MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPERS

Pulmonary hypertension during acute respiratory diseases in infants

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ABSTRACT

Objectives: *The study was undertaken to assess whether previously healthy infants with acute respiratory diseases develop elevated pulmonary artery pressures and to identify which type of disease is associated with pulmonary hypertension.*

Material and Methods: *We performed 2D and Doppler echocardiography in 137 infants, aged between 1 and 12 month, from November 2007 to December 2009. 75 infants had acute respiratory diseases (49 bronchiolitis, 16 interstitial pneumonia, 3 bronchopneumonia, 6 episodic wheezing, 1 lobar pneumonia) and 62 were in the control group. We excluded children with congenital heart diseases and other conditions associated with pulmonary hypertension. The method of time to peak velocity corrected for heart rate was used to estimate pulmonary arterial pressure (PAP). We analysed 2 age-subgroups: 1-2 months and 2-12 months. A Student's t-test for independent samples was used to compare the mean values of variables.*

Outcomes: *Increased mean pulmonary pressures (>25mmHg) were measured in 18 infants with respiratory diseases, with the next distribution: 14 bronchiolitis, 2 bronchopneumonia, 1 episodic wheezing, 1 interstitial pneumonia. The values were categorized as mild-moderate pulmonary hypertension. Mean PAP were significantly increased in subjects with clinically bronchoobstructive disease (bronchiolitis, episodic wheezing, bronchopneumonia) vs. control ($p=0.05$ in first age-subgroup and <0.001 in second age-subgroup). In infants with bronchoobstructive disease hospitalization was significantly longer in patients with pulmonary hypertension vs. normal PAP ($p= 0.04$ in first age-subgroup and 0.005 in second age-subgroup). In patients with bronchoobstructive diseases, mean PAPm and PAPs were significantly increased in subjects with a moderate/severe episode of wheezing at admission vs. a mild episode ($p=0.02$). Mean PAPm and PAPs were increased in subjects with interstitial pneumonia vs. control, but without statistic significance.*

Conclusion: *Echocardiography is a non-invasive investigation, which brings valuable information regarding pulmonary hypertension in infantile acute respiratory pathology. We found increased PAP almost exclusively in bronchoobstructive diseases; the mechanic effect of hyperinflation on pulmonary vessels is probably the dominant mechanism. PHT could be a criterion in establishing the severity of an acute wheezing episode, a prognosis factor and an element of therapeutic guidance.*

Key words: pulmonary hypertension, Doppler echocardiography, acute respiratory diseases

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INTRODUCTION

Noninvasive diagnosis of pulmonary hypertension and evaluation of its severity in respiratory diseases have been important clinical problems during last 20 years. Studies in children are definitely fewer then in adults and generally on little number of patients, most of them regarding neonatal respiratory pathology and cystic fibrosis. The impact of acute pulmonary diseases is even less studied.

If we consider only bronchiolitis, the results are discordant. Pahl E.&al (1) performed in 1987 pulsed Doppler assessment of pulmonary arterial flow in 19 patients with structurally normal hearts during acute bronchiolitis. No statistically significant differences in right ventricular systolic time intervals, or Doppler flow measurements were observed. They concluded that in patients with structurally normal hearts, respiratory syncytial virus bronchiolitis is not associated with significant depression of cardiac performance or elevation in pulmonary resistance.

One year later, Sreeram (2) published a report about 21 children with normal hearts studied during acute bronchiolitis. Doppler echocardiography showed tricuspid valve regurgitation in 11 patients, 5 having evidence of raised pulmonary artery systolic pressure: 2/8 with moderate bronchiolitis and 3/3 with severe disease. Serial studies in those with severe infection showed that tricuspid regurgitation disappears with clinical improvement. Fitzgerald (3) studied 6 previously well infants (four preterm, two term) ventilated for bronchiolitis. Four patients had mild pulmonary artery hypertension and two had normal pulmonary artery pressures.

Shann&McGregor (4) reported right ventricular cardiac failure secondary to pulmonary hypertension in 26% of 47 children with severe pneumonia. Tachycardia was not associated with right ventricular dilatation on ultrasound, but 3 of the 4 children with more than 3 cm of liver palpable in the abdomen had right ventricular dilatation. Only 4 of the 12 children with right heart failure had hepatomegaly, tachycardia, raised jugular venous pressure or peripheral edema. They concluded that right ventricular failure is common in children with severe pneumonia, and it is probably caused by pulmonary hypertension rather than septic toxemia.

In order to evaluate pulmonary arterial pressure, most echocardiografic methods relies on pathologic shunts or tricuspid and pulmonary regurgitations, which are rare in previously normal hearts.

Kitabatake et al (5) described the close correlation between pulmonary artery pressure and time to peak velocity (TPV) and its improvement by dividing TPV at right ventricular ejection time (ET) in 33 adult patients studied by Doppler and cardiac catheterization. In the pediatric age group, TPV and TPV/ET are influenced by heart rate, and may be corrected for its effect. In a study on 86 children undergoing cardiac catheterization, Serwer&al (6) created regression equations to correct TPV at heart rate (TPVN) and to estimate pulmonary pressure with good correlation coefficients:

$$TPVN = 182.3 - 0.79 \times AV,$$
$$r = -0.86,\ p < 0.001$$
$$\text{Systolic pressure} = e^{(5,8 - 2,5\ TAP/TAPN)},$$
$$r = -0.91,$$
$$p < 0.01$$
$$\text{Mean pressure} = e^{(5,5 - 2,7\ TAP/TAPN)},$$
$$r = -0.87,$$
$$p < 0.01$$

r = correlation cofficient, e = irrational constant approximately equal to 2.718281828, the base of the natural logarithm. ❑

OBJECTIVE

The purpose of this study was to determine whether previously healthy infants with acute respiratory diseases develop elevated pulmonary artery pressures and to identify which type of disease is involved in developing pulmonary hypertension (PHT). ❑

MATERIALS AND METHODS

137 infants were included in the present study. 75 had respiratory diseases, their mean age was 5.44 months and the male to female ratio was 2.5:1. In the control group were included 62 infants with a mean age of 4.54 months and a male to female ratio of 1.5:1. The patients were evaluated by the same physician, from November 2007 to December 2009, in the echocardiography laboratory of „Grigore Alexandrescu" Hospital. 75 infants had acute respiratory diseases (49 bronchiolitis,

16 interstitial pneumonia, 3 bronchopneumonia, 6 episodic wheezing, 1 lobar pneumonia); diagnosis was based on clinical, radiological and laboratory findings. Bronchiolitis, episodic wheezing and bronchopneumonia were considered bronchoobstructive diseases. The gravity of a wheezing episode was appreciated using the criteria of Severity of Asthma Exacerbations – GINA Guide 2006. In the control group were included 62 infants, healthy or hospitalised for pathology without cardiopulmonary involvement, referred to the echocardiography laboratory for evaluation of an innocent murmur or abnormal X-ray findings due to thymus hypertrophy. We excluded the patients with congenital heart diseases, portal hypertension, HIV infection, storage diseases, hemoglobinopathies, mieloproliferative diseases, familial pulmonary hypertension.

Echocardiographic studies were performed in all children using a real-time ultrasound imaging system General Electrics Logiq 500, equipped with S611, a 5MHz(4-6MHZ) transducer. Echocardiographic measurements were made in unsedated children. The procedure for each study was as follows: the pulmonary artery was visualised from the parasternal short axis view. The Doppler sample volume was placed just distal to the pulmonary valve and the pulmonary artery flow pattern was recorded. The pattern was frozen on the screen and the time intervals were measured using the incorporated Doppler measurement calipers. Time to peak velocity (TPV) was measured as the time interval between the systolic Doppler waveform leaving the baseline and reaching its peak velocity. ET was the time interval between the systolic waveform leaving and returning to the baseline. The length of a cardiac cycle was measured between two peaks to calculate the heart rate at the moment of the echo examination. A mean of five systolic waveforms was taken. Systolic and mean PAP (PAPs and PAPm) were calculated from the above regression equation. Pulmonary hypertension (PHT) was considered when PAPm exceeded 25mmHg. Mild PHT was considered when PAPs was less than 45 mmHg, moderate PHT when PAPs was between 45 and 70 mmHg and severe PHT when PAPs exceeded 70 mmHg.

A Student's t-test for independent samples was used to compare the mean values of study variables. $p<0.05$ was considered statistically significant. ❑

RESULTS

Increased mean pulmonary pressures (PAPm> 25mmHg) were measured in 18 infants with respiratory diseases, with the next distribution: 14 bronchiolitis, 2 bronchopneumonia, 1 episodic wheezing, 1 interstitial pneumonia. (Figure 1). The values were categorized as mild-moderate. At follow-up, all infants had completely recovered from the symptoms that prompted hospitalization.

In the control group, 2 infants had mild pulmonary hypertension, both aged under 2 months (PAPm=25.48 and 27.87mmHg).

We found measurable tricuspid regurgitation (TR) in only 3 infants; the values of systolic PAP calculated using Bernoulli formula were concordant with those calculated using the above regression equation. We haven't found right ventricle (RV) dilatation or hypertrophy in any subject and, regarding RV systolic function, TAPSE values were all above the lowest accepted limit for age (7).

It's well known that in healthy subjects PAP falls abruptly at birth and then more gradually, reaching adult levels by 3 to 6 weeks of age. (8) For this reason, we analysed separately the group aged between 1 and 2 months. In this subgroup, containing 38 subjects (18 ill and 20 control), we found 2 healthy infants with mild pulmonary hypertension (PAPm=25.48 and 27.87mmHg) and 6 respiratory patients with mean pulmonary pressures exceeding 25mmHg (3 mild and 3 moderate PHT), 3 having bronchiolitis, 2 bronchopneumonia and 1 interstitial pneumonia (Figure 2). Analytic statistics for this age group revealed:

- PAPm was significantly increased in subjects with bronchoobstructive diseases (23.43±12.66mmHg) vs. control (16.85±6.05mmHg). Results are presented as mean pressure± standard deviation. Mean difference was 6.58mmHg (p=0.05)
- PAPs was significantly increased in subjects with bronchoobstructive diseases (37.30±18.73mmHg) vs. control (27.62±9.23mmHg). Mean difference was 9.68mmHg (p=0.05)
- PAPm was increased in subjects with interstitial pneumonia (21.14±6.21mmHg) vs. control (16.85±6.05mmHg), but without statistic significance. Mean difference was 4.29mmHg (p=0.144)

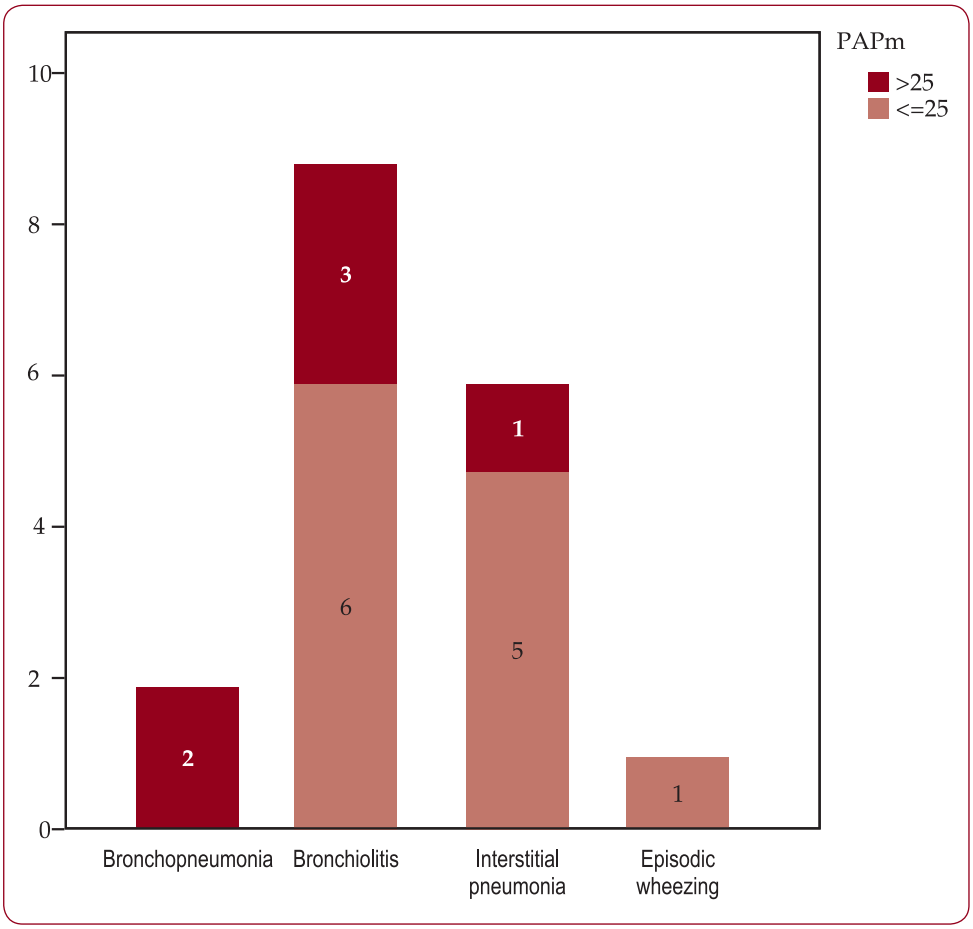

FIGURE 1. Diagnosis in infants aged 1-2 months and number of pulmonary hypertension cases corresponding to each diagnosis

- PAPs was increased in subjects with interstitial pneumonia (34.12±9.37mmHg) vs. control (27.62±9.23 mmHg), but without statistic significance. Mean difference was 6.5mmHg (p=0.145)
- In the subgroup with bronchoobstructive disease, hospitalization was significantly longer in infants with pulmonary hypertension (11±6.12 days) vs. normal PAP (5.29±1.97 days); mean difference was 5.71 days (p =0.04)
- In the subgroup with bronchoobstructive disease, PAPm was significantly increased in subjects with a moderate/severe episode of wheezing at admission (29.08 ±11.46 mmHg) vs. a mild episode (12.14±5.15mmHg). Mean difference was 16.94mmHg (p = 0.02)
- In the subgroup with bronchoobstructive diseases, PAPs was significantly increased in subjects with a moderate/severe episode of wheezing at admission (45.76 ±16.65mmHg) vs. a mild episode (20.36±8.13mmHg). Mean difference was 25.4mmHg (p= 0.018)

In the group aged between 2 and 12 months containing 99 subjects (57 ill and 42 control) we found 12 respiratory patients with PHT (5 mild and 7 moderate values), 11 having bronchiolitis and 1 episodic wheezing. Analytic statistics revealed:

- PAPm was significantly increased in subjects with bronchiolitis (19.08±7.83 mmHg) vs. control (13.85±5.01mmHg). Mean difference was 5.23mmHg (p = 0.001)
- PAPs was significantly increased in subjects with bronchiolitis (30.93±11.86 mmHg) vs. control (23.02±7.77mmHg). Mean difference was 7.91mmHg (p =0.001)
- PAPm was significantly increased in sub-

jects with episodic wheezing (21.98±11.07mmHg) vs. control (13.85±5.01 mmHg). Mean difference was 8.13mmHg (p=0.005)

- PAPs was significantly increased in subjects with episodic wheezing (35.26 ±16.27mmHg) vs. control (23.02±7.77 mmHg). Mean difference was 12.24mm Hg (p=0.006)
- PAPm was significantly increased in subjects with bronchoobstructive disease (19.19±8.19mmHg) vs. control (13.85± 5.01mmHg). Mean difference was 5.34 mmHg (p<0.001)
- PAPs was significantly increased in subjects with bronchoobstructive disease (31.08±12.34mmHg) vs. control (23.02 ±7.77mmHg). Mean difference was 8.06mmHg (p<0.001)
- PAPm was increased in subjects with pneumonia (interstitial and lobar) without bronchoobstruction (15.16±5.24 mmHg) vs. control (13.85±5.01mmHg), but without statistic significance. Mean difference was 1.31mmHg (p=0.45)
- PAPs was increased in subjects with pneumonia (interstitial and lobar) without bronchoobstruction (25.02±8.08 mmHg) vs. control (23.02±7.77mmHg), but without statistic significance. Mean difference was 2mmHg (p=0.47)
- In the subgroup with bronchoobstructive disease, hospitalization was significantly longer in infants with pulmonary hypertension (13.5±7.79 days) vs. normal PAP (7.97±4.35 days); mean differences were 5.53 days (p =0.005)
- In the subgroup with bronchoobstructive disease, mean PAPm was significantly increased in subjects with a moderate/severe episode of wheezing at admission (21.2±7.83 mmHg) vs. a mild episode (16.08±6.61mmHg). Mean difference was 5.12mmHg (p= 0.02)
- In the subgroup with bronchoobstructive disease, mean PAPs was significantly

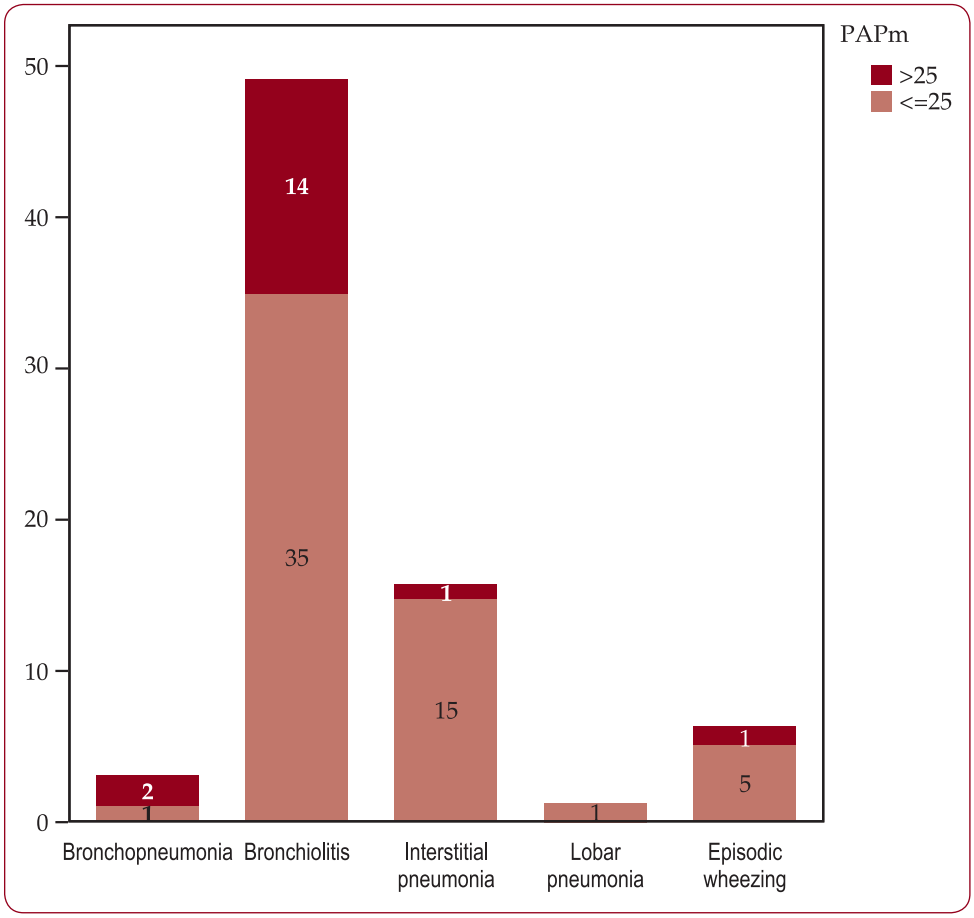

FIGURE 2. Diagnosis in infants aged 1-12 months and number of pulmonary hypertension cases corresponding to each diagnosis

increased in subjects with a moderate/severe episode of wheezing at admission (34.13±11.78 mmHg) vs. a mild episode (26.41±10.10mmHg). Mean difference was 7.72mmHg (p= 0.02)

We also analysed in all subjects if other variables as sex, birth-weight, number of days from the beginning of symptoms, pH in venous blood, minimal pulsoximetry saturation (SaO2) during hospitalization were significantly different in respiratory patients with PHT vs. patients with normal PAP. The results did not have statistical significance. We compared the mean heart rate between the group with PHT and the group with normal PAP (p=0.628), in order to prove that the significant differences obtained in children with more severe wheezing episodes weren't due to tachycardia. ❑

DISCUSSIONS

Previous studies in children with cor pulmonale concluded that chronic hypoxia is the main cause of pulmonary vasoconstriction and the phenomenon seems to be age –dependent, more profound in infants then in adults. It also seems to be variability among individuals of the same age in their pulmonary vascular reactivity. Structural remodeling may be seen in pulmonary vessels, even when increased vascular resistance has been present only for a few days, but it is reversible to normal oxygenation (7) Other factors include acidosis, through a direct pressure effect on pulmonary circulation, and polycythemia, which contributes to a rise in resistance. Hypercarbia appears to act by causing respiratory acidosis. In our study, these factors don't seem to play the main role. We found the most cases of PHT in children with bronchoobstructive disorders (17 from 18 cases), some of them having normal oxygen saturations or normal ASTRUP parameters. No one had polycythemia.

The mechanical effect of hyperinflation seems to be more involved in our findings. It 's also well known the relationship between lung volumes (or alveolar distension) and the status of the pulmonary vessels. In the pulmonary vascular bed, intra-alveolar vessels are submitted externally to the pressure of distal airways, which is normally close to the atmospheric pressure (the zero reference level for vascular pressures) in an open airway. If lung volumes increase above functional residual capacity (FRC), the alveolar capillaries become stretched, their luminal diameter falls and pulmonary vascular resistance increases (9). In obstructive lung disease, residual volume(RV) and FRC increase due to air trapping associated with difficulty in exhalation, thus explaining the changes in pulmonary resistances. In fact, a part of the criteria we used to establish the severity of a wheezing episode are the clinical correspondent of these spirometric data. The significant correlation we found between PAP and the intensity of the wheezing episode could be an argument for the involvement of this mechanism in PHT.

Echocardiography introduces a new criterion of severity in acute bronchoobstructive disease. Brooks & McBride (10) tried to predict deterioration in previously healthy infants hospitalized with respiratory syncytial virus infection. A respiratory rate>80 and an O2 saturation<85% at time of presentation each had a specificity>97% for predicting subsequent deterioration but a sensitivity</=30%. The conclusion was that only a small proportion of patients who clinically deteriorate presented with low oximetry and important polypneea and the clinical usefulness of these parameters is limited. Pulmonary hipertension could also be a prognosis factor, because we proved that it correlates with a longer hospitalization.

Echocardiographic investigation of pulmonary pressure using TPV doesn't ask special skills and isn't an expansive work-up. The regression equation above seems complicated but we could use the ratio TPV/ET as screening method, with cut-off 0.35 (11-13). Thus a "risk" group will be obtained, whose TPV will be further corrected for heart rate.

The method is also useful for therapy guiding, helping the clinician to select those respiratory drugs which are active on pulmonary circulation too: oxygen, aminophylline, isoproterenol, terbutaline. There is a known, direct relationship between alveolar carbon dioxide concentration and airway dilatation (7). Those alveoli with intact perfusion receive carbon dioxide-rich blood and develop a high internal carbon dioxide concentration. The airways that ventilate these alveoli dilate and thus promote carbon dioxide elimination. If perfusion and CO2 delivery are poor, airways do not dilate. Nitric oxide, a pulmonary vasodilator, has already been used with good results in children with severe bronchiolitis, improving oxygenation and respiratory system resistance (14).

CONCLUSION

Echocardiography is a non-invasive investigation, which brings valuable information regarding pulmonary hypertension in infantile acute respiratory pathology.

We found increased PAP almost exclusively in bronchoobstructive diseases; the mechanic effect of hyperinflation on pulmonary vessels is probably the dominant mechanism.

PHT could be a criterion in establishing the severity of an acute wheezing episode, a prognosis factor and an element of therapeutic guidance. ❑

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