 ng/mL. A significant difference is noted between the normal and TMI groups. No significant difference in MLC-I is noted in the FD, NA and FD + NA groups compared with the normal group. [ ], patient number of the group. FD, fetal distress; MLC-I, myosin light chain I; NA, neonatal asphyxia; NS, not significant; TMI, transient myocardial ischemia of the newborn infant.

Statistical analysis

Data were expressed as the mean ± SD. Differences between groups were examined for statistical significance by Mann-Whitney's *U*-test. A *P* value of less than 0.05 denoted the presence of a significant difference.

Results

MLC-I in normal neonates

In 12 of the 13 normal neonates, blood MLC-I concentrations were below the detection limit (< 1.0 ng/mL). However, in 1 neonate, a concentration of 3.1 ng/mL was noted on day 2. On day 5, the concentrations were below the detection limit in all 13 neonates. There was no significant difference in MLC-I between days 2 and 5.

MLC-I in the diseased group

Of the 38 patients, nine had elevated MLC-I concentrations, on day 0 in 8 and on day 2 in 1 (1.2–10 ng/mL). Of these, 8 had FD or NA, including 7 with TMI and 1 with MAS and PPHN. The remaining patient had shock caused by anencephaly. Thus, MLC-I was not elevated in patients with FD or NA who did not have associated TMI or PPHN. MLC-I was also not elevated in patients with circulatory/respiratory diseases not associated with FD or NA. The mean concentration of MLC- I in the TMI group was significantly higher than in the normal group ($P < 0.05$). But the mean concentrations in FD, NA and FD + NA groups were

Table 1. Patient data

Patient number	Sex	Disease	Gestational age (wk and d)	Body weight (g)	Apgar score (1/5 min)	MLC-I (ng/mL) [Age in d]	LVSF (%) [Age in d]
1	M	FD	37 wk 6 d	2529	7/ 9	<1 [0] → <1 [6]	38 [0] → 32 [6]
2	M	FD, TTN	35 wk 3 d	1241	9/10	<1 [0]	38 [0]
3	M	FD, TTN	34 wk 0 d	1866	9/ 9	<1 [0]	30 [0]
4	M	FD, MAS	40 wk 6 d	2308	8/ 9	<1 [0]	33 [0]
5	M	FD, TMI	37 wk 0 d	2674	8/ 8	5.0[0] → <1 [10]	15 [0] → 28 [10]
6	F	FD, TMI	32 wk 3 d	2144	9/ 9	1.9[0] → <1 [10]	11 [0] → 31 [10]
7	F	FD, NA	28 wk 3 d	995	1/ 4	<1 [0] → <1 [6]	30 [0] → 32 [6]
8	F	FD, NA	40 wk 2 d	3504	6/ 9	<1 [0] → <1 [3]	33 [0] → 34 [3]
9	M	FD, NA	39 wk 1 d	2928	4/ 9	<1 [0]	28 [0]
10	F	FD, NA	38 wk 6 d	2530	2/ 5	<1 [0] → <1 [2]	21 [0] → 38 [2]
11	M	FD, NA	29 wk 3 d	782	3/ 8	<1 [0]	27 [0]
12	F	FD, NA, RDS	31 wk 3 d	1942	3/ 7	<1 [0] → <1 [5]	24 [0] → 29 [5]
13	M	FD, NA, RDS	29 wk 4 d	1412	5/ 5	<1 [0] → <1 [2]	23 [0] → 30 [2]
14†	M	FD, NA, TMI	40 wk 2 d	3176	0/ 0	5.3[0]	20 [0]
15	F	FD, NA, TMI	31 wk 4 d	1974	1/ 6	<1 [0] → <1 [10]	6 [0] → 25 [10]
16	M	FD, NA, TMI	39 wk 3 d	3330	6/ 8	3.1[0] → <1 [10]	20 [0] → 32 [10]
17	M	FD, NA, TMI	32 wk 0 d	1836	1/ 2	1.2[0] → <1 [10]	24 [0] → 30 [10]
18	M	FD, NA, MAS/ PPHN	42 wk 2 d	3312	5/ 3	<6.3[0] → 7.4[2] → 3.7[6]	38 [0] → 32 [2] → 34 [6]
19	F	NA	39 wk 3 d	2928	5/ 8	<1 [0]	30 [0]
20	M	NA, TTN	28 wk 0 d	1144	6/ 8	<1 [0] → <1 [2]	25 [0] → 32 [2]
21*	M	NA, TTN	36 wk 6 d	2194	6/ 9	<1 [0]	29 [0]
22	M	NA, RDS	30 wk 0 d	1274	2/ 5	<1 [0]	29 [0]
23	F	NA, RDS	27 wk 4 d	954	1/ 2	<1 [0] → <1 [5] → <1 [8]	30 [0] → 34 [5] → 35 [8]
24*	M	NA, RDS	36 wk 6 d	2412	6/ 9	<1 [0]	36 [0]
25	M	NA, TMI	31 wk 6 d	1840	2/ 4	<1 [0] → 1.2[2] → <1 [6]	24 [0] → 27 [2] → 31 [6]
26	M	NA, TMI	27 wk 4 d	1042	3/ 6	3.0[0] → <1 [5] → <1 [8]	20 [0] → 24 [5] → 29 [8]
27	F	NA, TMI	32 wk 5 d	1654	3/ 7	<1 [0] → <1 [10]	22 [0] → 29 [10]
28	M	TTN	33 wk 5 d	2299	9/ 9	<1 [0] → <1 [3]	29 [0] → 29 [3]
29*	F	TTN	34 wk 2 d	1742	9/10	<1 [0] → <1 [3]	22 [0] → 29 [3]
30	F	TTN	36 wk 3 d	2494	8/ 9	<1 [0]	38 [0]
31	M	TTN	34 wk 4 d	2374	9/ 9	<1 [0] → <1 [2]	33 [0] → 35 [2]
32	M	TTN, PPHN	35 wk 5 d	2300	9/ 9	<1 [0] → <1 [5]	31 [0] → 31 [5]
33	M	RDS	34 wk 2 d	2000	8/ 8	<1 [0] → <1 [2]	17 [0] → 27 [2]
34	M	RDS	31 wk 6 d	1599	9/10	<1 [0]	38 [0]
35	M	TMI	36 wk 1 d	2862	8/ 9	<1 [0] → <1 [10]	17 [0] → 27 [10]
36	M	EFE-like	37 wk 3 d	2402	8/10	<1 [0] → <1 [6]	16 [0] → 22 [6]
37†	M	Anencephaly	36 wk 0 d	3000	8/ 8	<1 [0]	25 [0]
38	M	Latent FD	31 wk 6 d	1054	8/ 8	<1 [0] → <1 [2]	14 [0] → 35 [2]

d, day(s); EFE, endocardial fibroelastosis; F, female; FD, fetal distress; M, male; MAS, meconium aspiration syndrome; MLC-I, myosin light chain I; LVSF, left ventricular shortening fraction; NA, neonatal asphyxia; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; TMI, transient myocardial ischemia of the newborn infant; TTN, transient tachypnea of the newborn; wk, week(s).
*TTTS, twin-to-twin transfusion syndrome: patient numbers 21, 24 and 29.
†dead.

not significantly different from the normal group (Fig. 1). On days 2 through 10, MLC-I was measured again in 25 patients. Regarding the population breakdown by disease, 12 patients had FD, 14 with NA, 9 with FD + NA, 5 with TTN, 4 with RDS, 1 with MAS, 2 with PPHN, 9 with TMI, 1 with EFE-like disease, and 1 with latent FD with decreased LVSF without heart failure symptoms (overlap cases included). One patient with TMI and another with shock caused by anencephaly died on day 0. Of the 25 patients in whom MLC- I re-measurements were performed, 7 had elevated MLC-I concentrations (1 with MAS/PPHN and 6 with TMI). All these 7 had FD and/or NA. Patients No.18 and 25 showed a biphasic pattern (a rise followed by a fall) while in the other 5, MLC-I concentrations were high on day 0 and decreased below the detection limit on day 10. In these 5 patients, changes of MLC-I could not be measured (Table 1 and Fig. 2).

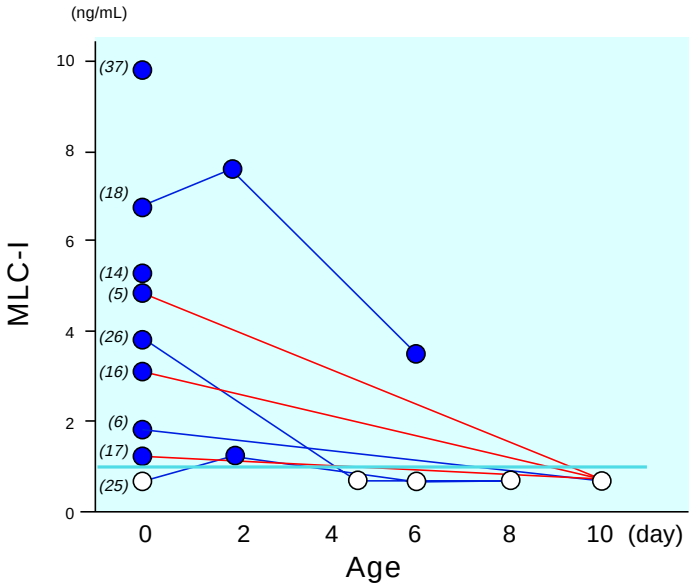

Fig. 2. Nine cases with elevated MLC-I concentrations. Numbers in parentheses represent patient numbers from Table1. Patient Nos. 18 and 25 showed a biphasic pattern of elevation followed by a fall in MLC-I. In the other patients, frequent measurements were not performed. MLC-I, myosin light chain I.

LVSF in normal neonates

The mean LVSF in normal neonates was 30.9 ± 3.6% on day 0 and 31.2 ± 3.0% on day 5, indicating no significant difference between the 2 days.

LVSF in diseased neonates

In the present study, a fall in LVSF was noted in 18 neonates (18.9 ± 5%). On day 0, 9 of 18 with FD, 11 of 21 with NA, 7 of 12 with FD + NA, 10 of 10 with TMI, 3 of 7 with RDS, 2 of 9 with TTN, 1 of 1 with EFE-like disease, and 1 of 1 with latent FD with reduced LVSF without heart failure symptoms, had reduced LVSF (Table 1). LVSF values in the NA, FD + NA and TMI groups were significantly lower than in normal neonates ($P < 0.05$). However, there were no significant differences between the normal group and the FD, RDS and TTN groups (Fig. 3). Of the 18 patients with reduced LVSF, one patient with TMI died on day 0, but we were able to measure LVSF again in the other 17 neonates on days 2 through 10. The data showed normalization in all but one neonate with EFE-like disease. In addition, of the 20 patients with normal LVSF on day 0, 8 showed normal LVSF values when this parameter was determined again at the time of re-measurement of MLC-I (Table 1).

Correlation between MLC-I and LVSF

Since MLC-I was not elevated, except in 1 normal neonate and neonates with diseases other than FD, NA, TMI and MAS/PPHN, it was thought that the correlation of MLC-I and LVSF was unlikely. In 10 patients with TMI and 9 with elevated MLC-I concentrations, the

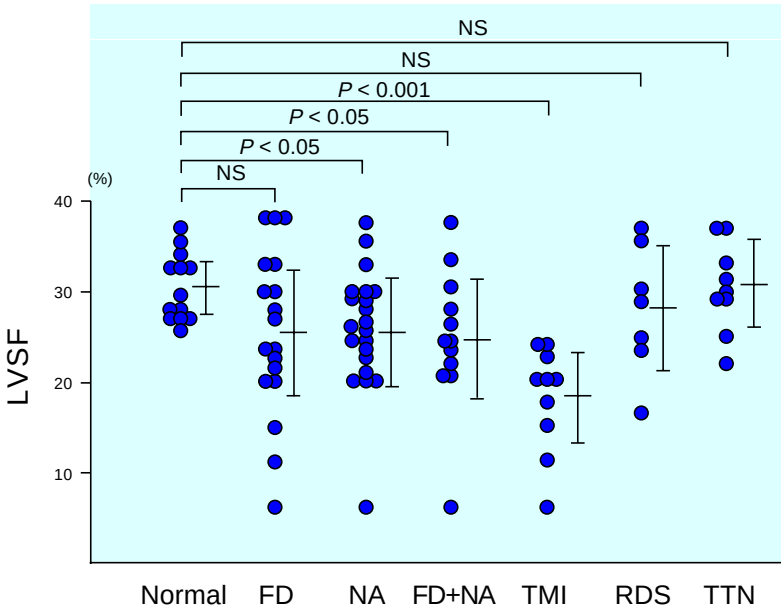

Fig. 3. LVSF in normal and different diseased groups. LVSF is significantly lower in neonates with NA, FD + NA and TMI than in normal neonates. There is no significant difference in LVSF among the FD, RDS and TTN groups and the normal group. FD, fetal distress; LVSF, left ventricular shortening fraction; NA, neonatal asphyxia; NS, not significant; RDS, respiratory distress syndrome; TMI, transient myocardial ischemia of the newborn infant; TTN, transient tachypnea of the newborn.

correlation between MLC-I and LVSF was analyzed using the peak MLC-I concentration obtained during the period from days 0 to 10, and the LVSF value measured on the day of peak MLC-I concentration. Although similar analysis was conducted in patients with FD, NA and FD + NA, no significant correlation was found (TMI; $r = 0.36$, 9 patients with elevated MLC-I concentrations; $r = 0.36$, FD; $r = 0.073$, NA; $r = 0.055$, FD + NA; $r = 0.26$). In the other patients, statistical analysis could not be performed due to the small sample size.

Discussion

Assessment of heart function by echocardiography is very useful because it is practical and simple. Unlike echocardiography, which only provides visual assessment of heart function, quantitative determination of serum proteins that originate from the myocardial muscles provide information on myocardial damage and such information is useful for management of the circulatory system. However, since creatine phosphokinase (CK), aspartate aminotransferase (AST), myoglobin, which are intracellular soluble proteins, readily move extracellularly due to increased permeability of the cell membrane during myocardial muscle dysfunction, these proteins are inappropriate indexes of myocyte necrosis, although they are highly sensitive in detecting ischemic-associated myocardial disorders. On the other hand, MLC-I, a structural protein of myocardial fiber, is very specific to myocardial muscle necrosis because blood levels of this protein become detectable only after necrosis of the myocardium (Khaw et al.,1978; Trahern et al., 1978). In this regard, CK and CK-MB are also non-specific for the myocardium in the neonate, unlike in the adult (Cao et al., 1968; Omokhodion et al., 1991; Primhak et al., 1985).

Concentrations under 1.0 ng/mL were considered normal, as shown in the study of Murano and coworkers (1995) , who measured

MLC-I on day 0. MLC-I concentrations under 1.0 ng/mL were considered normal in normal neonates, irrespective of age. Khaw and others (1978) reported a crossreaction rate of not more than 3% for myocardial MLC-I and skeletal muscle MLC-I. In our subject with a concentration of 3.1 ng/mL, the Apgar score, LVSF and troponin T (Katus et al., 1992) were 9 points, 27% and not more than 0.1 ng/mL, respectively, suggesting a cross-reaction between cardiac and skeletal muscles.

TMI is defined as a pathologic condition associated with heart failure caused by transient ischemia of the myocardium due to perinatal hypoxia (Rowe, 1977). Several pathophysiological mechanisms have been proposed (Kimura et al., 1982), including that of Rowe and Hoffman (1972), who attributed TMI to myocardial ischemia due to asphyxia and concurrent pulmonary vasoconstriction. Morrow and coworkers (1982) showed that a hypoxia-induced rise in thromboxane A_2 causes vasoconstriction of pulmonary and coronary arteries in TMI. They also hypothesized the same mechanism for the onset of PPHN and early neonatal acute myocardial infarction (AMI). On the other hand, PPHN is due to hypoxemia and acidosis that develops soon after birth (Fox and Duara, 1993). With regard to the mechanism for the onset, pulmonary vasoconstriction is induced by thromboxane A_2, prostaglandin $F_{2\alpha}$ and leukotrienes, and pulmonary vascular developmental abnormalities due to chronic hypoxemia (Morrow et al., 1982; Stenmark et al., 1983). In other words, PPHN can be viewed as a severe form of pulmonary vasoconstriction and TMI as coronary vasoconstriction, while AMI is a form of TMI resulting from the absence of re-perfusion due to thrombosis and/or embolism associated with coronary arterial constriction.

Of our 38 patients, none with FD, NA, or circulatory/respiratory diseases who did not have associated TMI or PPHN showed elevated MLC-I concentrations. In addition, statistical analysis demonstrated no significant differences in MLC-I, except for TMI, in comparison with normal neonates. These findings suggest that MLC-I is highly specific for TMI, PPHN and AMI. With respect to the single patient with shock caused by anencephaly who was transferred from a nearby clinic while in a shock condition, it appears that the shock was induced by the concomitant hypoxemia.

MLC-I is thought to begin to increase at about 4 h after the onset of AMI, reaching a peak concentration at 2 to 4 days, followed by a gradual decline, but remains elevated even at 10 days (Yazaki et al., 1980). In those neonates with unstable systemic conditions, such as those with FD, NA or TMI, minimal handling is an important component of overall management. In our patients investigated in the first half of the study, MLC-I was remeasured at the age of 10 days, as was recommended by Yazaki and coworkers (1980). However, in those with abnormalities, MLC-I was below the detection limit on day 10, unlike in adults. Since frequent measurements are very difficult in neonates with poor systemic conditions, just as in adults, MLC-I measurements were made as long as the systemic condition was not affected (days 2, 3, 5 and 8). Of the patients showing elevated MLC-I concentrations, 2 showed a single-peak change, in agreement with Yazaki and coworkers (1980). Furthermore, with regard to the time of the onset of changes in MLC-I, the MLC-I flow-out curves suggest that MLC-I can be elevated both in fetal life and after delivery; high concentrations were already found just after delivery in some patients, while the concentration was elevated on day 2 in another.

In older infants, LVSF does not depend on age, body surface area, or heart rate but are influenced by a variety of left ventricular loads. Therefore, the accuracy of any assessment is affected by abnormalities in left ventricular wall motion. Furthermore, in assessing LVSF, special attention should be paid to the fact that LVSF is elevated by an increased pre-load and a reduced after-load (Johnson et al., 1976). This is more important in low birth weight infants, who inevitably undergo therapeutic intervention; thus, it is substantially impossible to establish normal values for these infants. However, Murase and coworkers (1997) determined the mean value of LVSF in very low birth weight infants and demonstrated that this para-

meter is more useful when determined serially. LVSF values reported by these investigators are, in general, similar to those measured in the present study in normal neonates, suggesting that LVSF serves as an index that is unlikely to be affected by body weight and gestational age in neonates born after 28 weeks of gestation. We also examined the low LVSF values in some of our patients, using as a reference the mean values reported by Murase and coworkers (1997). As pointed out previously (Walther et al., 1985; Gill and Weindling, 1993), LVSF was significantly lower in the NA group than in normal neonates, with hypoxia as the likely cause. Although no difference was noted in the FD group, a significant difference was present in the FD + NA group, and the number of patients with low LVSF was smaller in the FD group without NA at delivery. These findings suggest that LVSF depends mainly on hypoxia at delivery rather than in fetal life. We also reported a case with a low LVSF and very low birth weight with no underlying disease and with a probable diagnosis of latent fetal distress, based on the rise in CK and AST concentrations at delivery.

As reported previously (Finley et al ., 1979; Oh et al., 1985; Mitomori et al., 1989), a significantly low LVSF was also noted in patients with TMI alone. Several TMI patients had elevated MLC-I concentrations, indicating the presence of some form of myocardial necrosis. In these patients, we anticipated a delayed recovery of LVSF, but we were unable to find differences compared with patients with NA. Although no differences were found in LVSF, left ventricular posterior wall motion was markedly decreased in all patients with TMI or PPHN in the present study, as pointed out previously (Rowe and Hoffman, 1972; Mitomori et al., 1989). This is in agreement with earlier studies demonstrating the relative frequency of myocardial infarction in the left ventricular posterior wall detected at autopsies of neonates with AMI (Ravich and Rosenblatt, 1947; Richart and Benirschke, 1959), supporting the above mentioned hypothesis of Morrow and others (1982). However, no similar finding was noted in any other cases of asphyxia or respiratory diseases, suggesting its usefulness in differential diagnosis by echocardiography. In addition, an index allowing quantitative assessment of left ventricular posterior wall motion would facilitate differential diagnosis. In one patient with PPHN and elevated MLC-I concentrations, the apparently normal LVSF was attributed to increased pre-load associated with moderate mitral insufficiency (Johnson et al., 1976). As for our patient with EFE-like disease, heart failure was attributed to long-term use in the mother of a high-dose of ritodrine throughout pregnancy (Katz and Seeds, 1989).

In adult patients with AMI, there is a significant negative correlation between the left ventricular ejection fraction and MLC-I during the acute stage (Isobe et al., 1987). We anticipated a similar correlation between LVSF and MLC-I in our patients with elevated MLC-I concentrations but unexpectedly failed to find such a correlation. Differences between adult and neonates may be due to the following factors: i) Right ventricular pressure load and volume load are accentuated by physiological pulmonary hypertension during early neonatal life or by pulmonary vasoconstriction inducing pulmonary hypertension in hypoxic neonates, which in turn adversely affects interventricular septal wall motion and hence influences LVSF; ii) Most patients with elevated MLC-I concentrations are in poor systemic condition necessitating therapeutic intervention that can influence LVSF, such as intubation, oxygen therapy and administration of catecholamines; also different patients receive different treatments that also invariably influence LVSF.

In conclusion, our study demonstrated that elevated MLC-I concentrations occur specifically in a series of pathologic conditions, i.e., TMI, PPHN and AMI in neonates, suggesting the potential usefulness of MLC-I for estimating the onset and severity of myocardial necrosis and as an index for the diagnosis and management of circulatory disorders in these conditions. In addition, echocardiographically-determined LVSF allowed estimation of the affected sites, although the establishment of the severity of this disorder remains elusive.

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