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Pentraxin-3 in late-preterm newborns with hypoxic respiratory failure

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1. ABSTRACT

The aim of this study was: echocardiographical assessment of cardiac alterations in late-preterm newborns with hypoxic respiratory failure (HRF), and, study serum pentraxin-3 (PTX-3) in relation to the severity of respiratory impairment and to some echocardiographic parameters (i.e. ejection fraction (EF), stroke volume (SV) and cardiac output (CO). We enrolled in this study 40 newborn infants whose 22 (group I) with moderate HRF and 18 (group II) with severe HRF. In group I the mean values of EF, SV and CO were significantly higher than in the group II. Our results showed a significant increase of PTX-3 in group II patients at 24h of life when compared to group I. Taking patients all together (n=40), we found a significant (R=-73) reverse correlation between EF and serum values of PTX-3. PTX-3 in our patients with HRF is affected by the severity of the hypoxic insult and correlate with the cardio-vascular impairment.

2. INTRODUCTION

The involvement of the cardio-vascular apparatus in the newborns with respiratory problems is a well known occurrence which may be associated to signs of myocardial ischaemia or to the reduction of both contractility and cardiac output (1, 2) Careful recognition of transitory or permanent cardiac alterations is possible by new echocardiographic techniques that allow to study minutely the cardiac function (3) Recently, there has been an increasing interest in the research of serum biomarkers of myocardial damage because of its simplicity of execution and low costs. In adults, troponin has been used as biochemical parameter to evaluate the entity, extension and prognosis of myocardial lesions mainly during the ischemic cardiopathy (4) Also in childhood the serum determination of troponin has been used to evaluate a possible myocardial damage during the cardiac catheterization or cardiac surgery (5) In addition, troponin has been found to be of

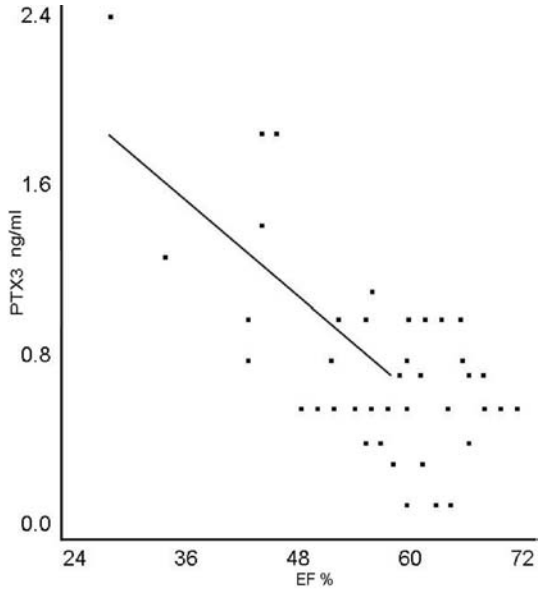

Figure 1. Reverse significant correlation between PTX3 levels and Ejection Fraction (EF) at 24 h of life.

clinical relevance in the evaluation of cardiac involvement in term infants with asphyxia and in preterm ventilated infants with idiopathic respiratory distress syndrome (RDS) (6, 7) Other biomarkers, such as creatine phospho-kinase (CPK) and reactive C protein (RCP), are considered aspecific because their serum levels can be affected by several factors (gestational age, sex, birth weight (BW), delivery modalities, extra-cardiac pathologies) and therefore may result in misleading diagnosis (8-10) The research of other new biochemical biomarkers of myocardial damage has led to the use of Pentraxin-3 (PTX-3), a protein produced by myocardial and endothelial cells after inflammatory and/or mechanic stimuli. PTX-3 has been successfully employed in adults for an early diagnosis and evaluation of the acute myocardial infarction (11, 12) However, to our knowledge, this protein has never been used in newborns.

The aims of the present investigation were: i) to evaluate by color-doppler echocardiography the status of cardiac function in a series of late-preterm newborns with hypoxic respiratory failure (HRF), and; ii) to study the serum variations of PTX-3 in these subjects in relation to the severity of the hypoxic insult and to the possible modifications of the echocardiographic parameters.

3. PATIENTS AND METHODS

We enrolled in this study 40 late-preterm out-born infants with HRF due to various causes (i.e. RDS, transient tachipnea of the newborn (TTN) or meconium aspiration syndrome (MAS) with persistent fetal circulation) admitted in the Neonatal Intensive Therapy Unit of the Pediatric Department of the University of Catania within the first hours of life. Newborns from mothers treated with tocolitics or affected by pre-eclampsia or cigarette smokers and infants with neonatal sepsis, congenital malformations, coagulopathies, AB0 or Rh incompatibility, central nervous system lesions found by echographic examination, were excluded from the study. All the patients were delivered by caesarean section for premature rupture of membranes (PROM, n=7) or for late decelerations at to cardiotocogram (n=33).

HRF diagnosis was based on the presence of clinical signs such as tachipnea, cyanosis, grunting, intercostal and sternal retraction, nasi alae flering and hemogasanalysis and on the chest X-ray examination. The gestational age (GA) was evaluated on the basis of maternal anamnesis, Ballard's cryteria (13) and confirmed by the examination of the anterior vessels of the lens (14) All patients (n=40) were divided into 2 groups: i) 22 infants with GA 35.7 ± 1.5 weeks, BW 2390 ± 461.7g and arterial blood pH 7.22 ± 0.001 affected by moderate HRF (OI/VI < 40) and treated with nasal CPAP; ii) 18 infants with GA 35.0 ± 0.1 weeks, BW 2461.9 ± 402.3g and arterial blood pH 7.14 ± 0.005 affected by severe HRF (OI/VI < 25) and treated with assisted ventilation (N-IPPV or ET-IPPV) HRF was retained moderate when O2 demand ranged from 0.40 to 0.50 and PaO2 was > 50 mmHg and severe when PaO2 was < 50 mmHg and O2 demand was > 0.80 (14).

Serum levels of PTX-3 were evaluated at 24 h of birth and repeated at 7 days of life. PTX-3 dosage was performed by enzyme linked immunosorbent assay (ELISA, DIESSE – SIENA) using monoclonal antibodies anti-PTX-3. Values are expressed as ng/ml.

The colordoppler echocardiography examination was performed by Sorus 2500 Philips scanner with 7.5 MHz transducer within 12 h of blood sampling for PTX-3 assessment. Echocardiographic examination was performed according to the recommendations of the American Society of Echocardiography (3) to study the following parameters: ventricular ejection fraction (FE %), stroke volume (SV ml/kg) and cardiac output (CO ml/min).

Statistical analysis was carried out by t test for paired data, the correlation index of Spearman and linear regression. Statistical significance was accepted at $p<0.05$.

4. RESULTS

The results are exposed in the Tables 1, 2 and 3 and in Figure 1. Tables 1 and 2 report clinical and laboratory parameters of each patient, respectively, with moderate HRF (group I, n=22) and with severe HRF (group II, n=18) In Table 3 are reported the mean values of EF, SV, CO and of PTX-3 levels found in both groups of patients. Our results showed that mean EF, SV and CO in the first group of patients with moderate HRF resulted significantly higher ($p < 0.05$) than in the second group of patients with severe HRF (60.54 ± 8.7% vs 50.5 ± 10.9%; 1.31 ± 0.62 ml/kg vs 0.68 ± 0.45 ml/kg; 155.5 ± 74.7 ml/min vs 75.4 ± 52.4 ml/min) Mean serum levels of PTX-3 in group I were 0.59 ± 0.22 ng/ml at 24 h of life and 0.56 ± 0.28 ng/ml at 7 days of life whereas in group II were 0.96 ± 0.5 ng/ml at 24 h of life and 0.63 ± 0.3 ng/ml at 7 days. All PTX-3 levels of both groups of patients were included

Table 1. Neonates with moderate hypoxic respiratory failure (HRF)

P	EG (wk)	Sex	BW (gr)	pH	Diagnosis	Ventilation	ECHOCARDIOGRAPY EF SV CO	PTX 3 ng/ml 24h 7d			
1	36	M	2400	7.22	RDS	N-CPAP	60	1.16	198	0.65	0.89
2	35	M	2190	7.25	RDS	N-CPAP	63	1.36	176	0.67	0.98
3	36	M	2210	7.25	RDS	N-CPAP	58	0.78	77	0.43	0.78
4	36	M	1850	7.24	RDS	N-CPAP	57	0.60	56	0.36	0.79
5	36	M	2880	7.28	TTN	N-CPAP	63	1.47	187	0.27	0.20
6	38	M	3130	7.28	TTN	N-CPAP	54	0.52	60	0.80	0.60
7	36	F	2490	7.21	TTN	N-CPAP	65	1.68	184	0.44	0.21
8	35	F	2320	7.22	TTN	N-CPAP	69	2.1	240	0.22	0.02
9	34	F	2830	7.20	RDS	N-CPAP	71	2.1	223	0.50	0.65
10	36	F	1950	7.28	RDS	N-CPAP	50	0.48	54	0.92	0.56
11	38	F	1830	7.21	TTN	N-CPAP	68	1.82	203	0.69	0.38
12	37	M	2600	7.20	TTN	N-CPAP	45	0.44	50	0.88	0.74
13	36	F	2250	7.20	TTN	N-CPAP	69	1.80	220	0.62	0.43
14	36	M	3100	7.22	TTN	N-CPAP	48	0.42	52	0.93	0.78
15	32	F	1430	7.21	TTN	N-CPAP	38	0.40	49	0.92	0.79
16	32	F	1540	7.20	RDS	N-CPAP	69	1.97	230	0.55	0.44
17	37	M	2250	7.24	RDS	N-CPAP	56	0.80	74	0.80	0.99
18	38	M	2970	7.22	TTN	N-CPAP	61	1.80	220	0.49	0.20
19	35	M	2500	7.22	TTN	N-CPAP	69	2.07	231	0.29	0.23
20	35	M	2820	7.20	RDS	N-CPAP	63	1.40	199	0.81	0.98
21	36	M	2630	7.24	TTN	N-CPAP	69	1.93	227	0.55	0.48
22	36	M	2410	7.22	TTN	N-CPAP	67	1.80	211	0.27	0.40
M DS	35.7 ±1.5		2390 ±461.7	7.22 ±0.001			60.54 ±8.7	1.31 ±0.62	155.5 ±74.7	0.59 ±0.22	0.56 ±0.28

GA=gestational age, BW=birth weight, RDS = respiratory distress syndrome, TTN = transient tachypnea of the newborn, N-CPAP = nasal CPAP, EF= ejection fraction (%), SV= stroke volume (ml/Kg), CO= cardiac output (ml/min), PTX3=pentraxin 3

Table 2. Neonates with severe hypoxic respiratory failure (HRF)

P	EG (wk)	Sex	BW (gr)	pH	Diagnosis	Ventilation	ECHOCARDIOGRAPY EF SV CO	PTX 3 ng/ml 24h 7d			
1	34	M	2760	7.12	RDS	ET-IPPV	52	0.48	54	0.43	0.42
2	36	M	1850	7.20	TTN	N-IPPV	70	1.97	210	0.54	0.81
3	32	M	1210	6.51	RDS	ET-IPPV	29	0.30	40	1.31	0.78
4	36	M	2350	7.14	RDS	N-IPPV	54	0.76	64	0.43	0.33
5	35	F	2310	7.18	RDS	N-IPPV	53	0.50	56	1.14	0.21
6	34	F	2650	7.18	RDS	N-IPPV	25	0.20	20	2.35	0.98
7	34	M	2490	7.20	RDS	N-IPPV	51	0.50	51	0.47	0.32
8	36	M	2420	7.19	TTN	N-IPPV	56	0.80	70	0.35	1.31
9	34	F	2830	7.15	RDS	N-IPPV	50	0.48	55	0.53	0.26
10	36	M	2850	7.18	TTN	N-IPPV	52	0.43	50	0.44	0.32
11	35	M	2430	7.16	RDS	N-IPPV	58	1.10	140	0.91	0.92
12	36	M	2600	7.11	TTN	N-IPPV	47	0.40	39	1.50	0.40
13	34	M	2245	7.00	RDS	ET-IPPV	55	0.60	65	1.08	0.50
14	36	F	2350	7.18	MAS	ET-IPPV	40	0.38	40	1.82	0.58
15	35	M	2700	7.20	MAS	ET-IPPV	58	0.80	103	0.98	1.14
16	36	M	2820	7.20	RDS	N-IPPV	49	0.47	51	0.42	0.28
17	36	M	2480	7.14	RDS	ET-IPPV	68	1.67	200	0.80	1.31
18	36	M	2970	7.12	TTN	ET-IPPV	43	0.46	50	1.78	0.59
M DS	35.0 ±01		2461.9 ±402.3	7.14 ±0.005			50.5 ±10.9	0.68 ±0.45	75.4 ±52.4	0.96 ±0.5	0.63 ±0.3

GA=gestational age, BW=birth weight, MAS=meconium aspiration syndrome, RDS = respiratory distress syndrome, TTN = transient tachypnea of the newborn, ET-IPPV=endotracheal IPPV; N-IPPV = nasal IPPV, EF= ejection fraction (%), SV= stroke volume (ml/Kg), CO= cardiac output (ml/min), PTX3=pentraxin 3

Table 3. Mean values of pentraxin 3 (PTX3 ng/ml), Ejection fraction (EF%), Stroke volume (SV ml/kg) and Cardiac output (CO ml/min) in the two goups of late preterm infants with moderate and severe hypoxyc respiratory failure (HRF)

Groups	Case (n°)	PTX3 (24h)	PTX3 (7 days)	EF (%)	SV (ml/Kg)	CO (ml/min)
Moderate HRF	22	0.59±0.22	0.56±0.28	60.54±8.7	1.31±0.62	155.5±74.7
Severe HRF	18	0.96±0.5	0.63±0.3	50.5±10.9	0.68±0.45	75.4±52.4

in the range of adult's normal values (12), but in patients of II group mean serum levels of PTX-3 were more elevated. The difference between the two groups was statistically significant (p=0.01) at 24 h of life with the highest mean values in infants with severe HRF (Table 3).

Considering all 40 patients, we found at linear regression analysis a statistically significant reverse correlation (R= -73) between EF and serological values of PTX-3 at 24 h of life (Figure 1) .

5. DISCUSSION

In spite of therapeutical progresses in these last years, respiratory pathologies are still frequent causes of

neonatal morbidity. Although low GA plays an important role in the development of respiratory complications, today, an increasing interest is focused on the late-preterm infants with GA ranging between 34 and 37 weeks (15) These subjects, in deed, have frequent respiratory problems leading to hospitalization in Intensive Care Units (16, 17) TTN, RDS and MAS with persistent fetal circulation are affections frequently observed in these patients. In USA about 33% of hospitalizations in the Neonatal Intensive Care Units are due to these pathologies (18) Although late-preterm newborns are considered functionally mature and, thus, treated according to therapeutical protocols of term newborns, these infants are more vulnerable than these latter. In fact, the last weeks of gestation are still relatively critical for the development and maturation of fetal organs (19, 20) and constitute a transition period in which mainly cardio-respiratory apparatus has limited ability to allow adequate tissue perfusion and effectiveness of respiratory changes. Moreover, at pulmonary level, functional immaturity of the alveolar epithelium and the presence of an excess of alveolar liquid can impair the effectiveness of surfactant (21, 22) Surfactant deficiency or its inhibition by various proteins contained in the alveolar liquid, are the most common causes of HRF in these patients (23-25) The need of assisted ventilation has a negative effect for the inevitable use of mechanic forces that can cause secondary injuries to the lung and the heart (2) During mechanical ventilation, there could be an over-production of plasmatic factors typical of inflammatory processes as cytokines, kallicrein, proteases, endotoxins and free radicals (26) In this pathological setting, a cardiovascular impairment can constitute a common association to the pulmonary damage. A decreased cardiac contractility with consequent reduction of the CO has been observed in preterm newborns with RDS (2) It has been suggested that this cardiac dysfunction is due to ischemia with consequent cellular myocardial damage. Cardiac function during RDS can be affected by both the severity of this affection and by the intensity of the mechanic support constituting an hemodynamic overload for the heart (2) *In vitro* experiments on cardiomyocytes show a correlation between myocardial parietal traction and the damage or even the death of myocardial cells. To this regard, it has been shown that several dangerous mechanisms for cardiomyocyte can be triggered following mechanic stimulations (27) The assessment of biochemical markers able to evaluate the damage of cardiomyocytes dates from some decades. In this context, an essential key role is played by Troponin-I because of its high myocardial specificity (4) Its utility has been shown even in the children (28) and in the newborn infants with RDS where it represents an efficient biomarker to evaluate the negative impact on the heart of mechanic ventilation (7) The association with other biochemical markers with different time of appearance and of half life, as PTX-3, could be, however, a major help in the establishment of a more careful diagnosis, prognosis and follow-up. After a cardiac injury, serum PTX-3 in adults is raised early within the first 12 h and disappears within few days with marked advantage, therefore, when compared with other biomarkers (11) This property allows to start therapeutical strategies more timely and make a more accurate prognosis. Because PTX-3 is released mainly following inflammatory stimulations that can be triggered by hypoxia and by mechanic factors correlated with hemodynamic overload, we believe that serum determination of PTX-3 in infants with HRF could constitute an useful help to evaluate more rationally the effects on the heart of hypoxia and of the mechanic ventilation.

Further investigations, however, need to confirm these results and especially to point out the physiological PTX-3 serum levels in the newborns and to better identify the proper clinical window of this biochemical marker in the various neonatal respiratory pathologies.

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