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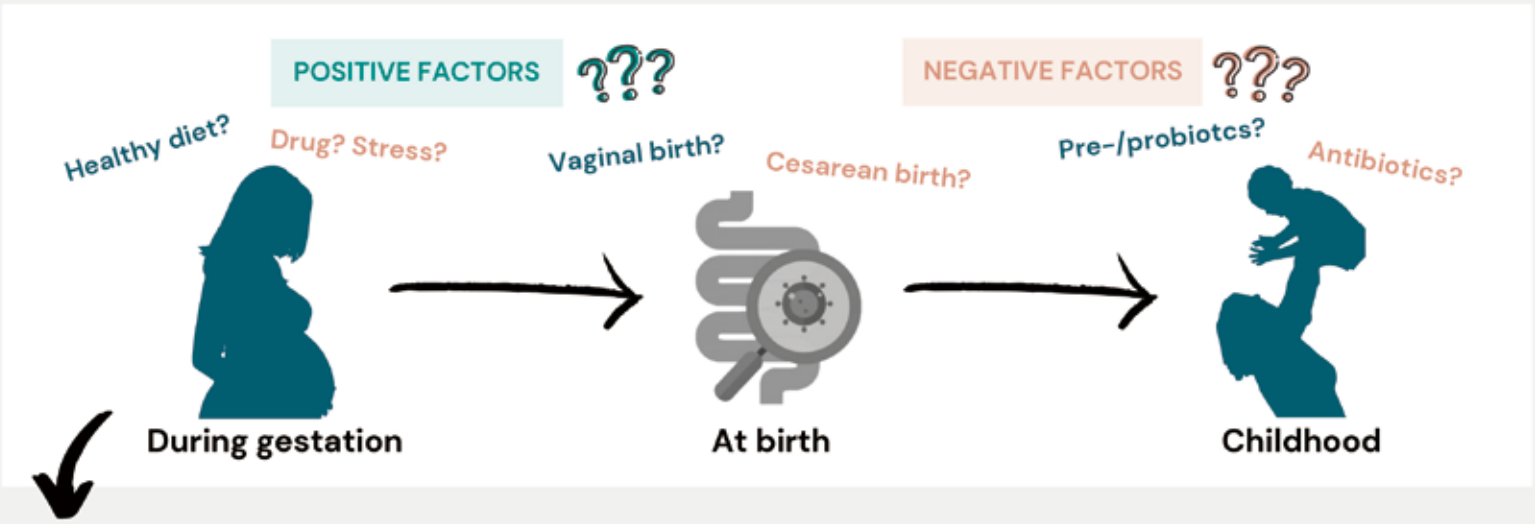

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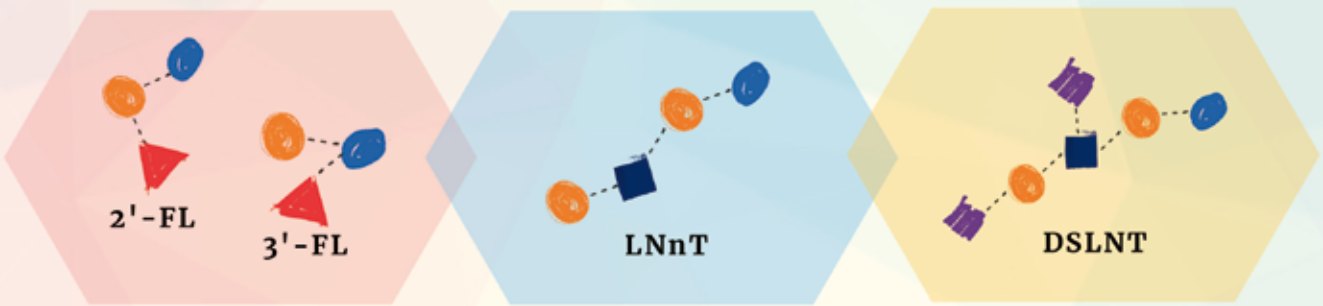

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Contents

From Acute Respiratory Infection, Chronic Atelectasis, to Intensive Hemodynamic Assessment

The current issue includes three very solid articles, from acute illness, chronic sequelae, to intensive care of critical illness, which are all related to the scope of the journal, namely technical and clinical studies in the field of basic and clinical research on pediatric respirology and pediatric critical care medicine. The first article evaluated the prevalence of viral and atypical bacterial infections in young children hospitalized due to acute lower respiratory tract infections in southern Thailand. The second article studied the clinical characteristics and outcomes of ambulatory children with chronic middle-lobe atelectasis (MLA). The third article assessed the correlations among three key noninvasive hemodynamic parameters in ventilated children, including aortic peak blood flow velocity variation (ΔVpeak), inferior vena cava diameter variation (ΔIVC), and stroke volume variation (SVV).

Acute lower respiratory tract infections (ALTIs) are the most common cause of hospitalization in children, and identifying the pathogen is very important because it determines the clinical course and treatment strategy. Several studies have investigated the pathogens that cause ALTIs in young children in Asian countries. Nathan *et al*. reported that the most common viruses identified in children with ALTIs below 2 years of age in Malaysia were respiratory syncytial virus (RSV), human rhinovirus (hRV), and parainfluenza virus.[1] Sung *et al*. reported that RSV was the most common pathogen causing ALTIs in young children <3 years of age in Taiwan.[2] Because the pathogens in Thailand have not been well established, Ruangnapa *et al*. conducted a retrospective study to determine the prevalence of viral and atypical bacterial infections in young children hospitalized due to ALTIs.[3] In their study, the viral pathogens such as RSV B (39.0%), RSV A (20.7%), and hRV (12.2%) were detected in 76% of the patients, while atypical bacteria were not found. These data help to understand the similarity of RSV in ALTIs in younger children in Thailand and other countries, such as Malaysia and Taiwan.

It is usually challenging for pediatricians to identify the etiology and make treatment strategies for atelectasis. Wong and Chiu conducted a retrospective chart analysis study to present their experience of ambulatory children with chronic MLA at a pediatric facility.[4] They found that only 13.3% of the patients were diagnosed with isolated MLA, and the other 86.7% had associated atelectasis or bronchiectasis in other parts of the lung. The most common causes of chronic MLA were postinfectious bronchiectasis (40%) and immunodeficiency (23.3%). The authors concluded that in certain MLA cases, a chronic suppurative lung disease with or without bronchiectasis should be considered, either postinfectious or related to recurrent aspiration.

Assessing hemodynamics is essential in critical patients and helps to improve outcomes. Recent noninvasive parameters including ΔVpeak, ΔIVC, and SVV assessed using ultrasound or Doppler have been shown to assist in rapidly assessing hemodynamics in critical care. Boonjindasup and Samransamruajkit conducted a prospective cohort study on mechanically ventilated children to assess correlations among ΔVpeak, ΔIVC, and SVV.[5] They found significantly positive correlations among ΔVpeak, ΔIVC, and SVV, which supports the interchange of monitoring. ΔVpeak and SVV in particular provided the best, though moderate, correlation (Pearson's correlation coefficient, $r = 0.539$; $P < 0.001$). These two parameters may be a surrogate of each other for hemodynamic monitoring in mechanically ventilated children.

These three articles are related to and expand the knowledge on "Pediatric Respirology and Critical Care Medicine." To share your research with a wide audience, we invite you to submit to this expanding and well-respected journal.

During the COVID-19 pandemic, we hope you are safe and well!

Yu-Tsun Su

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Original Article

Viral and Atypical Bacterial Infection in Young Children Hospitalized due to Acute Lower Respiratory Tract Infection in Southern Thailand

Kanokpan Ruangnapa[1], Phatthareeda Kaeotawee[1], Pornapat Surasombatpattana[2], Marisa Kemapunmanus[2], Utcharee Intusoma[1], Kantara Saelim[1], Wanaporn Anuntaseree[1]

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Abstract

Background: The etiology of acute lower respiratory tract infection (ALTI) in Thailand is not well established. **Aims:** This study aims to determine the prevalence of viral and atypical bacterial infections in young children hospitalized due to ALTI. **Settings and Design:** This was a retrospective study. **Subjects and Methods:** Eighty-two leftover nasopharyngeal specimens obtained from children with ALTI admitted from May to October 2017 in Songklanagarind Hospital were analyzed. Multiplex polymerase chain reaction and the bead hybridization method (NxTAG® Respiratory Pathogen Panel) were used to detect 18 instances of respiratory virus and atypical bacteria. The clinical data for the children were retrospectively reviewed and analyzed from the medical records. **Results:** From a total of 82 ALTI patients, 60% were male. The median (interquartile range) age was 14.8 (8.0–38.1) months. Seventy-six percent of the patients were positive for at least one viral pathogen. The three most identified pathogens were respiratory syncytial virus (RSV) B (39.0%), RSV A (20.7%), and hRV (12.2%), while atypical bacteria were not found. Patients with RSV infection had significantly higher fever on admission ($P < 0.01$) and a longer duration of fever (log-rank $P < 0.001$) compared to the non-RSV group. **Conclusions:** Viral pathogens were detected in 76% of the children hospitalized due to ALTI. Further, 79% were positive for RSV with significantly high-grade fever.

Keywords: Children, etiology, lower respiratory tract infection, virus

Introduction

Acute lower respiratory tract infection (ALTI) is a leading cause of hospitalization and death worldwide, especially among children <5 years old.[1,2] Respiratory viruses are detected in 15%–90% of ALTI episodes depending on the methods of detection and the spectrum of viral studies.[3-8] The prevalence of each respiratory pathogen varies from study to study due to population, seasonality, and geographic areas as well as detection techniques.

The aim of this study was to determine the prevalence of viral and atypical bacterial infections in young children hospitalized due to ALTI in Southern Thailand using multiplex polymerase chain reaction (PCR) and bead hybridization technique to specify the clinical symptoms for different respiratory pathogens.

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Subjects and Methods

This was a retrospective study conducted at Songklanagarind Hospital, Thailand, between May and October 2017 using electronic medical records and leftover nasopharyngeal specimens stored at the microbiological laboratory of Songklanagarind Hospital. Ethics committee approval was obtained [REC-60-388-01-1] before initiation of the study.

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The study population included hospitalized children younger than 5 years diagnosed with ALTI with discharge diagnosis of ICD-10 including J09-J18 (influenza and pneumonia) and J20-J22 (other ALTI). During the study period, patients were excluded if they were diagnosed with congenital heart disease, chronic lung disease or bronchopulmonary dysplasia, neuromuscular disease, cerebral palsy, or severe developmental delay with feeding difficulty. Data collection from electronic medical records included demographic data, birth history, past medical history, family history, clinical manifestations and physical examination on admission, medical treatment, oxygen supplementation, and initial laboratory investigation. Total respiratory distress score was estimated daily during hospitalization until discharged using information in the medical records, including vital signs, oxygen saturation (SpO_2), and the physician's and nurse's notes of a patient's clinical progression (level of consciousness, nasal flaring, chest retraction, and abdominal breathing). Disease severity was defined according to a respiratory distress score as mild (score < 3), moderate (score 4–6), or severe (score 7–9) respiratory distress.

Nasopharyngeal specimens were routinely collected for RSV and influenza antigen detection from every hospitalized child with ALTI during the study period. Further, leftover nasopharyngeal specimens were used for the potential detection of respiratory pathogens by multiplex PCR methods. Nucleic acid was extracted from specimens using the silica absorption spin column technique and tested for twenty viral and atypical bacterial respiratory pathogens using a NxTAG® respiratory pathogen panel kit. Multiplexing PCR and bead hybridization was performed for the detection of influenza (type A, AH1, AH3, and B), parainfluenza virus (PIV type 1–4), respiratory syncytial virus (RSV type A and B), rhinovirus/enterovirus (HRV/HEV), human metapneumovirus (hMPV), human bocavirus (HBoV), adenovirus (AdV), coronavirus (CoV HKU1, CoV NL63, and CoV 229E), and atypical bacteria including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.

Statistical analysis

Data were analyzed using R program (open source) with R studio. Descriptive data were presented as percentile, mean (standard deviation), and median (interquartile range). The comparison of continuous data and categorical data was carried out using Mann–Whitney *U*-test and Chi-square/a Fisher's exact test, respectively. Survival analysis was carried out using Kaplan–Meier analysis and log-rank test to explain and compare the probability of fever and respiratory distress score between different respiratory pathogens during hospitalization. $P < 0.05$ was considered statistically significant.

Results

A total of 87 hospitalized children with ALTI were enrolled from May to October 2017. Five were excluded due to incomplete medical records or inadequate leftover specimens. From the total of 82 children enrolled, 49 were male (59.8%) and the median (range) age was 15 (4–39) months. The median respiratory distress score on admission was 3 (2–4), considered to be mild respiratory distress, while the median length of hospital stay was 3 (2–5) days. The routine rapid antigen test for RSV and influenza detected RSV in 40 from 82 children (48.7%) but did not positive for influenza virus.

Using multiplex PCR method, the viral or atypical bacterial pathogens were detected in 62/82 (75.6%) children [Table 1]. The three most identified pathogens were RSV B (39.0%), RSV A (20.7%), and hRV (12.2%). Co-infection of RSV with other viral pathogens was detected in 6 patients (7.3%), with the most frequent combination being RSV B/hRV in 2 patients (2.4%). No atypical bacterium was detected in this study.

As RSV infection was the major pathogen detected in this study, we identified the clinical characteristics of the RSV-detected patients (PCR positive for RSV A or B) as "RSV group" ($n = 43$) and RSV nondetected patients (negative study or PCR positive for other pathogens) as "non-RSV group" ($n = 39$). There were no significant differences in median age, sex ratio, or clinical diagnosis between the RSV and non-RSV groups [Table 2]. Previous history of recurrent wheezing was significantly higher in the non-RSV group than in the RSV group (41% vs. 9%; $P = 0.02$).

The appearance of respiratory symptoms was not significantly different between the RSV and non-RSV groups, including cough (97.7% vs. 97.4%), dyspnea (86% vs. 97.4%), and rhinorrhea (83.7% vs. 84.6%) [Table 2]. Gastrointestinal symptoms reported in terms of diarrhea and vomiting, for 10.9% and 13.4% of the children, respectively, were not significantly different between the RSV and non-RSV groups. Peak body temperature on admission was significantly higher in the RSV group (38.6°C in RSV vs. 38°C in non-RSV; $P = 0.01$).

Overall, 86.5% ($n = 71$) of the children were treated with oxygen supplementation, including low-flow oxygen

Table 1: Prevalence of respiratory pathogens detected in 82 acute lower respiratory tract infection patients*

Pathogen	*n* (%)
Respiratory syncytial virus B	32 (39.0)
Respiratory syncytial virus A	17 (20.7)
Rhinovirus	10 (12.2)
Human metapneumovirus	2 (2.4)
Bocavirus	2 (2.4)
Coronavirus OC43	2 (2.4)
Influenza virus A	1 (1.2)
Parainfluenza virus type 2	1 (1.2)
Adenovirus	1 (1.2)
Atypical bacteria	0 (0.0)
No pathogen detected	20 (24.0)

*Six patients had respiratory syncytial virus co-infection with other viruses

support (n = 61) and high-flow nasal cannula (n = 10), but no patients required intubation or support with positive pressure ventilation. Antibiotics were prescribed for 10% of the children, which was not significantly different between the RSV and non-RSV groups (P = 0.86 and 1.00, respectively).

The Kaplan–Meier survival curve [Figure 1a] showed a nonsignificant difference in the probability of patients to recover from respiratory distress during hospitalization between the RSV and non-RSV groups. However, time to recover from fever among patients in the RSV group was significantly longer than the non-RSV group [Log-Rank $P < 0.001$], as shown in Figure 1b.

Discussion

The overall detection rate of viral respiratory pathogens with PCR technique in our study (75.6%) was comparable to other studies among children from developing countries including Bangladesh, Brazil, and Papua New Guinea, which ranges from 85% to 90% when using the comparable method with multiplex PCR technique.[4,7,8]

Table 2: Comparison of demographic data, symptoms and signs between respiratory syncytial virus (RSV) and non- RSV patients

	RSV (n=43)	Non-RSV (n=39)	P
Age (months), median (IQR)	13.1 (4.9-28.5)	16.5 (11.1-39.8)	0.09[a]
Male, n (%)	22 (51.2)	27 (69.2)	0.15[b]
Gestational age (weeks), median (IQR)	38 (37-39)	38 (37-39)	0.48[a]
History of previous wheezing, n (%)	4 (9.3)	16 (41.0)	0.02[b,#]
Diagnosis, n (%)			0.02[b,#]
Pneumonia	26 (60.5)	24 (61.5)	
Bronchiolitis	10 (23.3)	8 (20.5)	
Recurrent wheezing	1 (2.3)	7 (17.9)	
Bronchitis	6 (14.0)	0 (0.0)	
Respiratory symptoms, n (%)			
Cough	42 (97.7)	38 (97.4)	1.000[b]
Rhinorrhea	36 (83.7)	33 (84.6)	1.000[b]
Dyspnea	37 (86.0)	38 (97.4)	0.112[b]
Noisy breathing	10 (23.3)	6 (15.4)	0.536[b]
Respiratory distress score on first day, median (IQR)	3 (2-4)	3 (2-4)	0.214[a]
Nonrespiratory symptoms, n (%)			
Vomiting	5 (12.8)	4 (9.3)	0.730[b]
Diarrhea	9 (20.9)	2 (5.1)	0.076[b]
Fever			
Peak body temperature (°C), mean (SD)	38.6 (1.0)	38 (0.8)	0.009[c,#]
Duration of fever before being hospitalized (days), median (IQR)	3 (2-4)	1 (1-3)	0.038[a,#]

[a]Mann-Whitney U-test, [b]Fisher's exact test, [c]Student's t-test, [#]Statistically significant. ALTI=Acute lower respiratory tract infection, RSV=Respiratory syncytial virus, SD=Standard deviation, IQR=Interquartile range

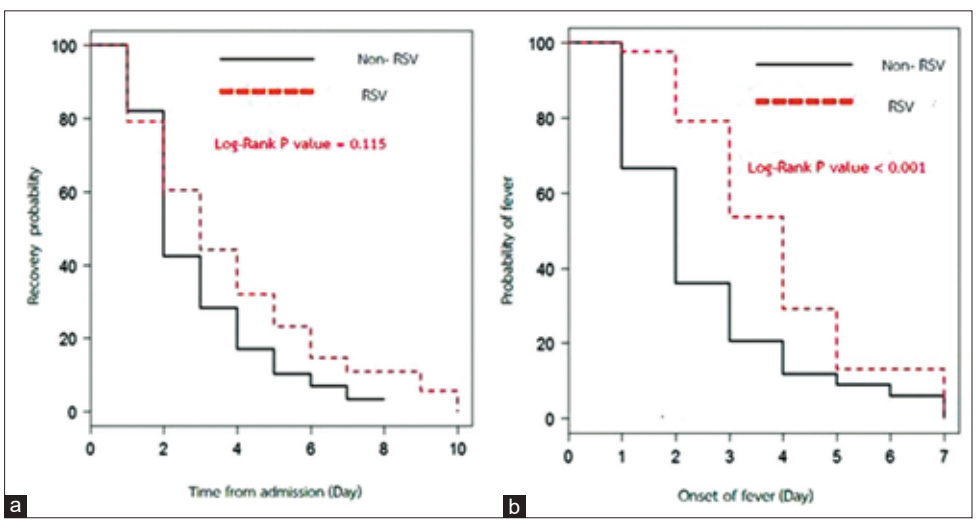

Figure 1: Kaplan–Meier survival curve comparing (a) the recovery from respiratory distress and (b) the recovery from fever.

Our detection rate was higher than a previous population-based study in Northeastern Thailand by Hasan *et al*.[6] which reported an overall viral detection rate of 36.5% in hospitalized ALTI children.This is because of the detection technique using a combination of conventional and real-time reverse transcription-PCR. The previous studies also had a limitation in terms of viral strains detection, as previously mentioned that RSV, influenza A and B, and adenovirus were tested throughout the study from 2005 to 2010, but PIV, hMPV, rhinovirus, bocavirus, and coronavirus were tested partly.

The RSV positivity rate in our study (59.7%) was higher than in other studies, which ranges from 19%–42%.[4-8] There are two possible causes of this finding. First, our study was conducted between May and October, which is considered the rainy season in Thailand and is related to the peak season for RSV infection. Same as the report from Northeastern Thailand by Hasan et al. [6] that 87% of the RSV-detected ALTI cases occurred during June to October. However, our results were markedly different from a study conducted in Shenzhen, China, which reported that RSV was detected primarily during the spring and summer, particularly in March and September.[3] This difference in viral detection may be related to a region's climate and demographic factors.

Second, our population was mostly younger than 2 years (median age of 13 months), which related to the peak incidence of RSV infection in the first 2 years of life. Further, the population of hospitalized patients was related to the severity of disease in children, especially those younger than 6 months old.[9-11]

Atypical bacteria including *M. pneumoniae* and *C. pneumoniae* were not detected in our study, which is different from a previous study conducted in Northeast Brazil that reported the incidence of *M. pneumoniae* at 9.8% for children < 5 years old who presented with acute respiratory tract infection at the emergency department.[4] The difference in detection rate of atypical pathogens may be attributed to the technique for specimen collection. While Reznikov *et al*.[12] reported that the PCR for atypical bacterial detection, especially *M. pneumoniae* in nasopharyngeal aspiration and nasopharyngeal swab, had similar positivity percentages (45% and 50%, respectively), some previous studies[13,14] argued that sputum samples from induced sputum technique were superior for the detection of *M. pneumoniae* because the number of bacteria is higher in the pulmonary alveolus than in the epithelium of the upper respiratory tract in patients with pneumonia.

Accordingly, the negative result of atypical bacterial infection by PCR detection method of our study could be also explained by a false negativity since the PCR technique is not a gold standard test. The currently accepted standard method for the diagnosis of *M. pneumoniae* infection is a combination of direct pathogen detection using molecular techniques and the serological testing.[15] The presence of organisms at numbers below the limits of detection of the assay due to previous antibiotic treatment could be another important contributing factor for probable false negative. Thus, we cannot conclude that the prevalence of atypical bacterial infection in our setting was low or negative.

Clinical characteristic comparison between viral pathogens cannot be determined due to the low detection rate of other viral pathogens besides RSV, so we stratified patients into the RSV and non-RSV groups to compare their clinical characteristics and the severity of disease estimated from median respiratory distress score on admission. We found no significant differences in clinical manifestations between these two groups.

Furthermore, respiratory distress score during hospitalization was not significantly different between the RSV and non-RSV groups, although the duration of fever was significantly longer in the RSV group. From previous studies, 60%–80% of the patients with a single RSV infection had fever (BT >38°C), which was not significantly different from other viral pathogens.[5,9] However, a lack of bacterial co-infection study was a limitation for this study. A previous study of bacterial co-infection in hospitalized children with RSV bronchopulmonary infections found that pathogenic bacteria, including *Haemophilus influenzae* (43.9%), *Streptococcus pneumoniae* (36.6%), and *Moraxella catarrhalis* (29.3%), were predominantly isolated from 43.6% of the children hospitalized due to RSV bronchopulmonary infections, causing high-grade fever and severe respiratory illness.[16]

Our data suggested that respiratory viruses caused a large number of hospitalizations due to ALTI among children <5 years old. Due to the limitations of this study, which included short duration and small population, the results may be insufficient to accurately describe the epidemiological and seasonal distribution of respiratory pathogens in the southern region of Thailand. Larger populations and longer durations of study are recommended for further research concerning the epidemiologic data and seasonal patterns of viral pathogens, as understanding of seasonal patterns for respiratory viruses is essential for effective resource allocation and planning of preventive and therapeutic interventions including vaccine, medications, and personnel.

Conclusions

Detection rate of respiratory pathogens in hospitalized ALTI patients in this study was 76% whereas RSV was the most commonly detected pathogen (60%) and RSV infected patients had significantly higher and longer duration of fever than non-RSV patients.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Chronic Right Middle Lobe Atelectasis in Ambulatory Children

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Abstract

Background: Intrinsic obstruction and extrinsic compression of the airway are the main causes of pulmonary atelectasis. The differential diagnoses of right middle lobe atelectasis (MLA) in children are lengthy, and practicing pediatricians usually are frustrated by the diagnostic possibilities in the clinic. **Objective:** The aim of our study is to present the experience of a children facility with chronic MLA in ambulatory children and guide a pragmatic approach. **Materials and Methods:** Retrospective chart analysis was performed by a computer search for discharge diagnosis of right MLA or MLA between January 2006 and December 2017 in a pediatric department in Northern Taiwan. Demographic data, underlying diseases, clinical symptoms, radiographic features, and course of treatment were collected and analyzed by descriptive statistics. **Results:** A total of 30 pediatric patients with chronic MLA were recruited in this study. Isolated MLA was identified in four (13.3%) patients. The remaining 26 patients had associated atelectasis or bronchiectasis in other parts of the lung. The most common causes of chronic MLA identified in our patients were postinfectious bronchiectasis (40%) and immunodeficiency (23.3%). Asthma was an uncommon cause of MLA in this study. **Conclusions:** Tumors, tuberculosis, retained foreign body, and asthma were all uncommon in the children identified with MLA. While chronic cough was common in the children studied, most were associated with bronchiectasis in other pulmonary segments. When faced with evidence of right MLA, one should consider a chronic suppurative lung disease with or without bronchiectasis, either postinfectious or related with recurrent aspiration.

Keywords: Ambulatory children, middle lobe atelectasis, middle lobe syndrome

Introduction

Atelectasis occurs in three ways: (i) airway obstruction; (ii) compression of the lung by extrathoracic, intrathoracic, or chest wall processes; and (iii) increased surface tension in alveoli.[1] Children are more prone to atelectasis due to smaller airway caliber, increased collapsibility, a greater number of mucous glands in the airway, more compliant chest wall, and less well-developed collateral ventilation.[1,2]

Middle lobe syndrome (MLS) refers to recurrent and chronic atelectasis of the right middle lobe atelectasis (MLA) of the left lingual lobe that may be associated with the MLS.[3] Reported predisposing causes of MLS in children include stenosis of the right middle bronchus and poor development of the interalveolar pores of Kohn and bronchoalveolar canals of Lambert.[4-7]

Our previous experience with chronic atelectasis in children demonstrated various etiologies.[8] Our objective for this report was to summarize our experience of children with MLA in a pediatric tertiary facility in Northern Taiwan after the year 2000.

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Materials and Methods

We performed a computer search for discharge diagnosis of right MLS or MLA of pediatric patients below 18 years of age from Chang Gung Memorial Hospital between January 2006 and December 2017. A retrospective chart review was performed for data collection and analysis. Patients with right MLA for <1 month of duration were excluded from the study. Other excluding criteria included patients with chronic debilitating diseases, bedridden neuromuscular disorders with a tracheotomy, and obvious swallowing disturbance, and patients with primary immunodeficiency who had undergone stem-cell transplantation.

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Demographic data obtained from the medical record of patients identified with MLA included gender and age at diagnosis. Clinical data included symptoms, associated diseases, radiographic features, bronchoscopic findings, and bacteria isolated from bronchoalveolar lavage fluid. Clinical course and treatment were collected. Data were presented as descriptive statistics. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Informed consent from the parents was waived because of retrospective chart analysis (201701857BO).

Results

A total of 30 pediatric patients with chronic MLA below 18 years of age were identified in this study. The median age of the patients was 10 years (range 2–18 years). Seventeen (56.7%) were male patients. Fifty percent presented with chronic cough, 30% with recurrent pulmonary infections, 13% with hemoptysis, and 7% with wheezing.

Isolated MLA was identified in only four (13.3%) patients. The remaining 26 patients had other associated radiographic finding including segmental or lobar collapse or bronchiectasis in other areas of the lung, either ipsilaterally or contralaterally. The frontal radiographs commonly showed blurring of the right heart border, irregular infiltrates, triangular shadow, mass-like lesion, or dilated bronchi.

In this series of 30 patients with MLA, 18 patients had bronchiectasis. Seven patients had a primary immunodeficiency disorder. Three had common variable immunodeficiency. One had low levels of IgG_1 and IgG_2. Wiskott–Aldrich and hyper-IgE syndromes and T-cell immunodeficiency were each identified in 1 patient [Table 1]. Two patients had gastroesophageal reflux disease (GERD), two had surgically corrected tracheoesophageal fistula (TEF), and two had chronic suppurative lung disease (CSLD). Single cases of Kartagener syndrome, bronchial asthma, recurrent aspiration, postinfectious bronchiolitis obliterans, and connective tissue disorder were identified. Various causes of bronchiectasis in our patient are presented in Figure 1.

Table 1: The underlying diseases of patients with chronic middle lobe atelectasis

Diagnosis	*n* (%)
Bronchiectasis/postinfectious	12 (40.0)
Immunodeficiency disorder	7 (23.3)
Common variable immunodeficiency disorder	3
Low IgG_1 and IgG_2	1
Wiskott-Aldrich syndrome	1
Hyper-IgE syndrome	1
T-cell immunodeficiency	1
Chronic suppurative lung disease	2 (6.7)
Tracheoesophageal fistula with surgical repair	2 (6.7)
Gastro-esophageal reflux disease	2 (6.7)
Kartagener syndrome	1 (3.3)
Postinfectious bronchiolitis obliterans	1 (3.3)
Bronchial asthma	1 (3.3)
Recurrent aspiration	1 (3.3)
Connective tissue disorder	1 (3.3)

Fifteen patients underwent diagnostic fiberoptic bronchoscopy. Bacterial growth from bronchoalveolare lavage included five isolates of either mixed flora or colony counts of $<10 \times 10^4$ colony forming units/ml. Ten specimens of bronchoalveolar lavage fluids that were available showed single growths of *Viridans streptococcus* in 2, *Haemophilus influenzae* in 2, *Streptococcus pneumoniae* in 2, and one patient with *Streptococcus mitis* and *Moraxella catarrhalis*; one patient with *V. streptococcus* and *Streptococcus salivarius*; one patient with *Stenotrophomonas maltophilia*, and one patient with *Pseudomonas aeruginosa* and *Serratia marcescens*.

Discussion

Our data demonstrate that chronic MLS in these patients differed from past observations and current reports elsewhere. Right MLS was originally reported in the 1940s associated with a high incidence of external compression due to tuberculous lymph nodes. In the adult population, the term was meant to be a potential red flag for lung cancer caused by compression of the bronchus from enlarged lymph nodes of the neoplasm.[3] The most common abnormality associated with MLA in our study was bronchiectasis [Table 1]. Further analysis of the group showed that many patients who had other abnormalities also had bronchiectasis and only four (13.3%) patients who had MLA lasting for 6 months had no bronchiectasis [Figure 2]. We found only one case of MLA due to asthma.

Pulmonary atelectasis caused by obstructive lesions in children was uncommonly observed in previous reports.[8,9] Asthma was reported to be the chief reason for isolated MLS in children.[5,10-13] The prevalence of MLS was examined in a study of 1126 children with asthma by Waldbott; only 6 cases of segmental or lobar collapse were found in that study.[12] In another study, Sekerel and Nakipoglu experienced 56 (1.62%) cases of right MLS among 3528 asthmatic children.[13] Springer *et al*. performed bronchoalveolar lavage in 21 children with asthma and right middle lobe or lingular collapse. Differential cell counts of the lavage fluid revealed predominance of neutrophils in 12 of the 21 patients (57%). Nine of these patient's cultures grew pathogenic bacteria, mainly *H. influenzae* and *S. pneumoniae*. There was no correlation between the severity of asthma and a positive bacterial culture. There was also no correlation between the duration of the right middle lobe collapse and a positive culture. The authors concluded that long-standing right middle lobe collapse in asthmatic children is often associated with a bacterial infection.[14]

Chronic pulmonary atelectasis was commonly seen in children with bronchiectasis.[15] Einarsson *et al*. reported a series of 18 children with MLS where bronchiectasis was common.[16] Studies in adults found that 25%–50% of the patients with MLS had bronchiectasis.[17,18]

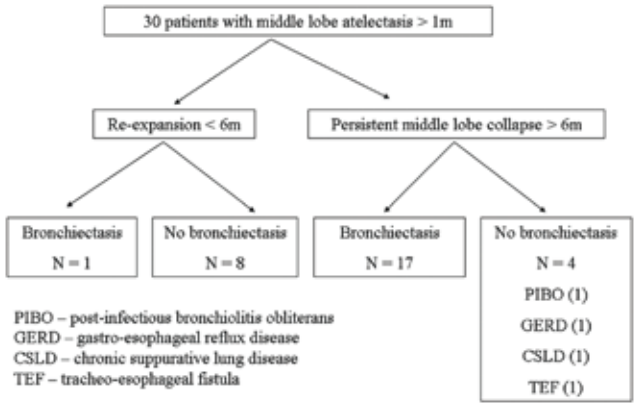

Figure 1: Etiologies of patients with bronchiectasis.

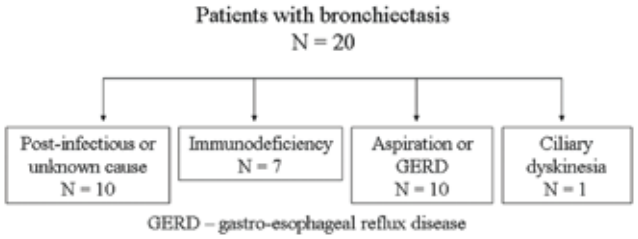

Figure 2: Outcome of patients with chronic middle lobe atelectasis.

Pulmonary infection was the major cause of non-cystic fibrosis (CF) bronchiectasis in Taiwanese children.[19] In a systematic review of 989 patients with bronchiectasis, the prevalent disease categories were infectious (17%), primary immunodeficiency (16%), aspiration (10%), and ciliary dyskinesia (9%).[20] Li *et al*. studied 136 non-CF children with bronchiectasis, and they found that immunodeficiency, aspiration, and primary ciliary dyskinesia were responsible 67% of the cases.[21] Seven children with MLA in this study had primary immunodeficiency which revealed a similar prevalence.[22] Literature reviews depicted that children with primary immunodeficiency usually are manifested as bronchitis, pneumonia, interstitial lung disease, chronic inflammatory airways, or atelectasis.[22] The causes of bronchiectasis in our studied group are presented in Figure 2.

Chronic lung aspiration had been an important cause of progressive lung disease, bronchiectasis, and respiratory failure.[23] Five patients in this study were due to pulmonary aspiration. For patients with esophagus atresia (EA), despite a surgical repair, they often are associated with esophageal dysmotility, residual esophageal stenosis, gastroesophageal reflux, or pulmonary aspiration.[24] Porcaro *et al*. studied 105 children with EA and TEF, 29 patients who had undergone chest computed tomography scans, 41% showed localized atelectasis, and 31% revealed bronchiectasis.[25,26] In contrast, Mirra *et al*. did not find GERD increased the risk of recurrent pneumonia.[27] Nonetheless, early detection and management of aspiration in this group of patients should be crucial to prevent long-term complications of atelectasis and bronchiectasis.

In the past decade, increasing numbers of articles highlighted the importance of persistent bacterial infection in cohorts of children with refractory cough and wheeze.[28-30] Lower airway infections with non-typeable *H. influenzae* cause localized damage and disruption of cilia, recurrent protracted bacterial bronchitis (PBB) predisposed to future bronchiectasis in children.[30-35] In our study, we saw a high percentage of patients with bronchiectasis, which may be due to delayed diagnosis of PBB, progressing to CSLD, and finally, resulting in the irreversible bronchiectasis. Increasing evidence supports the intensive treatment of CSLD that prevents poor lung function in recent years.[36,37] Therefore, more aggressive and prolonged antibiotics' use should be encouraged to decrease bronchiectasis in patients with PBB or CSLD.

The outcome of MLA depends on the presence of coexisting bronchiectasis. As shown in Figure 1, among the nine patients who had pulmonary re-expansion of the right middle lobe, only one patient had bronchiectasis, whereas in 21 patients with nonre-expanded middle lobe collapse, 17 patients had concomitant bronchiectasis. Treatments have been conservative and are directed to the cause of middle lobe collapse. Three patients in this study received lobectomy at other pulmonary segments instead of the middle lobe. In another study of 17 children with MLS, about one-third had persistent respiratory symptoms, mostly mild obstructive airway disease.[38] In a complicated situation such as bronchiectasis associated with persistent atelectasis over 6 months, aggressive medical treatment may require surgical lobectomy.[39,40]

Conclusions

Atelectasis of the right middle lobe in ambulatory children we studied was commonly associated with diseases in other lobes. Tumors, tuberculosis, retained foreign body, and asthma were all uncommon. When faced with evidence of right MLA, one should consider a more general process such as a chronic endobronchial bacterial infection, PBB, and CSLD with or without bronchiectasis. More aggressive and prolonged courses of antibiotics for PBB and CSLD may obviate the progression to bronchiectasis in such instances.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Correlation between Variation of Aortic Peak Blood Flow Velocity, Inferior Vena Cava Diameter Variation and Stroke Volume Variation in Children

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Abstract

Background: Non-invasive monitoring using ultrasound or Doppler assists in quick haemodynamic assessment and helps to improve outcomes in critical care. Parameters including aortic peak blood flow velocity variation (ΔVpeak), inferior vena cava diameter variation (ΔIVC) and stroke volume variation (SVV) have been commonly used in children. **Objectives:** The aim of this study was to assess the correlations between ΔVpeak from transthoracic echocardiography, ΔIVC from abdominal ultrasound and SVV from ultrasonic cardiac output monitoring. **Settings and Design:** A prospective observational cohort study was undertaken in the paediatric intensive care unit in a tertiary university hospital. **Methods:** ΔVpeak, ΔIVC and SVV were measured in mechanically ventilated children using ultrasound- or Doppler-based monitoring. **Statistical Analysis Used:** Pearson correlation coefficient was computed to assess the relationship. **Results:** A convenient sample of 55 patients with a median age of 31 months (range 6 months to 5 years) was enrolled. ΔVpeak, ΔIVC and SVV showed significant positive correlations between the three variables, i.e., ΔVpeak and ΔIVC ($r = 0.415$ with $P = 0.002$), ΔVpeak and SVV ($r = 0.539$ with $P < 0.001$) and ΔIVC and SVV ($r = 0.524$ with $P < 0.001$). **Conclusions:** In mechanically ventilated children, there is a positive correlation between ΔVpeak, ΔIVC and SVV. ΔVpeak and SVV provided the best, though moderate, correlation.

Keywords: Child, critical care, Doppler, echocardiography, haemodynamic monitoring, ultrasonography

Introduction

In paediatric critical care, haemodynamic monitoring is one of the key elements in resuscitation. The goal is to achieve adequate oxygen delivery by maintaining adequate stroke volume or cardiac output.[1,2] It is generally accepted that the assessment based on signs and symptoms from the physical examination is not accurate enough, especially in children,[3,4] so other parameters have been frequently used. The standard of haemodynamic assessment for fluid responsiveness is to assess the change in a haemodynamic parameter in response to volume administration. Advanced parameters using dilution method or arterial pulse contour analysis seem to be reliable predictors of fluid responsiveness when taking cardiac contractility into account.[5] However, the advanced parameters are not generally used because of the complexity for both the device and the procedure.

Other parameters frequently studied in both adult and children are dynamic parameters.[1-3] The dynamic parameters are measured based on the effect of the respiratory cycle on these parameters including flow velocity, stroke volume and pressure variation. Moreover, measurement of these parameters can be done using non-invasive monitoring which is relatively easy, safe and convenient.[6] Among non-invasive monitoring, aortic peak blood flow velocity variation (ΔVpeak) from echocardiography, inferior vena cava diameter variation (ΔIVC) from ultrasonography and stroke volume variation (SVV) from aortic Doppler or ultrasonic cardiac output monitoring (USCOM) are the parameters widely

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used in paediatric practice.[6-10] Values higher than the cut-off values for each parameter are predictive for fluid resuscitation responsiveness. These cut-off values in mechanically ventilated patients are ΔVpeak >7%–20%,[6,7] ΔIVC >8%–21%[9-11] and SVV from USCOM >9%–19%.[12] ΔVpeak requires developed skills to perform transthoracic or transoesophageal echocardiography correctly which may be a limitation for some paediatricians. In contrast, SVV from USCOM and ΔIVC from ultrasound are easier to perform and require less training.

Given that the choice of non-invasive monitoring depends on expertise and equipment availability, the correlation between these parameters would be important information supporting interchange of monitoring. To the best of our knowledge, there is no previous study demonstrating the relationship between common non-invasive haemodynamic parameters in children. Therefore, this study aims to determine the correlation between ΔVpeak from echocardiography, ΔIVC from ultrasonography and SVV from USCOM.

Methods

Design, setting and patients

After ethical approval was provided by the Institutional Review Board, we conducted a prospective observational study in our paediatric intensive care unit from June 2016 to May 2017. A convenient sample of 69 paediatric patients was potentially eligible by being clinically stable on mechanical ventilation. We included 55 consecutive participants whose parents provided written informed consent from this sample. The inclusion criteria were children aged 3 months to 15 years who were intubated and ventilated. The exclusion criteria were the presence of arrhythmia, congenital heart diseases, severe left ventricular dysfunction below 50% calculated by Teichholz method, use of high-frequency ventilator and the presence of abdominal distension and impediments to measurement such as morbid obesity, short neck and skin wound or infection.

Procedures

The following haemodynamic parameters were measured from each enrolled participant: ΔVpeak, ΔIVC and SVV were measured by echocardiography, ultrasonography and USCOM, respectively. All the patients were mechanically ventilated (Servo-i, Maquet, Solna, Sweden, or model 840, Puritan Bennett, Pleasanton, CA, USA) via an endotracheal tube in a supine position. To interpret the dynamic parameters accurately, the ventilator was monitored for regular respiration in continuous mandatory ventilation mode without spontaneous breathing activity during the measurements.

Standard two-dimensional echocardiography using portable ultrasound machine (Logiq e, GE Medical Systems) was performed as a transthoracic approach to identify the aortic valve in an apical five-chamber view. In Doppler mode, we demonstrated the velocity–time integral at the aortic valve area. From the integral, we measured two values, the maximum and the minimum, for peak blood flow velocity, which varied in the same respiratory cycle, and calculated ΔVpeak using the following formula.[13]

$$\Delta Vpeak\ (\%) = [(Vpeakmax - Vpeakmin)/(Vpeakmax + Vpeakmin)/2] \times 100.$$

Ultrasonography (Logiq e) was performed using a transabdominal approach to identify IVC in a longitudinal view. In M-mode, we demonstrated the change of IVC diameter at 2 cm before the right atrium. From the display, we measured two IVC diameters, the maximum and the minimum, which varied in the same respiratory cycle, and calculated ΔIVC using the following formula.[14]

$$\Delta IVC\ (\%) = [(IVCmax - IVCmin)/(IVCmax + IVCmin)/2] \times 100.$$

USCOM (model 1A, Uscom, Sydney, NSW, Australia) was performed using a suprasternal approach to detect blood flow in the ascending aorta. When an adequate velocity–time integral was displayed (including continuous wave, sharp peak flow and no artefact), the integral was captured. SVV was automatically calculated using data from the integral and demographic data of the patient including age, gender, ethnicity, weight, height, central venous pressure and systolic and diastolic blood pressure.

Each parameter was measured at least three times accepting repeatability within 10% variation and calculated as average value for each patient. All measurements in this study were conducted by a single investigator and quality of all results was approved by a single consultant in the paediatric intensive care unit. Unacceptable measurements, such as inaccurate measuring position and interrupted integral, were discarded from the study.

Statistical analyses

Categorical data were presented as frequency and percentage, and continuous data are presented as mean with standard deviation for normally distributed data or median with interquartile range where data were not normally distributed. Statistical analyses were performed using SPSS Statistics for Windows version 17 (Armonk, NY: IBM Corp.), and $P < 0.05$ was considered significant for all analyses of statistical inference. Associations among variables were evaluated using Pearson's correlation coefficient, and the strength of the association was gauged using the guidelines provided by Evans.[15]

Results

Table 1 presents the characteristics of paediatric patients in this study. We enrolled 55 eligible patients, consisted of 26 boys and 29 girls, with median age 31 months (range from 6 months to 5 years, interquartile range: 15–39 months). No patient was excluded by unacceptable measurement. Of the 44 patients who had underlying diseases, almost one-third (30%) had neurological diseases such as epilepsy and almost one-fifth (18%) had malignancies, including hematologic and solid tumour. The main reason for paediatric

Table 1: Characteristics of patients and the haemodynamic parameters (n=55)

Data	
Male, *n* (%)	26 (47.3)
Age in months, median (IQR)	31 (15-79)
Weight in kg, median (IQR)	15 (9-26)
Height in cm, median (IQR)	105 (80-120)
Underlying diseases, *n* (%)	
Neurological diseases	17 (30.9)
Malignancies	10 (18.1)
Craniofacial anomalies	5 (9)
Chronic lung diseases	4 (7.2)
Systemic lupus erythematosus	4 (7.2)
Others	4 (7.2)
Causes of PICU admission, *n* (%)	
Respiratory failure	30 (54.5)
Post-operative observation	12 (21.6)
Neurological diseases	7 (12.7)
Septic shock	5 (9)
Diabetic ketoacidosis	1 (1.8)
Ventilator setting, mean (SD)	
Tidal volume mL/kg	8.9 (2.1)
Mean airway pressure cmH_2O	9.2 (2.8)
Positive end expiratory pressure cmH_2O	5.1 (0.7)
Hemodynamic parameters, median (IQR)	
ΔVpeak (%)	6.7 (5.6-9.8)
ΔIVC (%)	11.4 (6.9-19.5)
SVV (%)	18 (16-24)

IQR: Interquartile range, SD: Standard deviation, PICU: Pediatric intensive care unit, SVV: Stroke volume variation, ΔIVC: Inferior vena cava diameter variation, ΔVpeak: Aortic peak blood flow velocity variation

intensive care unit admission was respiratory failure, followed by post-operative observation (including craniofacial surgery, solid tumour removal and adenotonsillectomy) and neurological diseases (including seizure, increased intracranial pressure and intracranial haemorrhage). The patients were mechanically ventilated using average ventilator setting as shown in Table 1. During the measurements, the patients were clinically and haemodynamically stable according to the references.[6-12] The median of ΔVpeak was 6.7%, ΔIVC was 11.4% and SVV was 18%.

Figure 1 presents scatter plots between ΔVpeak and ΔIVC, ΔVpeak and SVV and ΔIVC and SVV. Perusal of the scatter plots suggests a positive correlation between these three variables. Correlation analysis reveals weak correlation of ΔVpeak with ΔIVC (r = 0.415 with P = 0.002) and moderate correlation of ΔVpeak with SVV (r = 0.539 with P < 0.001) and ΔIVC with SVV (r = 0.524 with P < 0.001).

Discussion

We found weak-to-moderate linear associations between ΔVpeak, ΔIVC and SVV in children who were mechanically ventilated. The correlations of ΔVpeak with SVV and ΔIVC with SVV had closer correlation than ΔVpeak with Δ IVC.

Predictably, ΔVpeak measured by echocardiography and SVV measured by USCOM were correlated given that both are calculated from variations in peak velocity of blood flowing in the aorta. Echocardiography is looking upwards superiorly at the left ventricular outflow tract from the anterior, while USCOM is looking downwards at the ascending aorta from the suprasternal notch.

However, ΔVpeak from echocardiography seems to be more precise than SVV from USCOM because echocardiography can visually display aortic valve area for the measurement of blood flow, while USCOM blindly measures stroke volume assuming correct position from adequate velocity–time integral. Further, SVV from USCOM is calculated depending on the aortic valve area estimated from patient's demographic data. Therefore, the estimated valve area may differ from the actual value and consequently affects the accuracy of SVV.

ΔIVC and ΔVpeak had the lowest correlation among all parameters in this study. This finding may be explained by the characteristic of two measurement locations. ΔIVC reflects the variation of blood volume entering the heart, while ΔVpeak demonstrates velocity of blood flow exiting the heart. Change of blood volume may be disproportionate to change of blood flow because other haemodynamic factors such as driving pressure, resistance and compliance of vessels are different between two points, before and after cardiopulmonary system. Many conditions can affect the accuracy of ΔIVC, including intrathoracic pressure, abdominal pressure, central venous pressure and compliance of the vessel.[16] During critical illness, patients generally have increased abdominal pressure from decreased bowel function, and various central venous pressures depend on fluid status, heart contractility and vascular compliance.

The measurement technique of ΔIVC is another considerable issue. Most studies measured IVC diameter approximately 2 to 4 cm from the right atrium junction in the longitudinal axis. As a matter of fact, the location for obtaining the diameter greatly varies in the literature, ranging from the right atrium junction to the left renal vein junction, and there is no evidence suggesting the best location. Moreover, the diaphragm movement during respiration also frequently displaces the measured location.[17]

The current study's limitations included only establishing the relationship between the haemodynamic parameters but not the predictive ability in fluid responsiveness. We did not administer intravenous volume to evaluate the change of parameters and stroke volume nor did we evaluate the effect of various diseases and treatments on these parameters. For example, congenital heart disease, heart failure, sepsis, thoracic surgery, vasoactive agents, sedatives or neuromuscular blocking agents may differ in aspects of the measured parameters. Further studies to clarify these potential limitations are warranted.

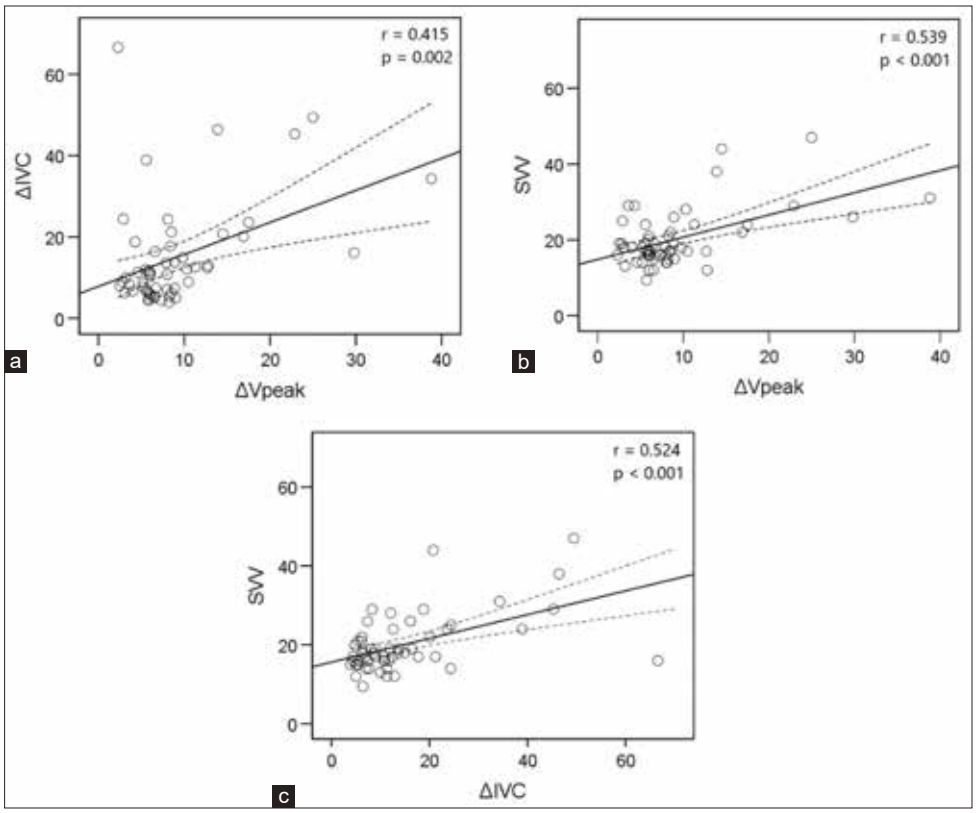

Figure 1: Scatter plots of variation in aortic peak blood flow velocity variation (ΔVpeak), inferior vena cava diameter variation (ΔIVC) and stroke volume variation (SVV). (a) ΔVpeak and ΔIVC (b) ΔVpeak and SVV (c) ΔIVC and SVV.

Conclusions

Among the correlation studied, the best was a moderate correlation between ΔVpeak from echocardiography and SVV from USCOM. These two parameters may be a surrogate of each other for haemodynamic monitoring in mechanically ventilated children.

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Conflicts of interest

There are no conflicts of interest.

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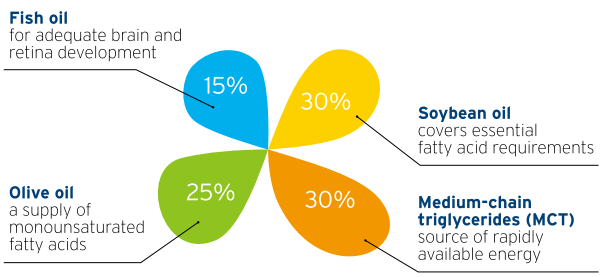

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