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ORIGINAL ARTICLE

Cardiovascular Changes in Children with Acute Lower Respiratory Tract Infections in Zagazig University Hospitals

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ABSTRACT

Background: The cardiovascular and respiratory systems function as a single unit and alteration in cardiorespiratory interactions, can cause significant changes in cardiac function. The aim of this study was to assess the effect of acute lower respiratory tract infection on cardiovascular system in children below 5 years of age.
Methods: The present study is a case-control study conducted in respiratory, and cardiology units in pediatric department in Zagazig University hospital, during the period from January 2017 to the end of November 2017. The study included (80) children, their ages ranged between 2 months – 5 years, they divided into 2 groups; patients group included 40 patients who admitted in chest unit with clinical and radiological evidence of acute lower respiratory tract infection, selected randomly by average of 3 cases every week and control group included 40 apparently healthy children, selected from a relative of our patients and properly matched with study group in term of age, sex, and exclusion criteria.
Results: Troponin I and CK-MB in patients of bronchiolitis group was higher than its value in other patient and control groups. There was a statistically significant positive correlation of cardiac troponin I with respiratory rate and Right Ventricular Systolic Pressure in bronchiolitis group.
Conclusions: Major cardiac complications occur in a substantial proportion of children with acute lower respiratory tract infection. Physicians and patients need to appreciate the significance of this association for timely recognition and management of these events.
Keywords: Cardiovascular; CK-MB; Bronchiolitis

INTRODUCTION

Acute lower respiratory tract infection such as pneumonia and bronchiolitis are the most common infectious causes of morbidity and mortality in children under 5 years of age **[1].**
In pneumonia the inflammation of the alveoli and interalveolar septum leads to exudation of fluid into the alveoli and edema of the interalveolar septum, that affect gas exchange resulting to hypoxia which causes pulmonary vascular vasoconstriction and raises the pulmonary arterial pressure, so that may lead to right side heart failure Also, in acute lower respiratory tract infection cardiac invasion by microorganism may occur leading to myocarditis **[2].**According to the Canadian Cardiovascular Society, myocarditis must be suspected in any child presenting with a viral prodrome and nonspecific respiratory symptoms associated with cardiovascular abnormalities such as tachycardia, hypotension and dysrhythmia **[3].**Cardiac troponins are proteins that regulate the calcium-mediated interaction of actin and myocin, producing myocardial contraction **[4].** Cardiac troponins T and I have been established as the gold standard biochemical markers for myocardial necrosis **[5].**Acute Lower Respiratory Tract Infections (LRTI) causes about 12.7% in Egypt in 2015 according to under-five mortality rate (U5MR) [The under-five mortality rate (U5MR) is the probability (expressed as a rate per 1,000 live births) of a child born in a specified year dying before reaching the age of five if subject to current age-specific mortality rates] [6]. Early intervention and prompt treatment of acute respiratory tract infection and pneumonia the best and easiest ways to prevent death **[7]**.The aim of this study was to assess the effect of acute lower

respiratory tract infection on cardiovascular system in children below 5 years of age.

METHODS

The present study is a case-control study conducted in respiratory, and cardiology units in pediatric department in Zagazig University Children Hospital, through a period from January 2017 to the end of November 2017. The study included 80 children, their ages ranged between 2 months – 5 years, they divided into 2 groups; patients group included 40 patients who admitted in chest unit with clinical and radiological evidence of acute lower respiratory tract infection, selected randomly by average of 3 cases every week and control group included 40 apparently healthy children, selected from a relative of our patients and properly matched with study group in term of age, sex, and exclusion criteria. The control group included (40) apparently healthy children, selected from a relative of our patients and properly matched with study group in term of age, sex, and excluded children whom parents refused to carry the invasive test study for their children.The Inclusion criteria were**:** Age ranged between 2 months – 5 years (60 months), Male and female, Acute lower respiratory tract infection (bronchiolitis, bronchopneumonia, and lobar pneumonia) and the Pneumonia Severity assessed according to Index (PSI) score as defined by **Fine et al [8]**The Exclusion criteria were: Age < 2months > 5 years, Children with pre-existing congenital or acquired heart disease, Children with pre-existing chronic (lung, renal, liver, blood) disease, syndromes, and malnutrition.All children included in this study (cases and control subjects) were subjected to:

Full history taking: Through a well-structured questionnaire designed including (Personal data as; name, age, and sex, Duration of disease, Cough (type, duration, severity, History of fever, Symptoms of respiratory distress as grunting, and cyanosis, feeding difficulty and vomiting, Past medical history to exclude any chronic problem, Feeding, vaccination, and developmental history.

Physical examination: Complete physical examination was performed with special emphasis on the following points:

General examination: vital sign (temperature, Respiratory rate, Heart rate), sign of cyanosis, wheezing, irritability and dyspnea.

Chest examination: Inspection (subcostal and intercostal recession), auscultation (breath sounds, air entry, vocal resonance, rhonchi, crackles, bronchial breath, and pleural rub).

Cardiac examination**:** Inspection (precordial bulge, pulsations, dilated veins), palpation (thrill, pulsations), auscultation of heart sounds (murmurs, either systolic or diastolic and additional sounds S3 gallop or rub).

Abdominal examination; if there is hepatomegaly or ascites. Diagnose and classification of pericardial effusion: The size of the effusion is classified based on measurements of a fluid pocket during diastole. Mild effusion is defined as less than 10 mm; moderate effusion, 10 to 20 mm; and large effusion, greater than 20 mm [9]

After complete history and full examination, the (study group) were classified according clinical presentation and chest x-ray finding into three groups:Group I: included 8 patients with bronchiolitis (characterized by low grade or absent fever, runny nose, progressing to cough, tachypnea, hyperinflation, chest indrawing and wheezes are the hallmark of the disease).

Group II included 16 patients with severe bronchopneumonia presented with a productive cough, dyspnea, pyrexia/fevers, rigors, malaise, pleuritic pain (plain radiograph characterized by multiple small nodular or reticulonodular opacities which tend to be patchy and/or confluent. This represents areas of the lung where there are patches of inflammation separated by normal lung parenchyma)**.**

Group III included 16 patients with lobar pneumonia (plain radiograph characterized by homogeneous opacification can be sharply defined at the fissures, although more commonly there is segmental consolidation. The non-opacified bronchus within a consolidated lobe will result in the appearance of air bronchograms).

Investigations:

General investigations: Blood samples were taken on admission for complete blood count, CRP, and chest X ray for diagnosis and follow up in the word.

Special investigations: Echocardiography, ECG, and cardiac enzyme (Troponin I & CK MB).

Echocardiography: Echocardiography exams were performed for all subjects. After normalization of the body temperature, child positioned in supine decubitus and left lateral decubitus with sedation if required using oral chloral hydrate. Echocardiographic exams were performed by the same operator using a vivid 7-dimension (General Electric) machine equipped with a multi-frequency matrix 5S transducers at the echocardiography laboratory of children's hospital, Zagazig University. Written informed consent was obtained from all participants' parents and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. **Statistical analysis** Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM

SPSS) version 20. The data were presented as number and percentages for the qualitative data, and as mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non-parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data. The comparison between more than two groups with quantitative data and parametric distribution were done by using One Way Analysis of Variance (ANOVA) test and Kruskall-Wallis test was used in the comparison between more than two groups with quantitative data and non-parametric distribution. the p-value was considered significant as P > 0.05: Nonsignificant (NS), P < 0.05: Significant (S), P < 0.01: Highly significant (HS)

RESULTS

There was no statistically significant difference between cases and controls group regarding demographic data **(table 1)**. There was no statistically significant difference in studied group regarding sex but there was significant difference regarding age **(table 2)**. In bronchiolitis group, Heart rate (HR) was higher than its value in all other groups. At the same time HR in patients with bronchopneumonia and lobar pneumonia was higher than that in control group. QRS axis was higher in bronchiolitis group than that in lobar pneumonia and control group, and was higher in bronchopneumonia than control group. PR interval was in bronchiolitis group longer than that in control group, and Corrected QT (QTc) interval was longer in bronchiolitis group than that in other groups. Fifth ICS, right midaxillary line (V_{6R}) was lower than in lobar pneumonia group than that in control group. No statistical difference as regard fourth intercostal space (ICS), left sternal border ($\mathbf{V_{1R}}$) and **T wave** between groups **(table 3)**. There were no statistically significant differences as regard left ventricle function (EF and FS) between different cases and control groups. In patients with lobar pneumonia group, Right Ventricular Systolic Pressure (RVSP) was higher than its value in bronchiolitis group and control group, at the same time, RVSP in patients with bronchopneumonia group and in patients with bronchiolitis group both was higher than that in control group (**table 4**). Troponin I and CK-MB in patients of bronchiolitis group was higher than its value in other patient and control groups **(table 5)**. There was positive correlation between Troponin I and CK-MB in Group II (bronchopneumonia) **(table 6)**. There was negative correlation between Troponin I and AXIS in Group III (Lobar pneumonia) **(table 7)**. There was positive correlation between Troponin I regarding respiratory rate and Right Ventricular Systolic Pressure in Group I (bronchiolitis) (table 8).

Table 1: Comparison between patient group & control group as regards demographic data

		Patient group (No.=40)	Control group (No.=40)	P-value
		No. (%)	No. (%)	
Sex	**Female**	15 (37.5%)	20 (50.0%)	0.260
	Male	25 (62.5%)	20 (50.0%)	
Age (months)	**Median (IQR)**	21(5-30)	15(6-42)	0.817
	Range	2-60	3-60	

***** * Kruskal wallis (age) ** Chi square (sex)

Table 2: Comparison between the studied patients as regard demographic data

	Group I (n = 8)	Group II (n=16)	Group III (n = 16)	p
Median (IQR)	2 (2-3.5)	21 (10.5-30)	26.5 (19-48)	**<0.001**
Range	2-5	5-36	2-60	
Sex	No(%)	No (%)	No (%)	**p**
Female	2(25%)	7(43.8%)	6(37.5%)	**0.670**
Male	**6(75%)**	**9(56.2%)**	**10(62.5%)**	

* Kruskal wallis (age) ** Chi square (sex)

When the data are not normally distributed (skewed), the median is used instead of mean ± SD.

Table 3: Comparison between different patients & control groups regarding ECG finding

variable	G1/G2	G1/G3	GI/G4	G2/G3	G2/G4	G3/G4
HR (bpm)	0.003	0.001	0.001	0.289	0.001	0.017
AXIS º	0.639	0.044	0.035	0.058	0.037	0.857
PR s	0.065	0.141	0.025	0.641	0.791	0.412
QTc s	0.017	0.008	0.013	0.744	0.796	0.517
V1R mm	0.197	0.665	0.211	0.291	0.800	0.313
V6R mm	0.879	0.446	0.174	0.263	0.120	0.005
T wave (mm)	0.246	0.406	0.710	0.684	0.225	0.465

** Post hoc test

Table 4: Comparison between patients and control groups as regard echocardiographic findings

variable	G1/G2	G1/G3	GI/G4	G2/G3	G2/G4	G3/G4
EF %	0.714	0.504	0.701	0.711	0.974	0.635
FS %	0.454	0.263	0.488	0.646	0.851	0.462
RVSP mHg	0.069	0.015	0.012	0.429	0.001	0.001

Table 5: Comparison between different groups as regard cardiac troponin I, and CKMB

	G1/G2	G1/G3	GI/G4	G2/G3	G2/G4	G3/G4
Troponin I ng/ml	0.001	0.001	0.001	0.936	0.423	0.373
CKMB ng/ml	0.034	0.001	0.001	0.150	0.162	0.746

Table 6: Correlation between cardiac troponin I and different parameters in group II (bronchopneumonia)

Group II (bronchopneumonia)	r	p
Age	-0.460	**0.073**
RR	0.407	**0.117**
HR	0.329	**0.213**
Hb	-0.054	**0.842**
WBC	0.083	**0.760**
CRP	-0.200	**0.459**
Axis	0.145	**0.593**
PR	0.169	**0.530**
QTc	0.353	**0.180**
EF	-0.472	**0.065**
FS	-0.460	**0.073**
RVSP	-0.346	**0.190**
CKMB	**0.566**	**0.022**

Table 7: Correlation between cardiac troponin I and different parameters in group III (lobar pneumonia)

Group III (lobar pneumonia)	r	p
Age	0.054	**0.841**
RR	0.441	**0.087**
HR	0.311	**0.240**
Hb	0.208	**0.440**
WBC	0.163	**0.547**
CRP	-0.243	**0.364**
Axis	-0.545	**0.029**

Group III (lobar pneumonia)	r	p
PR	-0.083	**0.760**
QTc	-0.232	**0.386**
EF	-0.283	**0.288**
FS	-0.257	**0.336**
RVSP	0.232	**0.386**
CKMB	**0.477**	**0.062**

Table 8: Correlation between cardiac troponin I and different parameters in group I (bronchiolitis)

Group I (bronchiolitis)	r	p
Age	-0.191	**0.651**
RR	0.724	**0.042**
HR	0.214	**0.610**
Hb	-0.619	**0.102**
WBC	-0.452	**0.260**
CRP	-0.024	**0.955**
Axis	0.072	**0.866**
PR	0.266	**0.524**
QTc	0.119	**0.779**
EF	-0.167	**0.693**
FS	-0.120	**0.778**
RVSP	0.732	**0.039**
CKMB	**0.619**	**0.102**

DISCUSSION

The functioning of the cardiovascular and the respiratory systems are dependent on each other in various ways and alteration in their interactions, can cause significant changes in cardiac function [10]. In the current study there were statistical difference in studied patients' groups as regard age, with a median of 2 months (IQR 2-3.5 months) in bronchiolitis group, which in agreement with the study of **Hasegawa et al. [11]** who enrolled a total of 40 infants hospitalized with bronchiolitis (cases) and 115 age-matched healthy infants (controls). Overall, the median age was 3 months (IQR, 2–5 months).Bronchopneumonia was found in 16 patients (56.2% were male and 43.8% were female), and lobar pneumonia was found in 16 patients (62.5% were male and 37.5 % were female), which in agreement with the study of **Amrit and Ashik [12]**, where a descriptive, cross-sectional study was carried out by accessing Health Management Information System (HMIS) register and patient records at DZH from July 16, 2008 to August 17, 2011 for a total of 772 children under five years were diagnosed with pneumonia based on the International Classification of Diseases 10 (ICD-10) version 2008. Of these children, majority 463 (60%) were males. Forty-nine per cent of pneumonia cases (379) were found among those aged 29 days to one year followed by 1–4 years of age (346, 44.8%) and the lowest incidence (47, 6.1%) was found in neonates (those under 28 days of age).In the current study hepatomegaly detected in 37.5%, and x-ray cardiomegaly detected in 25% of cases of bronchiolitis, **Thorburn et al. [13]** reported that right ventricular dysfunction was detected among 20% of cases with sever bronchiolitis. Whereas hepatomegaly detected in 31.2% in cases of lobar pneumonia lesser than that detected by **Sadoh and Osarogiagbon [14]** who found hepatomegaly in 60.3% in cases with pneumonia.In the current study, there were statistically significant differences between different cases groups and control group as regard heart rate. In bronchiolitis group heart rate was 160.75±29.37 which was higher than its value in other groups, and also was higher than that found by **Mona and Khalid [15]** that found heart rate 135.38±3.24 in severe bronchiolitis. At the same time, HR in patients with bronchopneumonia was 131.94±15.71 and lobar pneumonia was 123.88±18.65, which both higher than that in control group.In the current study, there was a statistical difference as regard QRS axis which was 77.63 ± 25.97 in bronchiolitis group higher than that in lobar pneumonia and control group, and was

73.63 ± 16.28 in bronchopneumonia higher than control group, as we found that PR interval in bronchiolitis group 0.13 ± 0.03 which was longer than that in control group, and QTc interval in patients with bronchiolitis was 0.51 ± 0.05 which was longer than that in other groups. Which in agreement with the study of **Koçak et al. [16]** who reported that the most common changes on electrocardiography were prolongation in QTc interval and QRS axis.In the current study, there were no statistically significant differences as regard left ventricle function (EF and FS) between different cases groups and control group, which in Agreement with the study of **Mona and Khalid [15]** which revealed normal ventricular dimensions and functions in all their cases in study for infant with pneumonia and bronchiolitis respectively. Whereas there was statistical high significant difference between groups as regard right ventricle systolic pressure (P value = 0.000).

Increased serum level of Cardiac Troponins (cTn) I in bronchiolitis group of the present study was in line with the study of **Mona and Khalid [15]**.

Regarding bronchopneumonia and lobar pneumonia cases, in the present study serum Cardiac Troponin (cTn) I and CKMB were normal. However, both diseased groups suffered from high right ventricle systolic pressure. This was in agreement with **Ahmed et al. [17]** who found no significant correlation between reduced left ventricle or right ventricle performance with elevated cTnI and cTnT (myocardial damage or strain) respectively. A feature further dispelling this hypothesis was the finding of a normal cTnT level in a child with severe right ventricular dysfunction. Regarding bronchopneumonia and lobar pneumonia cases, in the present study serum cTn I and CKMB were normal. However, both diseased groups suffered from high right ventricle systolic pressure. This was in agreement with **Ahmed et al. [17]** who found no significant correlation between reduced left ventricle or right ventricle performance with elevated cTnI and cTnT (myocardial damage or strain) respectively.

Frank et al. [18] also found 26% of 47 children with pneumonia developed right ventricular cardiac failure secondary to pulmonary hypertension, and no child had raised cardiac isoenzymes (Creatine kinase and lactate dehydrogenase). While in our study Troponin I level was positive correlated with CKMB in bronchopneumonia group and negative correlated with QRS axis in lobar pneumonia group.

One case only from sixteen patients in both bronchopneumonia and lobar pneumonia group (6.25%) had high cTnI, too lesser than **Fadime et al. [19]** who found that 68% of their studied infant with pneumonia had high CK-MB in the absence of severe hypoxia, acidosis and sepsis.

Limitations: Limited number of individuals was incremented in the study; lager samples are needed for future studies.

Conclusions: Major cardiac complications occur in a substantial proportion of children with acute lower respiratory tract infection. Physicians and patients need to appreciate the significance of this association for timely recognition and management of these events.

RecommendationsEchocardiography should be done to all children with acute LRTI to exclude congenital heart disease and to assess pulmonary artery systolic pressure.cardiac enzyme and ECG should be done for children with bronchiolitis especially with severe respiratory distress, and echocardiographic follow up of cases which develop myocarditis to exclude post-myocarditis cardiomyopathy.

Conflict of interest: None

Financial disclosure: None

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