

Article

Characterization of cardiopulmonary interactions and exploring their prognostic value in acute bronchiolitis: A prospective cardiopulmonary ultrasound study

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Abstract: We aimed to delineate cardiopulmonary interactions in acute bronchiolitis and to evaluate the capacity of a combined cardiopulmonary ultrasonography to predict the need for respiratory support. This was a prospective observational single-center study that includes infants < 12 month of age admitted to a hospital due to acute bronchiolitis. All the included patients underwent clinical, laboratory and cardiopulmonary ultrasonographic evaluation at the same time point within 24 hours of hospital admission. The existence of significant correlation between cardiac and respiratory parameters was the primary outcome. The association of different cardiopulmonary variables with the need of respiratory support higher than O₂, the length of stay hospitalization, the PICU stay, and the duration of respiratory support were a secondary outcome. We enrolled 112 infants (median age 1 (0.5-3) months; 62% males) hospitalized with acute bronchiolitis. Increased values of the pulmonary variables (BROSJOD score, pCO₂ and LUS) showed moderate correlations with NT-proBNP and all echocardiographic parameters indicative of pulmonary hypertension and myocardial dysfunction. Up to 36 (32%) infants required respiratory support during the hospitalization. This group presented with higher lung ultrasound score (p<0.001), and increased values of Tei index (p<0.001) and pulmonary artery pressures (p<0.001). All the analyzed respiratory and cardiac variables showed moderate to strong correlations with the LOS hospitalization and the time of respiratory support. Lung ultrasound and echocardiography showed a moderate to strong predictive accuracy for the need of respiratory support in the ROC analysis, with AUC varying from 0.74 to 0.87. Conclusion: Those cases of bronchiolitis with a worse pulmonary status presented with a more impaired cardiac status. Cardiopulmonary ultrasonography could be a good strategy to easily identify high-risk population for a complicated acute bronchiolitis hospitalization.

Keywords: Acute bronchiolitis; Lung ultrasound; Echocardiography; Point of care ultrasonography; Cardiopulmonary ultrasound; Cardiopulmonary interactions; Pulmonary hypertension; Myocardial strain; NT-proBNP

1. Introduction

Bronchiolitis is the viral lower respiratory infection that most often affects children under 2 years of age, with a peak of incidence and morbidity in young infants (under 3 months of age) [1,2]. It is characterized by small-airway inflammation, edema, mucus production, and necrosis, leading to obstruction of distal bronchioles and pulmonary air trapping with subsequent acute impairment in gas exchange between lungs and blood resulting in hypoxia with or without hypercapnia, and secondary acidosis. Of note, approximately 5%-10% of infants with acute bronchiolitis develop acute respiratory failure (ARF) requiring respiratory support and PICU admission [1,2].

The existence of a physiological interdependence between the cardiovascular and respiratory systems has long been recognized. The heart and lungs are anatomically coupled through the pulmonary circulation and coexist within the sealed thoracic cavity, making the function of these systems highly interdependent. During ARF these interactions are magnified, with a striking effect on pulmonary vasculature and myocardial function [3,4]. An understanding of the interplay between the cardiac and respiratory systems could be important in the management of severe bronchiolitis. However, the presence and the clinical consequences of adverse cardiopulmonary interactions (CPI) in common respiratory diseases, such as bronchiolitis, remain incompletely understood and poorly studied.

Clinical scores have proven to be inaccurate in predicting prognosis in acute bronchiolitis, with weak interobserver reliability and limited construct validity [5]. Thus, lung ultrasound (LUS) is now emerging as a valuable tool in assessment of respiratory status in bronchiolitis. **Literature supports the use of LUS as a reliable imaging test that could benefit the clinical management of bronchiolitis [6-8].** The presence of myocardial strain assessed by echocardiography is also being increasingly recognized in this setting, where approximately 20% of patients present myocardial dysfunction (MD) or pulmonary hypertension (PHT) at the time of hospitalization [9]. The integrative cardiopulmonary ultrasound (CPU) approach is an emerging non-invasive technique that combines lung ultrasound (LU) and echocardiography to evaluate lung and cardiac conditions simultaneously, especially in the critical care setting [10,11]. To date, there are few investigations evaluating concomitant dysfunction of the pulmonary and cardiac systems in critically ill children [12], and no publications in infants with acute bronchiolitis. Using bedside CPU would allow for a rapid and thorough assessment of both the cardiovascular and respiratory state in these setting. We hypothesized that patients with more severe respiratory status will present with higher rates of pulmonary hypertension and myocardial dysfunction. Although these findings could be theoretically plausible, there is still scarce evidence documenting CPI and their prognostic implications in this setting, and there are no publications using CPU as a noninvasive tool for prognosis assessment in bronchiolitis.

The primary objective of this study was to explore the influence of the respiratory state over the heart and pulmonary circulation using CPU in infants with bronchiolitis at early stages of the disease. A secondary objective was to evaluate the prognostic implications of adverse CPI and the predictive values of different CPU measurements in this setting.

2. Materials and Methods

2.1. Design, setting and study population

We conducted a single center, prospective and observational study from October 2018 to March 2020 at the Pediatric Department of a tertiary University hospital in Spain. We included infants hospitalized with acute bronchiolitis. The diagnosis and management were made by the pediatrician on charge following current international recommendations [13]. Exclusion criteria were chronic lung diseases, congenital heart diseases, immunodeficiency, previous cardiopulmonary resuscitation, detection of bacterial superinfection, initiation of respiratory support or administration of epinephrine or intravenous fluid before the research intervention, incomplete research intervention or medical records, and poor-quality ultrasound images. The local Ethics Committee approved the protocol and informed parental consent was obtained from all patients.

2.2. Research intervention

All the included patients underwent clinical, laboratory and cardiopulmonary ultrasonographic evaluation at the same time point within 24 hours of hospital admission.

PCR analysis of nasopharyngeal mucus for the respiratory syncytial virus was routinely analyzed in all patients during hospitalization.

2.2.1 Pulmonary status assessment

The respiratory state was clinically measured using the bronchiolitis of Saint Joan de Déu (BROSJOD) score [14]. This score includes five parameters: heart rate, respiratory rate, SpO₂, pulmonary auscultation, and costal retractions. It ranges from 0 to 14 points. A score greater than 10 points is defined as severe bronchiolitis. Venous pH and pCO₂ levels were used as laboratory markers of the respiratory state. A significant hypercarbia was defined as pCO₂ > 55 cmH₂O independently of pH levels. Lung ultrasound (LU) was performed by 3 intensive care pediatricians with at least 2 years of experience in LU in routine practice according to the recommendations for point of care lung ultrasound by Volpicelli et al [15]. Sonographic examinations were obtained in supine position in calmed patients without need of sedation during the procedure. A Doppler ultrasound machine (SonoScape S8) equipped with a high-frequency (16-4 MHz) linear transducer was used to explore 3 chest projections in each hemithorax (Figure 1). We did not evaluate posterior/paravertebral projections due to the difficulty in performing them in these patients, which makes them not very feasible in clinical practice, and furthermore, we believe that these would only provide limited information, since the posterior fields are the ones, most frequently affected in the initial phases of acute bronchiolitis, probably due to the supine position of these patients. However, the involvement of the anterior lung fields may reflect greater severity and worse evolution, as shown by the study by Bueno-Campaña et al [16]. Each area was longitudinally explored in a cephalocaudal direction evaluating each intercostal space. In each area, the presence of B-lines and sub-pleural consolidations was analyzed using a lung ultrasound score (LUS) (Figure 2 & 3). A higher LUS means a more severe pulmonary involvement. A LUS > 10 was considered a moderate to severe pulmonary disease in this study. Pleural line abnormalities were not analyzed, as they add little value to consolidations and interstitial syndrome with respect to the assessment of acute bronchiolitis severity and prognosis [16, 17].

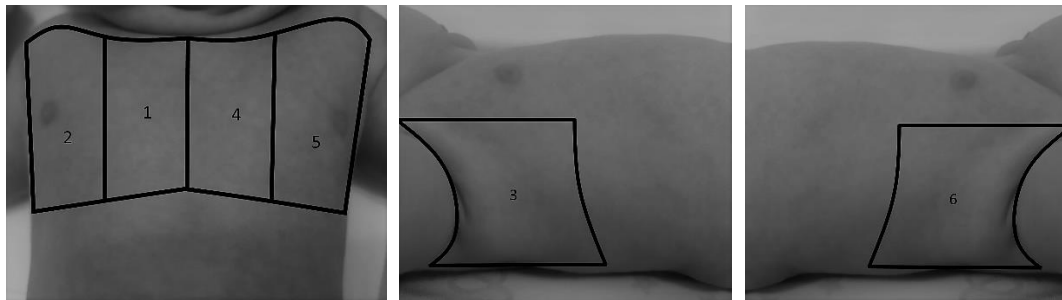


Figure 1. Chest projections used in our study protocol. 1: right anteromedial (from parasternal line to right mid-clavicular line); 2: right anterolateral (from right mid-clavicular line to right anterior axillary line); 3: right lateral (from right anterior axillary line to right posterior axillary line); 4: left anteromedial (from parasternal line to left mid-clavicular line); 5: left anterolateral (from left mid-clavicular line to left anterior axillary line); 6: left lateral (from left anterior axillary line to left posterior axillary line).

LU Score (LUS)						
B-lines				Consolidations		
0	1	2	3	0	1	2
< 3 B lines	≥ 3 B lines per intercostal space or white lung in an intercostal space	≥ 2 intercostal spaces with adjacent white lung	Consolidation	No consolidations	1 consolidation < 1 cm	Consolidation ≥ 1 cm or multiple consolidations

Figure 2. Lung Ultrasound Score (LUS): based on number of B-lines, extension of B-lines and the presence of subpleural consolidation. A score from 0 to 5 was given for each projection in each hemithorax for a maximum LUS of 30 points.

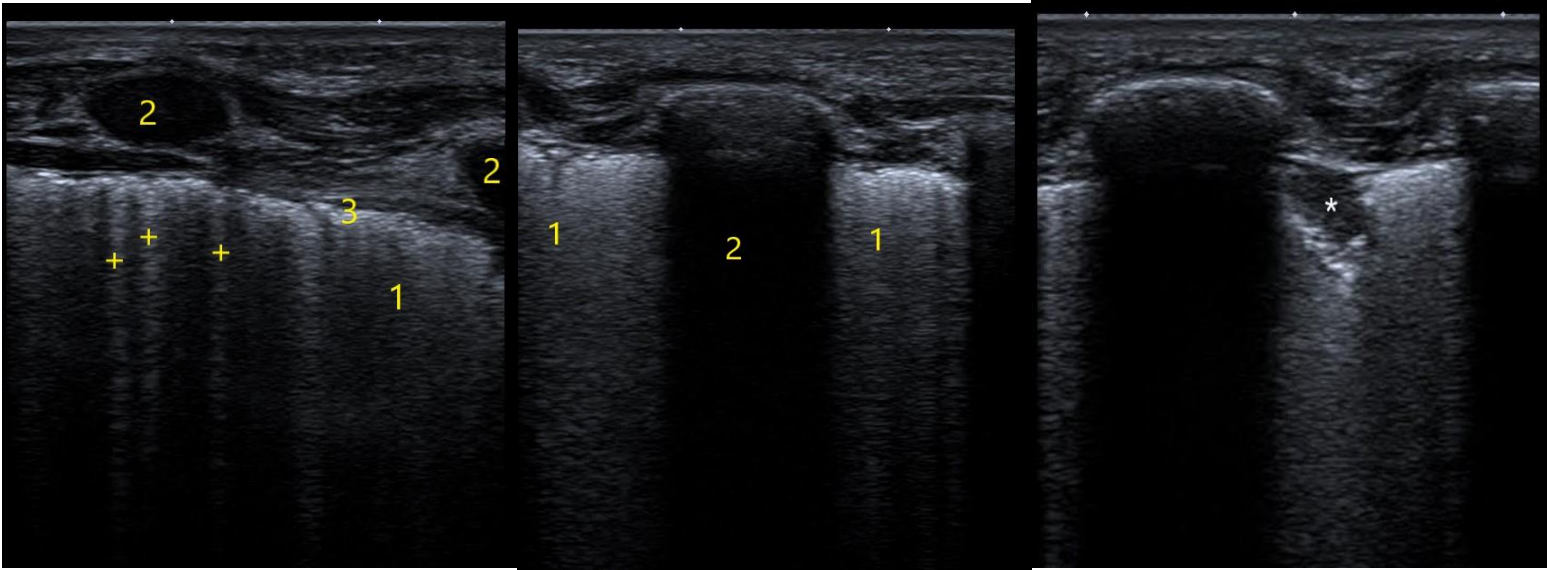


Figure 3. This is a lung ultrasound image showing: A. Left side panel: B lines. In this image multiple B lines (+) are observed in the intercostal space, some coalescing, giving rise to a white lung image. Irregular and poorly defined pleuropulmonary line. 1: coalescing b lines, white lung; 2: ribs; 3: pleuropulmonary line. B. Central panel: Coalescing b lines or white lung (1) in two adjacent intercostal spaces delimited by a rib (2). C. Right side panel: Subpleural consolidation. Hypoechoic image with frayed edges (*).

2.2.2 Cardiac status assessment

NT-proBNP was used as a laboratory parameter of myocardial strain. Serum NT-proBNP levels were determined within 2 hours of venous blood samples collection using the electrochemical luminescence immunoassay Elecsys proBNP II (Roche Diagnostics; 5 pg/ml of limit of detection, 1.5% intra-run variation; less than 3% inter-run variation). Serum levels plus than 1121 pg/ml (99th percentile for 1-12 months of age) were considered elevated [18].

Standard techniques to obtain M-mode, two-dimensional and Doppler (colour, pulsed, continuous and tissue Doppler) echocardiograms were performed by the same experienced paediatric cardiologist as recommended in the guidelines for the paediatric echocardiography [19-23]. Images were obtained using a Phillips IE33 ultrasound scanner with an 8 or 12-MHz sectorial transducer. Each examination was recorded, and all the studies were reviewed off-line by 1 observer who was blinded to the patient’s clinical profile. All echocardiographic measurements represent the average of 5 beats. Echocardiographic parameters used for cardiac function and pulmonary pressures evaluation

included: Left ventricle (LV) ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), LV and RV Tei index (LVTX and RVTX) (Figure 3), systolic gradient

of the tricuspid regurgitation jet (TRJG), RV outflow tract acceleration time to ejection time ratio (ATET), LV systolic eccentricity index (LVEI), and RV to LV ratio (RVLV) (Table 1 & Figure 4).

Table 1. Echocardiographic parameters used to evaluate myocardial involvement in our population.

Echo parameter	Cardiac parameter evaluated	Abnormal value	Significance
LVEF	LV systolic function	< 50%	Myocardial dysfunction
TAPSE	RV systolic function	< 2 SD for BS	Myocardial dysfunction
LVTX	LV global (systolic and diastolic) function	> 0.50	Myocardial dysfunction
RVTX	RV global (systolic and diastolic) function	> 0.50	Myocardial dysfunction
TRJG	Pulmonary pressures	> 40 mmHg	Pulmonary Hypertension
ATET	Pulmonary pressures	< 0.29	Pulmonary Hypertension
LVEI	RV systolic pressure	>1.3	Pulmonary Hypertension
RVLV	RV dimension	>0.6	Dilated RV

Legend: LVEF: left ventricle ejection fraction; TAPSE: tricuspid annular plane systolic excursion; LVTX: left ventricular Tei index; RVTX: right ventricular Tei index; TRJG: tricuspid regurgitation jet gradient; ATET: acceleration time/ejection time ratio; LVEI: left ventricular eccentricity index; RV/LV: right ventricular/left ventricular ratio

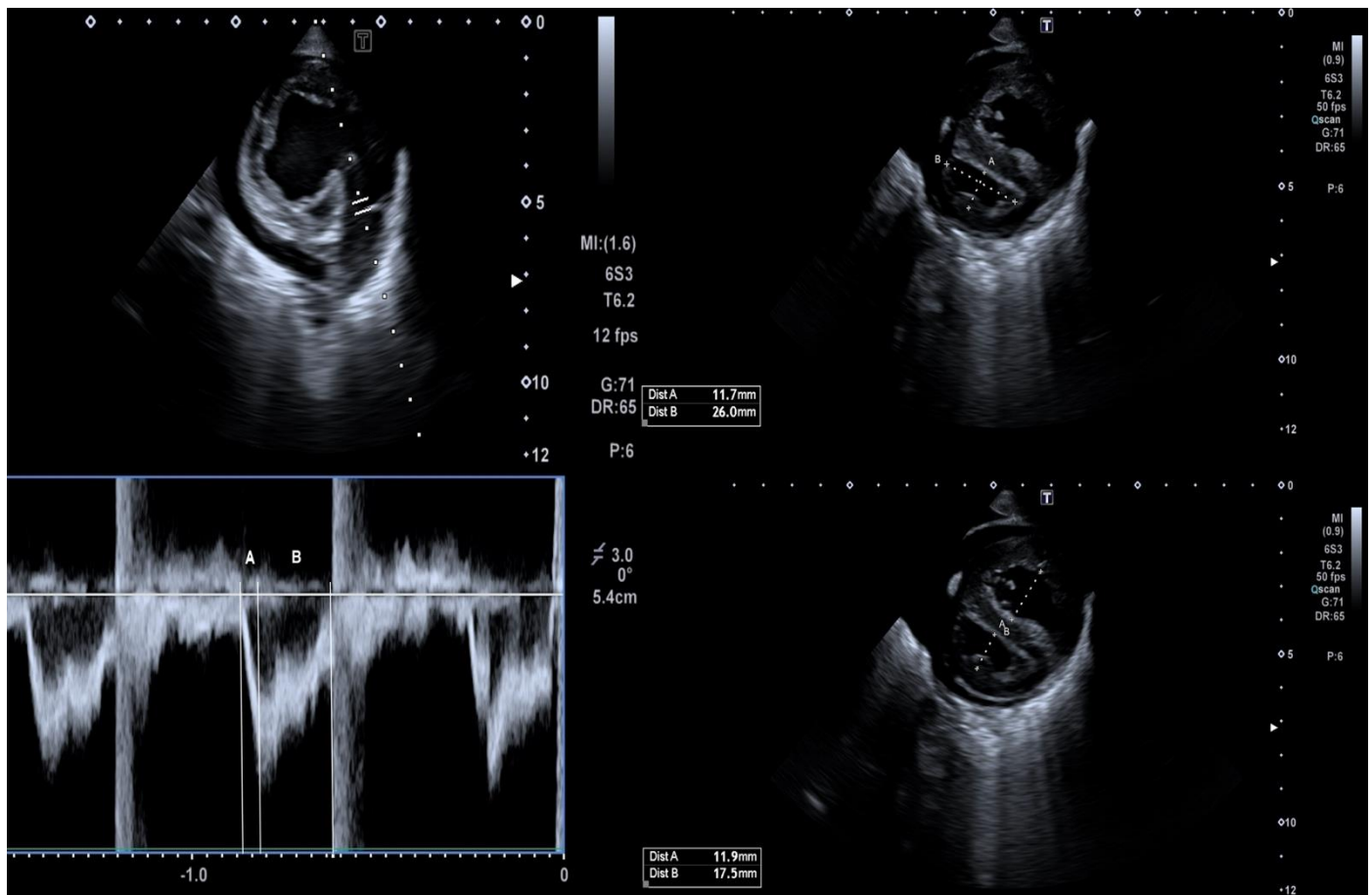


Figure 4. This figure shows the semiquantitative echocardiographic parameters used to assess pulmonary artery pressures in this study. In a short axis view we interrogated the RV outflow tract flow with Pulsed wave Doppler (Left sided image) and calculated from resultant spectral Doppler imaging the ATET ratio (A/B). We also calculated the systolic LVEI at the level of the papillary muscles (right-up sided image) as the ratio between mediolateral and anteroposterior diameters of the LV (A/B). Finally, we calculated the RVLV ratio at the same level (B/A).

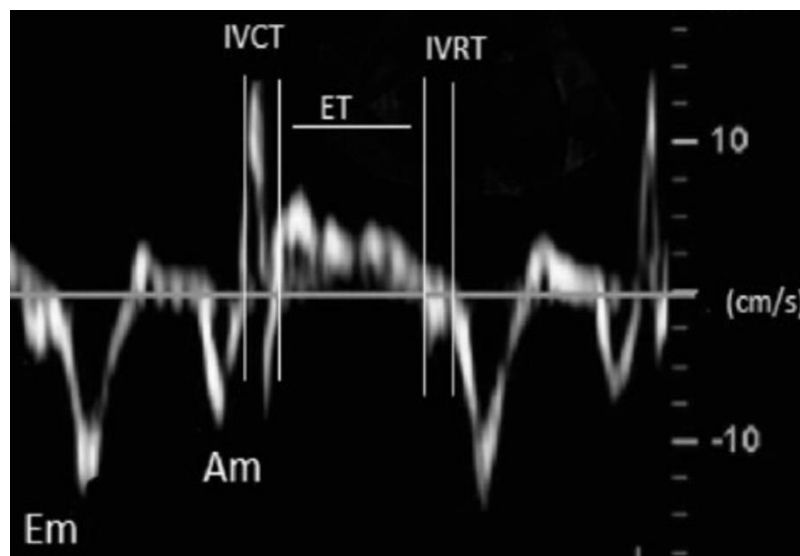


Figure 5. This figure shows a Doppler tissue imaging obtained at the mitral annulus for the calculation of the TEI index as a parameter for estimation of LV function in this study. IVCT (isovolumetric contraction time); IVRT (isovolumetric relaxation time); ET (ejection time).

2.3 Follow-up, data collection and outcome measures

The follow-up started at the research intervention time and finished at hospital discharge. At the end of the study period an independent observer collected participants data through our institution's electronic medical records and included in a relational database. Baseline information included demographic, clinical, laboratory and ultrasound data.

Outcome variables included the need of PICU admission, PICU stay, type and duration of respiratory support: oxygen (O₂), high-flow oxygen (HFO), noninvasive ventilation (NIV), or mechanical ventilation (MV); and LOS hospitalization. The existence of significant correlation between cardiac and respiratory parameters was the primary outcome in this investigation. The association of different cardiopulmonary variables with the need of respiratory support higher than O₂, the length of stay hospitalization, the PICU stay, and the duration of respiratory support were a secondary outcome of this study.

2.4 Statistics

Continuous data are presented as median (range) or mean (standard deviation) after testing normality with the Shapiro-Wilk test. Categorical data are presented as frequencies and percentage. Mean and median comparisons were performed using Student's t-test or Wilcoxon Mann-Whitney test as appropriate. Proportions were compared using the Chi-square test or exact methods as necessary. Spearman's coefficient test was used to verify correlation between variables. Logistic regression and receiver operator curve (ROC) analysis were used to explore the predictive accuracy of each marker for respiratory support. Odds ratio (OR), sensitivity, specificity, and predictive values with 95% confidence interval were estimated for the cut-off value at which they are considered abnormal. A significance level of 0.05 was used for all statistical tests. Statistical analyses were performed with the use of Stata 16.0 (Stata Corp., College Station, Texas).

3. Results

3.1 Baseline characteristics

We enrolled 112 infants (median age 1 (0.5-3) months; 62% males) hospitalized with acute bronchiolitis. Table 2 summarizes the baseline characteristics and clinical variables related to clinical evolution. Table 3 shows the prevalence of abnormal values of respiratory and cardiac parameters evaluated in our population.

3.2. Cardiopulmonary interactions in bronchiolitis

Increased values of the pulmonary variables (BROSJOD score, pCO₂ and LUS) showed moderate correlations with NT-proBNP and all echocardiographic parameters indicative of pulmonary hypertension (TRJG, ATET, LVEI, and RVLV) and global myocardial dysfunction (LVTX and RVTX), but not with parameters of systolic myocardial dysfunction (LVEF or TAPSE) (Table 4).

3.3. Relationship of cardiac and respiratory variables with a severe course of the disease.

Of the 112 (%) participants, up to 36 (32%) required respiratory support during the hospitalization (Table 5). Regarding the respiratory evaluation, the respiratory support group presented with higher BROSJOD score ($p<0.001$), pCO₂ (<0.001), LUS ($p<0.001$), and lower pH levels ($p<0.001$). With respect to the cardiac assessment, this group showed higher levels of NT-proBNP ($p<0.001$), increased values of LVTX ($p<0.001$), RVTX ($p<0.001$), TRJG ($p<0.001$), LVEI ($p<0.001$), RVLV ($p<0.001$), and lower values of ATET ($p<0.001$). All the analyzed respiratory variables and all cardiac variables, except to LVEF and TAPSE, showed moderate to strong correlations with the LOS hospitalization and the time of respiratory support. None of the studied variables analyzed presented association with the PICU stay (Table 6). All the cardiac and respiratory variables explored, except to LVEF and TAPSE, were associated with increased risk for the need of respiratory support

and also showed a moderate to strong predictive accuracy for the need of respiratory support in the ROC analysis, with AUC varying from 0.74 to 0.87 (Table 7).

Table 2. Demographic and outcome data of the study population

Patient number 112	Results
Age (months)*	1 (0.5-3)
Weight (kg)*	4.6 (3.7-5.8)
Gender (male)^	62 (55)
Time from onset of symptoms to ED evaluation (days)*	1 (0-2)
RSV positive^	86 (77)
Nebulizations^	63 (58)
Oxygen therapy (nasal canulae) ^	56 (50)
Duration (days)*	2 (1-4)
HFNC ^	3 (2.5)
Duration (days)*	1 (1-2)
PICU admission^	36 (32)
PICU stay (days)*	6 (4-9)

NIV (CPAP, BiPAP) ^	28 (25)
Duration (days)*	3 (2-5)
MV^	6 (5)
Duration (days)*	11 (10-11)
LOS hospitalization (days)*	5 (2-10)
Inotropic support	0 (0)
Death or sequel^	0 (0)

^ Data presented in frequency and percentage. * Data presented in median and interquartile range. ED: emergency department. BROSJOD: Bronchiolitis Score of Sant Joan de Déu; RSV: respiratory syncytial virus; HFNC: high flow nasal cannula; PICU: pediatric intensive care unit; NIV: noninvasive ventilation; MV: mechanical ventilation; LOS: length of stay.

Table 3. Prevalence of abnormal or severe respiratory and cardiac parameters evaluated in this cohort.

Patient number (112)	N (%)
Respiratory variables	
BROSJOD score > 10 points^	24 (21)
pH < 7.30	30 (26)
pCO2 > 55 cmH20	51 (45)
LUS > 10 points^	25 (22)
Cardiac variables	
NT-proBNP > 1121 pg/ml *	57 (51)
Myocardial function	
LVEF<50%	0 (0)
TAPSE < 2 Zscore for BSA	4 (3.5)
LVTX > 0.5	26 (23)
RVTX > 0.5	25 (22)
Pulmonary pressures	

TRJG < 40 mmHg (n=50)	11 (22)
ATET < 0.29	31 (27)
LVEI > 1.3	31 (27)
RVLV > 0.6	39 (35)

Legend: BROSJOD: Bronchiolitis Score of Sant Joan de Déu; LUS: lung ultrasound score; NT-proBNP: N-Terminal Pro Brain Natriuretic Peptide; LVEF: left ventricle ejection fraction; TAPSE: tricuspid annular plane systolic excursion; LVTX: left ventricular Tei index; RVTX: right ventricular Tei index; TRJG: tricuspid regurgitation jet gradient; ATET: acceleration time/ejection time ratio; LVEI: left ventricular eccentricity index; RV/LV: right ventricular/left ventricular ratio

Table 4. Correlation of the cardiac variables with the respiratory variables studied in this investigation.

Cardiac variables	BROSJOD score		pCO ₂		LUS score	
	ρ	P-Value	ρ	P-value	ρ	P-value
NT-proBNP (pg/mL) *	0.37	0.001	0.48	0.000	0.46	0.000
LVEF (%) **	0.01	Ns.	-0.05	Ns.	-0.05	Ns.
LVTX**	0.25	0.006	0.39	0.000	0.33	0.000
TAPSE**	-0.10	Ns.	-0.18	Ns.	-0.19	Ns.
RVTX**	0.35	0.000	0.44	0.000	0.37	0.000
TRJG (mmHg) **, n 50	0.36	0.010	0.56	0.000	0.34	0.014
ATET**	-0.37	0.001	-0.43	0.000	-0.34	0.000
LVEI**	0.38	0.000	0.48	0.000	0.45	0.000
RVLV**	0.26	0.005	0.30	0.002	0.32	0.000

n: sample size. CC: Spearman's or Pearson correlation coefficient. BROSJOD: Bronchiolitis Score of Sant Joan de Déu; LUS: lung ultrasound score.; NT-proBNP: N-Terminal Pro Brain Natriuretic Peptide; LVEF: left ventricle ejection fraction; LVTX: left ventricular Tei index;; TAPSE: tricuspid annular plane systolic excursion; RVTX: right ventricular Tei index; TRJG: tricuspid regurgitation jet gradient; ATET: acceleration time/ejection time ratio; LVEI: left ventricular eccentricity index; RV/LV: right ventricular/left ventricular ratio. Ns. (p>0.05)

Table 5. Respiratory and cardiological evaluation according to the need of respiratory support during hospitalization.

Variable	Respiratory support (n= 36; 32%)	No Respiratory support (n=76; 68%)	P -Value
Demographic and outcome data			
Age (months)*	1 (0.5-2.5)	1 (0.5-3)	Ns.
Weight (kg)*	4.3 (3.5-5.8)	4.8 (4-6.2)	Ns.
Gender (male)^	19 (53)	43 (56)	Ns.
Time of symptoms previous admission (days)*	1 (0-2)	1 (0-2)	Ns.
RSV positive^	32 (89)	54 (71)	Ns.
Pulmonary assessment			
BROSJOD score (points)*	11 (9-13)	6 (4-8)	0.000
pH^ **	7.28 (0.07)	7.34 (0.05)	0.000
pCO2 (cmH2O) *	62 (47-80)	47 (42-54)	0.000
LUS (points)*	10 (5-13)	4 (1-6)	0.000
Cardiac assessment			

NT-proBNP (pg/mL) *	3949 (2249-6042)	722 (309-1461)	0.000
LVEF (%) **	39.7 (2.4)	39.6 (2.6)	Ns.
LVTX**	0.60 (0.17)	0.41 (0.10)	0.000
TAPSE**	14 (2.5)	15 (2.2)	Ns.
RVTX**	0.59 (0.12)	0.42 (0.10)	0.000
TRJG (mmHg) **, n 50	38 (14)	25 (9.5)	0.000
ATET**	0.28 (0.05)	0.37 (0.06)	0.000
LVEI**	1.36 (0.21)	1.1 (0.13)	0.000
RVLV**	0.62 (0.12)	0.49 (0.10)	0.000

^ Data presented in frequency and percentage. * Data presented in median and interquartile range. ** Data presented in mean (standard deviation). Ns (p 0.05). RSV: respiratory syncytial virus. BROSIOD: Bronchiolitis Score of Sant Joan de Déu; LUS: lung ultrasound score; NT-proBNP: N-Terminal Pro Brain Natriuretic Peptide;LVEF: left ventricle ejection fraction; LVTX: left ventricular Tei index;; TAPSE: tricuspid annular plane systolic excursion; RVTX: right ventricular Tei index;; TRJG: tricuspid regurgitation jet gradient; ATET: acceleration time/ejection time ratio; LVEI: left ventricular eccentricity index; RV/LV: right ventricular/left ventricular ratio.

Table 6. Correlation of cardiac and respiratory variables with outcome data.

Cardiac and respiratory variables	LOS Hospitalization		PICU stay		Duration of RS	
	ρ	P-Value	ρ	P-value	ρ	P-value
BROSIOD score	0.55	<0.001	-0.08	Ns.	0.47	<0.001
pH	-0.34	<0.001	-0.21	Ns.	-0.23	0.021
pCO2	0.42	<0.001	0.03	Ns.	0.29	0.004
LUS	0.58	<0.001	0.06	Ns.	0.02	Ns.
NT-proBNP	0.60	<0.001	0.14	Ns.	0.50	<0.001
LVEF	0.01	Ns.	-0.05	Ns.	-0.05	Ns.
LVTX	0.49	<0.001	0.17	Ns.	0.40	<0.001
TAPSE	-0.10	Ns.	-0.18	Ns.	-0.19	Ns.
RVTX	0.58	<0.001	0.23	Ns.	0.42	<0.001
TRJG, n 50	0.48	<0.001	-0.13	Ns.	0.31	0.024
ATET	-0.52	<0.001	-0.18	Ns.	-0.45	<0.001
LVEI	0.58	<0.001	0.20	Ns.	0.44	<0.001
RVLV	0.54	<0.001	0.21	Ns.	0.38	<0.001

n: sample size. CC: Spearman’s or Pearson correlation coefficient. LOS: length of stay; PICU: pediatric intensive critical care unit; RS: respiratory support;. BROSJOD: Bronchiolitis Score of Sant Joan de Déu; LUS: lung ultrasound score; NT-proBNP: N-Terminal Pro Brain Natriuretic Peptide;; LVEF: left ventricle ejection fraction; LVTX: left ventricular Tei index; TAPSE: tricuspid annular plane systolic excursion; RVTX: right ventricular Tei index; ATET: acceleration time/ejection time ratio; LVEI: left ventricular eccentricity index; RV/LV: right ventricular/left ventricular ratio. Ns. (p>0.05).

Table 7. Predictive value of different cardiopulmonary parameters for the need of advanced respiratory support.

Predictive variables	OR (CI95%)	AUC (CI95%)	S	Sp	PPV	NPV
BROSJOD >10 points	28 (12-125)	0.87 (0.78-0.93)	0.91	0.61	0.91	0.76
pH < 7.30	3.5 (1.5-8.5)	0.72 (0.61-0.83)	0.44	0.81	0.53	0.75
pCO2 > 55 cmH2O	4.3 (2-10)	0.74 (0.62-0.86)	0.69	0.65	0.49	0.82
LUS > 10 points	6 (2.3-15)	0.77 (0.67-0.85)	0.44	0.88	0.64	0.77
NT-proBNP > 1121 pg/mL	9 (3.3-24)	0.83 (0.73-0.91)	0.85	0.71	0.55	0.90
LVTX > 0.5	8.5 (3-22)	0.80 (0.69-0.89)	0.50	0.89	0.70	0.79
RVTX > 0.5	18 (5.8-54)	0.84 (0.76-0.92)	0.55	0.93	0.80	0.81
LVEI > 1.3	15 (5.5-40)	0.84 (0.75-0.92)	0.64	0.89	0.74	0.84
ATET < 0.29	7.4 (3-18)	0.83 (0.75-0.91)	0.55	0.85	0.65	0.80
RVLV > 0.6	8.4 (3.3-21)	0.77 (0.68-0.86)	0.61	0.84	0.64	0.82

AUC: Area under the receiver operator curve. S: sensitivity. Sp: specificity. PPV: positive predictive value. NPV: negative predictive value. BROSJOD: Bronchiolitis Score of Sant Joan de Déu; LUS: lung ultrasound score; NT-proBNP: N-Terminal Pro Brain Natriuretic Peptide;; LVTX: left ventricular Tei index; RVTX: right ventricular Tei index; LVEI: left ventricular eccentricity index; ATET: acceleration time/ejection time ratio; RV/LV: right ventricular/left ventricular ratio

4. Discussion

In this prospective study we employed an integrative cardiopulmonary approach to comprehensively assess the pulmonary and cardiac condition of previously healthy infants with acute bronchiolitis at the time of hospitalization. Under normal conditions, CPI are inconsequential; however, they may become exaggerated and of great importance in certain acute pulmonary diseases. Through simultaneous clinical, laboratory, and CPU assessment we shown that a more severe respiratory state with hypoxia, respiratory acidosis and increased respiratory effort, resulted in increased rates of raised pulmonary pressures

and declined myocardial dysfunction, even in absence of underlying heart disease. Of note, the presence of adverse CPI at early stages of the disease were associated with a severe course of the disease, with higher rates of respiratory support, PICU admission and prolonged hospitalizations. Therefore, the early recognition of cardiopulmonary impairment could be crucial to identify high risk population for a complicated acute bronchiolitis.

4.1. Pulmonary status in acute bronchiolitis

The viral induced inflammatory response causes peri bronchial inflammatory infiltrate, interstitial edema, and epithelial desquamation, leading to small-airway obstruction, air trapping, and compromise of the lung parenchyma (consolidations and atelectasis). Almost all studies in AB describe elevated inspiratory and expiratory resistance, reduced tidal volume, increased auto-PEEP, lung hyperinflation, increased FRC, and, finally, decreased respiratory compliance [24,25]. Clinically, these lung conditions manifest in most severe cases as increased respiratory effort and impaired gas exchange with subsequent hypoxemia and acidosis. As we showed in this study, LU in infants with bronchiolitis can show diffuse and heterogeneous alveolar-interstitial involvement, which can range from mild alterations, such as pleuropulmonary line abnormalities and B-line pattern, to large pulmonary consolidations [6-8,12,16]. Most studies about LU in bronchiolitis used an own score as we did. Evaluating children with this LUS up to 25% of patients hospitalized with bronchiolitis presented a moderate to severe pulmonary impairment. This high rate of patients with pulmonary alterations reinforces the need of LU screening early after admission. According previously reported, we observed a good correlation between clinical and ultrasound findings [12,16]. Of note, LU can identify lung abnormalities not revealed by chest-X-ray [17]. Given the short time needed to get a LU report, this technique could become the routine imaging modality for assessment of pulmonary status in infants with bronchiolitis.

4.2. Cardiac status in acute bronchiolitis

Although these infants are usually admitted to the hospital for management of respiratory distress and hypoxia, the relevance of the cardiovascular involvement in these patients is increasingly documented. Cardiovascular complications are described in up to 9% of hospitalized patients [26]. Significant cardiac output and stroke volume changes have been demonstrated in infants without heart disease who were hospitalized for bronchiolitis in relation with their respiratory distress [27]. Up to 50% of patients have a positive troponin or NT-proBNP assay at the time of hospitalization. In addition, infants with bronchiolitis admitted to intensive care with hemodynamic instability and acute respiratory failure are associated with increased levels of cardiac biomarkers (cardiac troponin and NT-proBNP) compared with mild cases [28-32]. A recent meta-analysis showed the presence of pulmonary hypertension (pooled incidence of 20% (95% CI, 11-30%) and myocardial dysfunction (pooled incidence of 5% (95% CI, 1-9%) in 395 previously healthy infants with acute bronchiolitis [9]. Interestingly, myocardial dysfunction is frequently biventricular, as demonstrated by strain rate echocardiography (STE) in the cohort of Massolo et al (32% of infants with BA) [33]. Consistent with previous evidence, approximately 20%-30% of our patients developed PH and subsequent MD; and 50% presented raised NT-proBNP levels. Also, the presence of echocardiographic alterations correlated well with clinical score, pH and pCO₂. These results remark the potential utility of early point of care echocardiographic evaluation in infants hospitalized with acute bronchiolitis as a non-invasive tool to assess severity and guide management in a similar way that LU.

To detect myocardial dysfunction in BA, echocardiographic study by tissue Doppler imaging (TDI) and speckle track echocardiography has proven to be a more sensitive method than conventional echocardiography. Tissue Doppler and STE imaging has provided more load-independent methods to assess myocardial function with the additional

advantage that high quality two-dimensional images are no longer essential for reproducible recordings. Consistently, we observed that the TDI-derived Tei Index, was significantly impaired in those patients with a more compromised respiratory state. In addition, a combined systolic and diastolic measurement such as Tei index, may be more reflective of overall myocardial dysfunction than those conventional methods for assessing only systolic function. Regarding estimation of pulmonary pressures, we did not detect any difference in pulmonary arterial pressure based on standard TRJG findings between groups of severity. TRJG jet can be difficult to be detected and alternative semiquantitative parameters could be useful in this setting. Remarkably, the ATET, LVEI, and RVLV could be measured in all infants unlike tricuspid regurgitation, which was detectable in approximately a half of them in our study. As previously reported, the inclusion of these parameters in the echocardiographic evaluation of these patients could improve the detection of PHT in this setting [9].

4.3. *Cardiopulmonary interactions in acute bronchiolitis*

Our major finding was that echocardiographic parameters assessing myocardial function and pulmonary pressures and the biomarker of myocardial strain NT-proBNP showed a moderate correlation with the respiratory clinical score that includes the respiratory rate and hypoxemia, with respiratory acidosis, and with our LUS. Therefore, our study documented those factors such as lung edema, consolidations and airway obstruction leading to hypoxia, respiratory acidosis and increased respiratory effort, causes a deleterious effect in the cardiac performance in bronchiolitis. Of note, this is the first clinical study to apply a homogeneous prospective methodology investigating cardiopulmonary interactions by a combined and integrative cardiopulmonary approach in this clinically relevant setting.

The most likely underlying mechanism explaining our findings might be an increase in pulmonary vascular resistances and right heart after load and subsequent reduced right and left ventricular functions [29,30]. Pulmonary vasoconstriction can be induced by several factors in acute bronchiolitis including respiratory acidosis, hypoxemia, release of vasoactive inflammatory mediators, direct inflammatory endothelial damage, direct compression of pulmonary blood vessels secondary to the reduction in functional lung volume and the increased alveolar pressure, and a vascular remodeling phenomenon. Recent basic science studies in mouse models by Kimura et al., shows that there are structural changes in pulmonary vasculature in AB, and that suppression of tumorigenicity 2 factor (ST2) signaling is involved in the development of RSV-associated PH **providing** histopathological and pathophysiological substrate for this hypothesis [34,35].

With the increased pulmonary vascular resistance, RV structure and function will be impaired by the increased after load and because of ventricular interdependence, can also cause LV myocardial dysfunction due to an abnormal pattern of relaxation and contraction secondary to geometric changes occurring in the LV [36]. In addition, the reduction in pulmonary flow generated by RV dysfunction leads to a reduced LV preload, which is followed by a reduce stroke volume ejected by LV [37]. Furthermore, the exaggerated respiratory effort in bronchiolitis, can increase the importance of these interactions. The dominant effect of a spontaneous inspiratory effort is an increased filling of the right heart and diastolic ventricular interaction with reduced LV preload and combined increased LV after load [3,4,38]. The increase in the work of breathing also activates the sympathetic nervous system and renin-angiotensin-aldosterone systems, contributing to increases in ventricular after load, altogether contributing to a decrease in LV output [3,4,38]. Also, oxygen consumption is increased to values over 50% of total oxygen consumption due to the higher activity of the diaphragm and respiratory muscles during respiratory distress [3,4,38]. Altogether, MD and reduced pulmonary and systemic CO with increased oxygen consumption could explain the sepsis-like or myocarditis-like appearance of some infants with severe AB.

4.4. Predictive accuracy of cardiopulmonary ultrasound for adverse outcomes in acute bronchiolitis

LU is increasingly used to assess the respiratory state and even to predict evolution and guide treatment in bronchiolitis with promising results [8,12]. In the study by Bueno-Campaña et al. the ultrasound lung score combined with the WDF scale and age shows a moderate prognostic accuracy for the need of respiratory support, with an AUC of 0.84 (95%CI: 0.781-0.909) and, both posterior consolidations > 1 cm and greater extension of the interstitial pattern in anterior fields, present a higher correlation with the need of respiratory support [16]. Consistently, we found that the group of patients requiring respiratory support had a worse LUS and the 10-point LUS showed a moderate prognostic accuracy for the need for respiratory support (AUC 0.78. 95% CI 0.685-0.873) in bronchiolitis. The differences regarding accuracy could be explained by the different characteristic of the populations studied and the different LUS employed.

Echocardiography is emerging as another useful tool to assess severity in AB. The use of echocardiography was first applied to assess the cardiac state in children with underlying heart disease [39]. However, in recent years there is evidence supporting the presence of myocardial dysfunction and pulmonary hypertension also in previously healthy infants. Of note, cardiac involvement is related with the severity and prognosis of AB (pooled relative risk = 16; 95% CI, 8.2-31.5) [9]. In our cohort, DTI-derived Echo analysis reveals increased pulmonary pressures and reduced myocardial function in relation with more impaired respiratory status. Beyond the predictive capacity provided by clinical and pulmonary ultrasound, most variables analyzed showed a moderate or good predictive value for the need of respiratory support at the cut-off value at which they are abnormal in our ROC analysis. Notably, conventional echocardiographic parameters for myocardial function and pulmonary hypertension such as TAPSE, LVEF and TRJG were not useful to predict the need of PICU in this study. As LVEF and TAPSE are dependent of the ventricular geometry, preload and afterload, myocardial dysfunction could not be properly reflected by them in the acute respiratory setting, where the exaggerated respiratory efforts induce significant differences in lung volume leading to marked changes in left and right ventricular loading conditions. Regarding parameters for detection of PHT, the ATET is a good surrogate marker for pulmonary artery pressure. ATET < 0.30 has been validated against RHC to have 97% sensitivity and 95% specificity at detecting pulmonary hypertension in children [40]. **In our cohort the ATET showed a good predictive accuracy for the need of respiratory support with an AUC of 0.83 (95%CI: 0.75-0.91). Therefore, ATET could be a rapid and accurate parameter for PHT in acute bronchiolitis.**

Both echocardiography and LU have been well described as having utility for guiding the diagnosis and management of the critically ill patient [10,41]. Both techniques can be performed rapidly, safely, and repeatedly at point of care by the pediatrician on charge of the case. We observed that the presence of adverse CPI at early stages of the disease were associated with a severe course of the disease, with higher rates of respiratory support, PICU admission and prolonged hospitalizations. As there is no parameter with perfect predictive capacity in AB our results support the use combined CPU as a non-invasive tool to improve the early identification of patients that will require PICU admission or respiratory support. Notably, previous studies showed that CPU has obvious advantages in investigating the etiology of acute respiratory failure in the pediatric ED setting [42]. Most unknown severe cardiac conditions in infants can mimic the presentation of AB. Hence, infants with respiratory insufficiency from bronchiolitis may have similar clinical features to infants with congestive heart failure, presenting with irritability, fever, tachypnea, tachycardia and a mottled appearance. Therefore, we believe that a CPU approach will have broad application prospects in the initial evaluation of AB.

5. Limitations

This was a single-center study with relatively few patients, so for stronger conclusions a larger study is needed. Also, it may not be possible to extrapolate our findings to clinical practice in other hospitals. CPU is high operator dependent, and this is an inherent limitation. Echocardiographic measures were not analyzed for intra-reader or inter-reader variability, although all parameters analyzed were already described to have high inter-reader and intra-reader agreement in previous studies. There is no validated LUS in bronchiolitis, and the classification of the ultrasound findings employed in the study was developed specifically for using in this study. Another limitation of our study was the lack of gold standard diagnostic tests for myocardial dysfunction and PHT, mainly cardiac magnetic resonance imaging and right heart catheterism.

6. Conclusions

Our study documented that pulmonary and cardiac function are closely connected in children hospitalized with bronchiolitis. Those patients with a worse pulmonary status presented with a more impaired cardiac status. As those patients with adverse CPI developed a more severe bronchiolitis, the current findings demonstrate that CPU examination could be a good strategy with an added value to easily identify high-risk population for a complicated AB hospitalization. Rather than compartmentalizing the two techniques, we favor integration of echocardiography with LU in this setting.

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