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## RESEARCH ARTICLE

# ASSOCIATION OF SEVERE ACUTE LOWER RESPIRATORY TRACT INFECTIONS WITH PULMONARY HYPERTENSION IN INFANTS AGED 2 MONTHS TO 1 YEAR, A PROSPECTIVE STUDY

***Kotyal B. Mahendrappa and Nandakishore Reddy**

Department of Paediatrics, JSS Medical College and JSS Academy of Higher, Education and Research Mysore, Karnataka, India

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**ABSTRACT**

**Introduction:** Acute lower respiratory tract infection (LRTI) is the major cause of morbidity and mortality in infants. Acute LRTI is known to affect the pulmonary pressure. Noninvasive early diagnosis of pulmonary arterial hypertension (PAH) and intervention in infants with acute LRTI may reduce the progression of disease to advanced stage and improves the survival rate. **Objective:** To determine hospital based incidence and association of pulmonary hypertension in infants aged 2 months to 1 year with severe acute lower respiratory tract infections. **Materials and Methods:** A prospective cross sectional study was conducted in a tertiary care hospital of south India. The study included 80 infants aged between 2 months to 1 year, admitted in PICU with severe acute lower respiratory infections (diagnosed as per WHO criteria). Majority of cases included under acute LRTI were Bronchopneumonia (58), remaining 14 cases had bronchiolitis and 8 cases had wheeze associated lower respiratory infection (WALRI). Infants with congenital heart diseases, infants with PPHN, with portal hypertension and familial pulmonary hypertension are excluded from the study. Pulmonary pressure was measured using 2D Doppler Echocardiography once within 24 hours of admission in all study subjects. Repeat 2D Doppler ECHO was done after treatment of acute LRTI at the time of discharge in infants with pulmonary hypertension to know the degree of decrease in pulmonary pressures and outcome. Appropriate statistical methods were used to calculate the incidence. **Results:** There was a direct correlation between severe lower respiratory tract infections and pulmonary pressure. Hospital based incidence of pulmonary arterial hypertension in severe acute LRTI was 56.3%. Infants between age group of 2-4 months had higher incidence of PAH, which contributes to 47.5%. Incidence of PAH in males was 58.3% and in females was 50%. Incidence of PAH in bronchopneumonia was 53.4%, in Bronchiolitis it was 64.2% and in WALRI it was 62.5%. Repeat 2D Doppler ECHO after treatment of severe acute LRTI revealed decrease in pulmonary pressure. **Conclusion:** This study revealed a direct correlation between severe lower respiratory tract infections and increase in pulmonary pressure. Treatment of severe acute LRTI has resulted in decrease in pulmonary pressure. 2D Doppler Echocardiography may be a simple non invasive tool to diagnose pulmonary hypertension in children with severe LRTI.

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## INTRODUCTION

Every year ARTI in young children is responsible for an estimated 3.9 million deaths worldwide (Goeal *et al.,* 2012). In India about 26.3 million cases of ARTI were reported in 2011 (Sharma *et al.,* 2013). Acute LRTI contributes to 15-30% of all under 5 mortality in India (Goeal *et al.,* 2012). There is a relationship between lung volumes or alveolar distension and status of pulmonary vessels. If lung volumes increase above functional residual capacity (FRC), alveolar capillaries become stretched; their luminal diameter falls and pulmonary vascular resistance increase and thus increases in pulmonary pressure.

**Corresponding author:* **Kotyal B. Mahendrappa,**
Department of Paediatrics, JSS Medical College and JSS Academy of Higher, Education and Research Mysore, Karnataka, India.

In obstructive lung diseases, residual volume (RV) and FRC increase due to air trapping thus explain the changes in pulmonary resistance (Luiza Bardi Peti and Eugen Pascal Coifu, 2010). The vascular endothelium is now recognized as an important source of locally acting mediators that contribute to the control of vasomotor tone and structural remodeling and it appears to play a crucial role in the pathogenesis of PAH (Wagenvoort *et al.,* 1977). Stewart and Gaid reported elevated circulating levels of endothelin, a potent vasoconstrictor and mitogen , in patients with various PAH with increased local production of endothelin by the pulmonary arterial endothelium reported in the PAH patients (Stewart *et al.,* 1991; Giaid, 1998). Pulmonary hypertension is defined as pulmonary arterial systolic blood pressure >35 mm Hg as per 2D Doppler echocardiography (Lanzarini *et al.,* 2005).

Pulmonary hypertension can be implicated in the morbidity and mortality in many areas of cardiac and non cardiac pathology. Traditionally a diagnosis of pulmonary hypertension was accomplished by bleak prognosis with survival rates <2.8 years. Noninvasive diagnosis of pulmonary hypertension and evaluation of its severity in respiratory diseases has been a clinical challenge in the last two decades. There are not many studies on the effect of LRTI on pulmonary pressure in children. Hence, this study was intended to determine hospital based incidence and association of pulmonary hypertension in infants aged 2 months to 1 year with severe acute LRTI.

## MATERIALS AND METHODS

A prospective cross sectional study was conducted in a tertiary care hospital of south India. All infants aged between 2 months to 1 year admitted in PICU, during the study period with severe acute LRTI (as per WHO criteria) were included in the study until the sample size is met. Infants with congenital heart diseases, those infants previously diagnosed to have PPHN, portal hypertension, familial pulmonary hypertension were excluded. According to WHO, severe ARI is defined as ARI with rapid breathing more than upper limit for age, lower chest retraction, feeding difficulties, respiratory distress and pulse oximetry reading of less than 90%, requiring hospital treatment with intravenous medications and management with oxygen therapy Respiratory rate of >50 breaths/min in infants aged 2 to <12 months was taken as abnormal. After taking a valid consent from the parents of study subjects, each infant was examined and subjected for routine blood investigations, blood gas analysis and chest x ray. Based on the clinical and chest x ray findings, infants were diagnosed to have bronchopneumonia, bronchiolitis and WALRI. Within 24 hours of admission, 2D Doppler echocardiography was done on all study subjects to measure pulmonary artery pressures. 2D Echocardiography was done by cardiologist using phased array pediatric probe (7 MHz). Doppler technique was used to measure Right ventricular systolic pressures (RVSP). Pulmonary arterial systolic blood pressure of <35mmHg was considered as Normal. Based on RVSP, PAH was graded into >35 mmHg moderate PAH and > 60mmHg Severe PAH. 9 Infants included in the study were treated for the underlying condition with appropriate antibiotics and oxygen supplementation for resolution of acute respiratory infections. After resolution of respiratory infection and before discharge repeat 2D ECHO was done on the infants with pulmonary hypertension to know the degree of decrease in pulmonary pressures. Summary statistics was done using mean, median, standard deviation, IQR and proportions. Inferential statistics is done using chi-square test, independent t test, Mann Whitney test, kruskal Wallis test and ANOVA. SPSS version 21.0 is used for all measurements. Graphical representation is done using Microsoft Excel and SPSS.

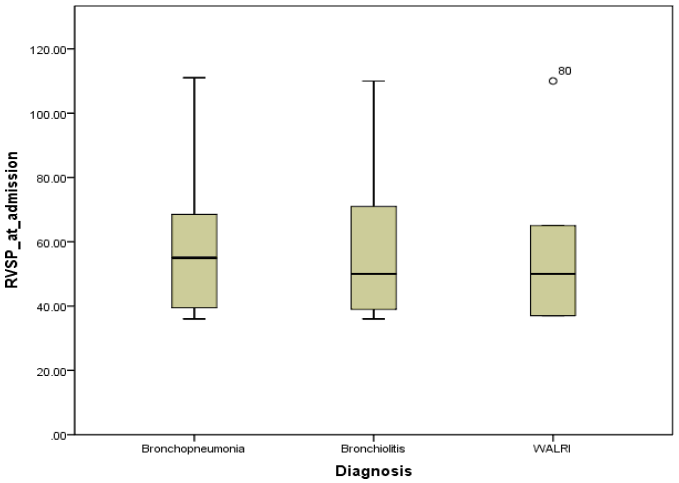
## RESULTS

Study population included 80 infants, of which majority of them (38) were in the age group of 2-4 months (47.5%). The mean age of study subjects was 5.2+ 3.2months and median age of study subjects was 5 months. Out of 80 cases with severe ALRTI, 45 (56.3%) infants developed pulmonary hypertension and 35(43%) had normal pulmonary pressure. So hospital based Incidence of PAH in the present study was 56.3%. Out of 45 infants with PAH, 31(68.9%) had bronchopneumonia, 9(20%) bronchiolitis and 5(11.1%) had WALRI. Out of 60 males, 35 had pulmonary hypertension (58.3%) and out of 20 females 10 (50%) had pulmonary hypertension. Maximum incidence of PAH (63.2%) was noted in infants between age group of 2-4 months. Out of 45 infants with PAH, 14(31.1%) infants had mild PAH, 12(26.6%) had moderate PAH and 19(42.2%) had severe PAH.

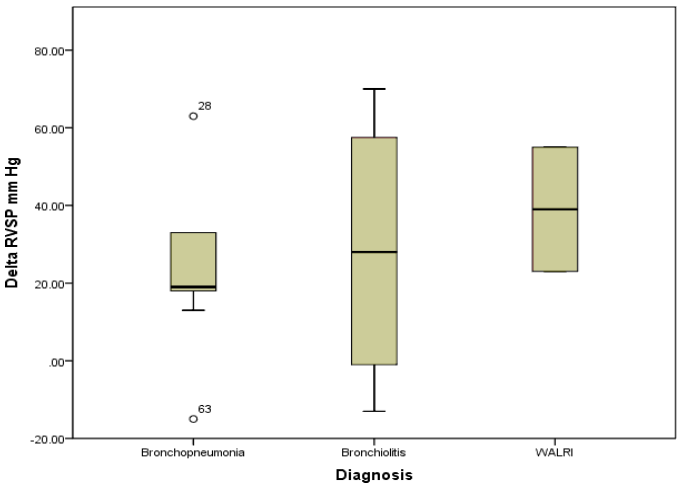
**Table I. Age distribution**

| | | Count | Column N % |
|---|---|---|---|
| Age category | 2-4 months | 38 | 47.5% |
| | 4.01 to 6 months | 20 | 25.0% |
| | 6.01 to 8 months | 8 | 10.0% |
| | 8.01 to 10 months | 6 | 7.5% |
| | >10.01 to 12 months | 8 | 10.0% |

Out of 80 cases 60 (75%) were males and 20 (25%) were females. Distribution of LRTI included 58(72.5%) cases of bronchopneumonia, 14 (17.5%) bronchiolitis and 8(10%) WALRI.




**Graph I. Whisker box plot showing Median RVSP values of study subjects with PAH with respect to Diagnosis**




**Graph II. Whisker box plot showing Median Δ RVSP values of PAH subjects with respect to diagnosis after resolution of respiratory pathology**

Median RVSP in infants with bronchopneumonia (55 mmHg), was greater than that of bronchiolitis (50 mmHg) and WALR I (50 mmHg). The median RVSP after resolution of respiratory pathology grossly reduced in cases with bronchopneumonia (19mm Hg from 55mm Hg) compared to WALRI (39mm Hg from 50mmHg) and bronchiolitis (28mmHg from 50 mmHg). The mean Heart rate of study subjects was 143+ 23.05 per min. Mean heart in infants with severe PAH was higher when

compared to infants with mild and moderate PAH, which was statistically significant. The median respiratory rate of study subjects with PAH was 64 per min and without PAH was 62 per min; there was no statistically significant difference in Respiratory rate (p value-0.8). Median SPO2 level in infants without PAH was 86% and in infants with PAH was 84%. There was no statistically significant difference in spo2 levels in room air in infants with PAH and without PAH (p value-0.98). Median PaO2 levels in infants without PAH was 107 mm Hg and with PAH was 80.8 mmHg, there was a statistically significant difference in PaO2 levels in infants with and without PAH. Median O2 requirement for infants without PAH was 3 liters and with PAH was 5 liters. Statistically there was a significant difference in oxygen requirement between infants without and with PAH in the present study, (P value 0.001). Mean PH value of study subjects was 7.31 in infants without PAH and 7.29 in infants with PAH There was no statistically significant difference in PH value in infants with PAH and without PAH (P value-0.7) Mean duration of hospital stay in PAH infants with bronchopneumonia was 8.42+ 2.9 days, with that of bronchiolitis was 7.67+ 2.6 days and with WALRI was 7.20+ 1.9 days. There was no significant difference in duration of hospital stay of study subjects with PAH, with respect to diagnosis.

## DISCUSSION

Secondary Pulmonary hypertension due to acute respiratory infections was a common complication, encountered in the present study. A total of 80 infants aged between 2 months to 1 year with severe LRTI as per WHO criteria formed the study subjects. In the present study, mean age of study subjects was 5.2+ 3.2 months and median age of study subjects was 5 months, which was similar to study done by Luiza bardi peti et al with the median age of their study subjects 5.4 months3. In the present study, maximum number of cases (38 out of 80) were in the age group of 2-4 months (47.5%). Maximum incidence of PAH (63.2%) was also noted in infants was between age group of 2-4 months. Male to female ratio of the study population was 4:1.which was similar to study done by Ilten *et al.* in turkey who studied 50 patients with 36 (72%) males and 14(28%) females (Ilten *et al.,* 2003). There was no significant difference in the incidence of PAH in males (58.3%) and females (50%) in the present study. The hospital based incidence of pulmonary hypertension secondary to severe acute lower respiratory infections in our study was 56.3% which is comparable to a study by Ilten *et al.* who has noted 64.2% incidence. Sreeram *et al.* in his study has noted 45% incidence of pulmonary hypertension infants with bronchiolitis (Sreeram *et al.,* 1989).

The incidence of pulmonary hypertension in bronchiolitis was higher compared to that of WALRI and Bronchopneumonia which may be due to bronchial obstruction and vasoconstriction mechanism in bronchiolitis and WALRI. Similar observation was noted in the present study wherein out of 58 infants with bronchopneumonia, 31(53.4%) developed PAH. In 14 infants with Bronchiolitis, 9(64.2%) had developed PAH. In 8 infants with WALRI 5(62.5%) developed PAH. So the incidence of PAH in bronchopneumonia was 53.4%, in Bronchiolitis it was 64.2% and in WALRI it was 62.5%. In the present study we noted a relatively higher Pulmonary pressure (> 50 mm) in infants with LRTI compared to a study done by Luiza Bardi-peti *et al.* who observed >25mm Pulmonary pressure in 25 out of 75 patients with acute respiratory infections and Uner *et al*. 43 in turkey has noted >35mm hg of systolic pulmonary arterial pressures in 15 children (40.5%) out of 37 patient.12 Ilten *et al.* (2003) noted high Right ventricular systolic pressure (RVSP) in 35(70%) of 50 patients and also noted a direct correlation between the severity of the pneumonia and RVSP. In the present study majority of cases 19(42.2%) had severe PAH, the remaining 14(31.1%) infants had mild PAH and 12(26.6) had moderate PAH. In the present study, infants with bronchopneumonia had a higher median pulmonary pressure compared to bronchiolitis and WALRI which is contrary to study done by Luiza Bardi Peti et al who noted the increased mean pulmonary pressures in bronchoob structive diseases like bronchiolitis. In his study the median delta RVSP was more in bronchiolitis than WALRI and bronchopneumonia and they concluded that the possible mechanism for increased PAP in children with bronchoob structive diseases was the mechanical effect of hyperinflation on pulmonary vessels. Shann *et al.* reported that, out of 31 children with severe pneumonia, 12 (26%) children had right ventricular failure secondary to pulmonary Hypertension.

They concluded that right ventricular failure is common in children with severe pneumonia and it is probably caused by pulmonary hypertension rather than septic toxemia10, but no case of right ventricular failure was noted in the present study. In a study by Fitzgerald *et al.* (2001) Four infants out of 6 patients had mild pulmonary hypertension and 2 patients had normal pulmonary artery pressures. Sreeram *et al.* (1989) in 1989 studied 21 children with normal hearts during acute bronchiolitis. Doppler echocardiography showed tricuspid valve regurgitation in 5 out of 11 children with severe LRTI, evidence of raised pulmonary artery systolic pressure. Also observed decrease in pulmonary artery pressure after treatment of severe LRTI, a similar finding noted in our study. A study done by Bardi peti L et al. in 94 infants aged between 2 months to 12 months with 47 controls and 47 cases showed increased mean pulmonary pressures in 13 infants with bronchiolitis (Bardi-Peti *et al.,* 2010). Repeat measurement of pulmonary arterial pressure after resolution of respiratory pathology showed significant drop in pulmonary pressure especially in cases of bronchopneumonia. The median RVSP after resolution of respiratory pathology grossly reduced in cases with bronchopneumonia (19mmhg from 55mmHg) compared to WALRI (39mmhg from 50mmHg) and bronchiolitis (28mmhg from 50 mmHg). This observation supports a direct association of infection and pulmonary pressure. Other variables like Heart rate, Respiratory rate, Spo2 levels, Pao2, PH, Oxygen requirement were compared in infants with PAH and without PAH. We noted a statistically significant difference in mean heart rate and median Pao2 in infants with PAH and without PAH.

### Conclusion

The present study revealed a direct correlation between severe acute lower respiratory tract infections and increase in pulmonary pressure. Early treatment of severe LRTI has resulted in decreased pulmonary pressure. 2D Doppler Echocardiography may be a simple non invasive tool to diagnose pulmonary hypertension in children with severe LRTI. The study suggests screening of infants admitted in PICU with severe acute lower respiratory infections for PAH. Further studies with larger study population and follow up of these subjects, may be needed to know the effect of severe LRTI on pulmonary hypertension and prognosis.

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