Original Article

# Evaluation of cardiac biomarkers in children with acute severe bronchial Asthma-A prospective study from tertiary care center in northern India

Meghna Jain [a], Dharmendra Jain [b, *], B.K. Das [a], Rajniti Prasad [a], Bhupendra Kumar Sihag [c]

[a] Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India
[b] Department of Cardiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India
[c] Department of Cardiology, PGIMER, Chandigarh, India

ABSTRACT

Objectives: During the attacks of acute severe bronchial asthma there are marked cardiopulmonary changes leading to hypoxia. The study aims to find the incidence of myocardial dysfunction in patients of acute severe bronchial asthma based on cardiac enzyme levels at admission and see whether the myocardial damage is transient or persistent even after stabilization of the patient based on enzyme levels at discharge.
Materials and methods: This prospective, case control study was done at Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University between October 2016 to May 2018. Sixty pediatric patients of acute severe bronchial asthma were taken as cases and 15 age and sex matched children served as controls. Blood samples were collected in Ethylene diamine tetra acetic acid vials before the start of treatment, for measurement of cardiac biomarkers Troponin I (TnI), Brain natriuretic peptide (BNP) and Creatine Kinase-muscle/brain (CK-MB) and repeat samples were taken before discharge.
Results: Fifty percent of the cases had abnormal TnI levels, 15% had abnormal CK-MB levels and 8.3% had abnormal BNP levels at admission. At discharge, only 1 (1.7%) case had abnormal levels of CK-MB, whereas the levels of TnI and BNP normalized in all. The level of cardiac biomarkers were significantly raised at admission when compared to discharge values ($p$ value < 0.001).
Conclusions: The raised cardiac biomarkers suggest myocardial stress during acute exacerbation of bronchial asthma. Though, the present study showed that the changes are of transient nature, larger follow up studies are required to document any permanent damage to myocardium.

## 1. Introduction

Severe acute asthma is characterized by severe respiratory distress because of increasing bronchoconstriction, leading to ventilation perfusion mismatch,[1] hypoxia, respiratory muscle fatigue, carbon dioxide retention and respiratory acidosis.[2]

In acute severe asthma, the use of beta 2 agonists, together with hypoxia and tachycardia might cause increased myocardial workload further leading to myocardial infarction. Cardiac biomarkers including Brain Natriuretic Peptide (BNP), Troponin I (TnI) and Creatine kinase muscle/brain (CK-MB) are used to detect myocardial injury.[3]

The objective of the present study was to find out the incidence of myocardial dysfunction in patients of acute severe bronchial asthma based on cardiac biomarker levels at admission and to see whether the myocardial dysfunction was transient or persistent even after the stabilization of the patient. As far as it could be reviewed, no study relating BNP levels in pediatric asthma patients could be found in literature.

## 2. Methods

The present study was carried out in Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi,

* Corresponding author. Department of Cardiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005, India.
E-mail address: djaincard@gmail.com (D. Jain).

Uttar Pradesh, India. It was an observational, prospective, case-—control study done between October 2016 and May 2018.

The study included 60 pediatric cases between the age of 5—15 years with acute severe bronchial asthma who were admitted in Pediatric ward or Pediatric Intensive Care Unit. Fifteen age and sex matched healthy children served as controls. Children with congenital or acquired heart diseases, foreign body aspiration, tuberculosis or pneumonia were excluded from the study.

Acute severe asthma was defined as episodes of asthma not responding to repeated doses of short acting beta 2 agonists.

Ethical approval was taken from Institute Ethics Committee, Institute of Medical Sciences, Banaras Hindu University.

Informed written consent was taken from the parents or the legal guardian of the patient. Thereafter, a detailed history was taken and clinical examinations were carried out. The investigations included chest roentgenograms, electrocardiogram (ECG), oxygen saturation, arterial blood gas analysis, pulmonary function tests and echocardiography. Estimation of cardiac biomarkers including CK-MB, BNP and cardiac Troponin I was done by taking 2 ml of venous blood by venipuncture in Ethylene diamine tetra acetic acid (EDTA) vials and whole blood specimens were tested within 1 h of sample collection.

Patients were managed according to the departmental management protocol (based on British guidelines for the management of asthma). Only 3 patients required mechanical ventilation and the rest were managed conservatively. After initial stabilization of the patient, pulmonary function test (reversibility could not be done in all the patients) and 2 Dimensional echocardiography (2D Echo) was done. Cardiac biomarkers were re-evaluated before discharge.

### 2.1. Biomarker kit

The Alere Triage® Cardio3 Panel: It is a fluorescence immunoassay, which was used with the point-of-care Triage® MeterPro for quantitative measurements of CK-MB, cardiac TnI and BNP. The abnormal range for CK-MB, cardiac TnI and BNP were >4.3 ng/ml, >0.02 ng/ml and >100 pg/ml, respectively (Normal values are: CK-MB ≤4.3 ng/ml, TnI ≤0.02 ng/ml, BNP≤100 pg/ml).

### 2.2. Statistical analysis

The data of clinical features, biochemical, and hematological parameters, cardiac biomarkers and ECG parameters were recorded in standard pretested proforma. Then the collected data was analyzed with Statistical Package for the Social Sciences (SPSS) version 16.0 software and appropriate table and diagrams were generated. For various signs and symptoms and background characteristics, number and percentage of cases and controls were determined. For clinical and continuous parameters, mean and standard deviation was determined at admission, paired *t*-test, Mann Whitney *U*-test was applied in various parameters with non-Gaussian distribution and Wilcoxon test was applied in various parameters to test the significance of difference between admission and discharge. One way Analysis of variance (ANOVA) test was applied to test the significance between more than 2 groups.

### 3. Results

Mean age of the patients was 10.28 years and most of the cases (65%) were males. 46.6% of the cases belonged to middle lower socioeconomic status according to Modified Kuppuswamy scale (Table 1). Forced expiratory volume in 1 s (FEV1) % predicted value was more than 80 in 1/3rd, 61—80 in 1/3rd and ≤60 in 1/3rd of the cases as acute exacerbation of asthma can occur in any patient irrespective of their baseline FEV1 value. Most of the patients (65%)

**Table 1**
Basic parameters.

| Age | Cases | | Control | | Total | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| 5—9 years | 24 | 40 | 4 | 27 | 28 | 37 |
| 10—15 years | 36 | 60 | 11 | 73 | 47 | 63 |
| **Gender** | | | | | | |
| Male | 39 | 65 | 9 | 60 | 48 | 64 |
| Female | 21 | 35 | 6 | 40 | 27 | 36 |
| **Socioeconomic status** | | | | | | |
| Lower—lower | 2 | 3.3 | 0 | 0 | 2 | 3 |
| Lower-upper | 14 | 23.3 | 0 | 0 | 14 | 18 |
| Middle-lower | 28 | 46.6 | 8 | 53.3 | 36 | 48 |
| Middle-upper | 14 | 23.3 | 3 | 20.0 | 17 | 23 |
| Upper | 2 | 3.3 | 4 | 26.7 | 6 | 8 |
| **SpO$_2$ (%)** | | | | | | |
| ≤90 | 50 | 83.3 | 0 | 0 | 12 | 16 |
| 91—95 | 8 | 13.3 | 2 | 13 | 45 | 60 |
| >95 | 2 | 3.4 | 13 | 87 | 18 | 24 |
| Total | 60 | 100 | 15 | 100 | 75 | 100 |
| **FEV1% Pred.** | | | | | | |
| >80 | 20 | 33.3 | 13 | 87 | 33 | 44 |
| 61—80 | 20 | 33.3 | 2 | 13 | 22 | 29 |
| ≤60 | 20 | 33.3 | 0 | 0 | 20 | 27 |
| **Chest-x Ray Findings** | | | | | | |
| **Hyperinflated lungs** | 12 | 20 | 0 | 0 | 12 | 16 |
| **Peribronchial cuffing** | 9 | 15 | 0 | 0 | 9 | 12 |
| **Normal** | 39 | 65 | 15 | 100 | 54 | 72 |
| Total | 60 | 100 | 15 | 100 | 15 | 100 |

SpO2- percentage saturation of oxygen.
FEV - forced expiratory volume.

had a normal chest x ray, 20% had hyperinflated lung fields and 15% had peribronchial cuffing (Table 1).

Use of accessory muscles was seen in 92% of cases. Inspiratory and expiratory wheeze was heard in 78.3% cases, 18.3% had only expiratory wheeze and 3.3% cases had silent chest. The mean pulse rate (128.6 ± 17.32 beats per minute) and the mean respiratory rate (30.43 ± 5.85 breaths per minute) were significantly higher in cases (*p* value < 0.001) as compared to controls. 83.3% of the cases had an oxygen saturation of less than 90% (Table 2).

Fifty percent of the cases had abnormal TnI levels, 15% had abnormal CK-MB levels and 8.3% of the cases had abnormal BNP levels at admission, whereas none of the controls had abnormal levels of any of the cardiac biomarkers. There was a statistically significant difference (*p* value < 0.001) when the cases and controls were evaluated for TnI levels at admission. There was a statistically significant difference between the mean values of TnI (*p* = 0.001) and BNP (*p* = 0.023) in case and control at admission while it was comparable for CK-MB. However, analysis of individual values showed that 20 (33.3%) cases had CK-MB values beyond 2 Standard deviation (SD) of control mean while another 8 (13.3%) were between 1SD and 2 SD. At discharge, only 1 (1.7%) case had abnormal levels of CK-MB, whereas the levels of TnI and BNP normalized in all. There was no statistically significant difference between the mean values of any of the cardiac biomarkers at discharge when compared with control. The level of all the cardiac biomarkers measured were significantly (*p* value < 0.001) raised at admission when compared to discharge values (Table 3).

**Table 2**
Vitals and arterial blood as parameters in cases and controls.

| Parameters | Case(Mean ± SD) | Control (Mean ± SD) | *p* value |
|---|---|---|---|
| Pulse rate | 128.6 ± 17.32 | 86.53 ± 10.46 | <0.001 |
| Respiratory rate | 30.43 ± 5.85 | 24.4 ± 2.53 | <0.001 |
| pH | 7.354 ± 0.08 | 7.43 ± 0.069 | 0.001 |
| pO$_2$ | 63.31 ± 16.42 | 81.79 ± 8.301 | <0.001 |
| pCO$_2$ | 48.41 ± 7.39 | 32.31 ± 5.31 | <0.001 |

**Table 3**
Cardiac biomarkers in asthma.

| At admission | Cases | | | Controls | | | p value (CK-MB,TnI,BNP) |
|---|---|---|---|---|---|---|---|
| | CK-MB | TnI | BNP | CK-MB | TnI | BNP | |
| Normal | 51 | 30 | 55 | 15 | 15 | 15 | 0.110,<0.001,0.247 |
| Abnormal | 9 | 30 | 5 | 0 | 0 | 0 | |
| Mean ± SD | 3.6 ± 3.41 | 0.14 ± 0.3 | 22.76 ± 42.84 | 1.94 ± 0.57 | 0.01 ± 0 | 5.13 ± 0.51 | 0.07,0.001,0.023 |
| **At discharge** | | | | | | | |
| Normal | 59 | 60 | 60 | 15 | 15 | 15 | 0.474,-,- |
| Abnormal | 1 | 0 | 0 | 0 | 0 | 0 | |
| Mean ± SD | 1.61 ± 0.99 | 0.01 ± 0 | 7.56 ± 8.04 | 1.4 ± 0.32 | 0.01 ± 0 | 5.13 ± 0.516 | 0.846,1,0.145 |

CK-MB - creatine kinase-muscle/brain,TnI- troponin I, BNP-brain natriuretic peptide, SD - standard deviation.

On ECG, 90% of the patients had sinus tachycardia, 25% had ST segment depression, 35% patients had inverted T waves and 20% cases had prolonged QT segments (Table 4). The cardiac biomarkers values were analyzed according to FEV1% predicted value and no statistical significance was noted in all the three cardiac biomarker levels (p value > 0.05) (Fig. 1).

## 4. Discussion

Mean age of patients was 10.28 years. Majority of the cases (60%) belonged to the age group of 10–15 years. Mallol et al (2013) also showed higher prevalence of asthma in 13–14 years of age as compared to 6–7 years.[4] Most of our patients were males (65%); the reason being male gender is a known risk factor for bronchial asthma and also reporting for treatment is more with male children as a result of gender discrimination. The findings are similar to as reported by Mallol et al (2013). Maximum number of the cases (46.6%) belonged to middle lower socioeconomic status. This is consistent with the fact that asthma prevalence is increasing in middle income countries. Paramesh et al (2002) also showed increasing prevalence of asthma in industrialized areas suggesting that its incidence is less in lower socioeconomic groups.[5]

The mean pulse rate and respiratory rate amongst the cases was significantly higher (p value < 0.001) than in controls. Also the oxygen saturation was less than 90% in most of the patients conforming to the definition of acute severe bronchial asthma.

The mean $pO_2$ (63.31 mmHg) was lower and mean $pCO_2$ (48.41 mmHg) was higher amongst cases, which is consistent with the fact that acute severe asthma leads to hypoxia and hypercapnia ($pCO_2 > 45$ mmHg).

In the present study, most of the patients (65%) had a normal chest x ray, 20% had hyperinflated lung fields and 15% had peri-bronchial cuffing. Similar findings were seen in a study done by Simon et al in 1973. The authors reported normal radiograph in 73%, overinflation in 15% and hilar vessel enlargement in 12%.[6]

Sinus tachycardia was found in 90% of our patients, 35% had T wave inversion, 25% showed ST segment depression and 20%

showed QT prolongation. Table 4 shows the comparative findings of the present study with the studies done earlier.[7–9]

All the ECG findings noted are suggestive of myocardial ischemia. Although the children included in this study are not at risk of coronary artery disease, still these ECG findings should not be ignored as hypoxemia, inhalation of beta 2 adrenergic medications and tachycardia can lead to increased workload of heart and myocardial injury.

At discharge all the patients had a normal ECG, which suggests that the changes were transient and not related to overt myocardial dysfunction.

Cardiac biomarker at admission showed that 50% of the cases had abnormal Tn I levels, 15% had abnormal CK-MB levels and 8.3% had abnormal BNP levels. Table 4 shows the comparative findings of the present study with the studies done earlier.[7,8,10–13]

Of the above-mentioned studies, the study done by Chang et al[13] was in adult chronic obstructive pulmonary disease (COPD) patients. As far as it could be reviewed, no study relating BNP levels in pediatric asthma patients could be found in literature.

The mean levels of all the three cardiac biomarkers were raised at admission. Though the mean CK-MB level failed to achieve statistical significance, the individual values showed rising trend as 1/3rd values were beyond 2SD of the control mean. However, the values normalized at discharge. The findings suggest that the elevation was only a transient phenomenon which returned to normal levels once the acute episode was controlled. In the present study, only 1 case (1.7%) had abnormal CK-MB at discharge.

All the patients had a normal ECG at discharge suggesting that there was no permanent cardiac damage. Also 2D Echo done in one third of the patients once stabilized was normal; with no patient showing any feature of myocardial ischemia.

One should be careful while the patient is on beta adrenergic therapy which can cause coronary artery vasodilatation and redistribution of flow from the subendocardium to subepicardium ("steal phenomenon") due to stimulation of coronary arteries' beta-2 receptors, mismatch between supply and increased myocardial oxygen demand created by b-1 and b-2 stimulation and systemic

**Table 4**
Electrocardiograph changes and Cardiac biomarkers in acute severe bronchial asthma: comparative findings of the present study with the studies done earlier.

| Parameter | Current study | Fagbuyi et al, 2008 | Kulkarni et al, 2013 | Lovis et al, 2001 | Kalyanarayanan et al, 2011 | Zanoni et al, 2000 | Chang et al, 2011 | Kern et al, 1999 |
|---|---|---|---|---|---|---|---|---|
| Abnormal CK-MB | 15% | – | – | 27% | – | 6.6% | – | – |
| Abnormal TnI | 50% | 24% | 57% | – | 50% | – | – | – |
| Abnormal BNP | 8.3% | – | – | – | – | – | 27.5% | – |
| ECG changes | | | | | | | | |
| Sinus Tachycardia | 90% | – | – | – | – | – | | 96% |
| ST segment changes | 20% | 30% | – | – | – | 20% | – | – |
| T wave inversion | 35% | – | – | – | – | – | – | 28% |
| QT prolongation | 20% | – | – | – | – | – | – | 15% |

CK-MB - creatine kinase-muscle/brain,TnI- troponin I, BNP-brain natriuretic peptide, SD - standard deviation.
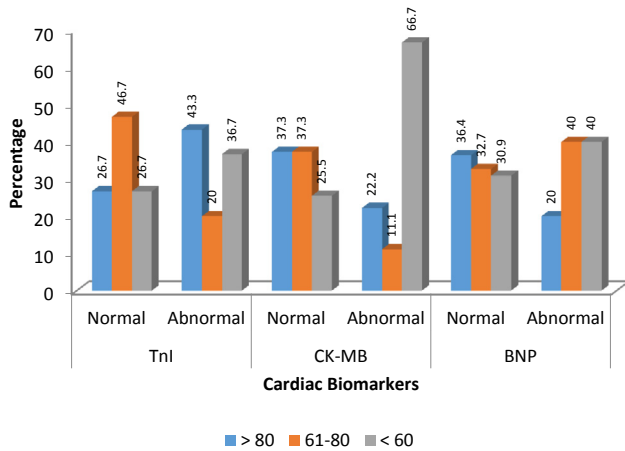
**Fig. 1.** Cardiac biomarkers in acute severe bronchial asthma according to FEV1% Predicted value. FEV - forced expiratory volume.

vasodilatation leading to increased myocardial stress.[8] The raised cardiac biomarkers and the ECG changes suggest myocardial stress during acute exacerbation of bronchial asthma. This could be due to combined effect of hypoxia and hypercapnia.

## 5. Study limitations

The present study showed that the changes are of transient nature, larger follow up studies are required to record any permanent damage to the myocardium in acute severe bronchial asthma.

## 6. Conclusion

The raised cardiac biomarkers and the ECG changes suggest myocardial stress during acute exacerbation of bronchial asthma. This could be due to combined effect of hypoxia and hypercapnia and also decreased coronary perfusion due to decreased diastolic duration during tachycardia.

## Conflict of interest

All authors have none to declare.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ihj.2018.10.416.

## References

1. Roca J, Ramis L, Rodriguez-Roisin R, et al. Serial relationships between ventilation-perfusion inequality and spirometry in acute severe asthma requiring hospitalization. *Am Rev Respir Dis*. 1988;137:1055–1061.
2. Rodriguez-Roisin R, Ballester E, Roca J, et al. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. *Am Rev Respir Dis*. 1989;139:732–739.
3. Sear MR. Adverse effects of beta agonists. *J Allergy Clin Immunol*. 2002;110:S322–S328.
4. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. ISAAC phase three study group. The international study of asthma and allergies in childhood (ISAAC) phase three: a global synthesis. *Allerg Ilmmunopathol*. 2013;41:73–85.
5. Paramesh H. Epidemiology of asthma in India. *Indian J Pediatr*. 2002;69:309–312.
6. Simon G, Connolly N, Littlejohns DW, McCallen M. Radiological abnormalities in children with asthma and their relation to the clinical and some respiratory function test. *Thorax*. 1973;28:115–123.
7. Zanoni LZ, Palhares DB, Consolo LC. Myocardial ischemia induced by nebulized fenoterol for severe childhood asthma. *Indian Pediatr*. 2005;42:1013–1018.
8. Fagbuyi DB, Venkataraman S, Ralphe JC, et al. Diastolic hypotension, troponin elevation, and electrocardiographic changes associated with the management of moderate to severe asthma in children. *Acad Emerg Med*. 2016;23:816–822.
9. Kern JH, Salim A, Agarwala S, Rubin DH. Electrocardiographic findings in children with severe asthma. *Pediatr Res*. 1999;45.
10. Kalyanaranan M, Bhalala U, Leoncio M. Serial cardiac troponin concentrations as marker of cardiac toxicity in children with status asthmaticus treated with intravenous terbutaline. *Pediatr Emerg Care*. 2011;27:933–936.
11. Kulkarni H, Akwei S, Luyt DK, Gaillard EA, Mulla H, Pandya HC. Cardiac troponin I levels in children with acute severe asthma treated with IV salbutamol. Lung Dis Treat Lung Dis Treat 1:102. doi:10.4172/2472-1018.1000102.
12. Lovis C1, Mach F, Unger PF, Bouillie M, Chevrolet JC. Elevation of creatine kinase in acute severe asthma is not of cardiac origin. *Intensive Care Med*. 2001;27:528–533.
13. Chang CL, Robinson SC, Mills GD, et al. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax*. 2011;66:764–768.