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Evaluation of Burden and Predictors of Arrhythmia in Hospitalized Asthmatic Children

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ABSTRACT
Background: Arrhythmias and disturbed cardiac conduction can exacerbate uncontrolled asthma. Asthma medications have been linked, either directly or indirectly, to irregular heartbeats. There are few data about risk of arrhythmia in asthmatic children. **Objective:** The aim of the present study was to assess occurrence of arrhythmia and conduction disturbances in hospitalized asthmatic children and to investigate the predictors and impact of arrhythmia.
Patients and methods: A cross-sectional study was conducted in the Pediatric Chest and Pediatric Intensive Care unit of Zagazig University Children hospital. This study was conducted on 56 asthmatic children. In absence of documented spirometric measurements, diagnosis of bronchial asthma was relied on medical basis. Clinical diagnosis relied on the updated 2022 GINA Guidelines. Assessment of severity of acute exacerbation was based on British National Guidelines and updated 2022 GINA Guidelines. **Results:** There was significant increase heart rate in children with sinus tachycardia compared to other asthmatic children. Otherwise, there was no difference on other vital signs. There was no difference in serum electrolytes and occurrence of sinus tachycardia. There was no relation between treatment of bronchial asthma and occurrence of sinus tachycardia.
Conclusion: Asthmatic children were at increased risk of developing sinus tachycardia. There were significant association between sinus tachycardia with increased heart rate, and reduced hemoglobin level.
Keywords: Asthma, Arrhythmia, Asthmatic children, Cross sectional study, Zagazig University.

INTRODUCTION
Asthma is a chronic inflammatory obstructive airway disease. It is the most prevalent chronic illness among children. It is characterized by; variable and recurring Symptoms these include wheezing, chest pain, shortness of breath, and coughing. Asthma is a clinically classified into; mild, moderate and severe persistent asthma [(1)]. Bronchial Asthma is a multifactorial disorder with a complex etiology that involves interactions between genetic susceptibility, host factors, and environmental exposures [(2)].

Several studies have suggested that asthma is an independent risk factor for cardiovascular disease (CVD) and arrhythmias. Previous research found a high prevalence of tachycardia, premature ventricular contractions, and atrial fibrillation (AF) in adult asthma patients [(3)].

The precise mechanism of arrhythmia in asthma disease is unknown, but it is likely multifactorial. Asthma pathogenesis is characterized by chronic inflammation of the airways. Because inflammation is a well-known risk factor for arrhythmias, this inflammation may play a role in the development of arrhythmias in asthmatics [(4)].

For asthma control, GINA recommends using low-dose inhaled corticosteroids in conjunction with short acting 2-agonists (SABAs), followed by the addition of long acting 2-agonists (LABAs) if symptoms persist [(5)].

High doses of 2-agonists for asthma have been linked to an increased risk of arrhythmias. Furthermore, as many as 98% of severe asthma patients have electrolyte disturbances associated with the use of 2-agonists, a well-known cause of cardiac arrhythmia [(6)]. Electrocardiography (ECG) is the gold standard for detecting rhythm disturbances. As a result, ECG analysis in BA patients is an important component of their management [(7)].

The aim of the present study was to assess occurrence of arrhythmia and conduction disturbances in hospitalized asthmatic children and to investigate the predictors and impact of arrhythmia.

PATIENTS AND METHODS
A cross-sectional was conducted in the Pediatric Chest and Pediatric Intensive Care unit of Zagazig University Children hospital. This study was conducted on 56 asthmatic children.

Inclusion criteria: Age from 3-12 years old, a diagnosis of bronchial asthma, hospitalization due to asthma exacerbations.
Exclusion Criteria: The presence of pneumonia or fever. Known cardiac or other chronic diseases.

All patients underwent a thorough history of the present illness including presence of symptoms suggestive of presence of bronchial asthma. The questionnaire of the International Study of Asthma and Allergies in Childhood Organization was used after its translation into Arabic, as well as a clinical examination that included heart rate, blood pressure, respiratory rate, edema, cyanosis, pallor, or congested pulsating neck veins. Cardiac exam for chamber enlargement, weak heart sounds, gallop or new murmur, and chest exam. Basic laboratory investigations including CBC (complete blood count) was drawn from venous blood that had been properly mixed after being anticoagulated with the anticoagulant ethylene diamine tetra-acetic acid (EDTA). Because certain tests' results are affected by prolonged durations of storage, the blood sample was tested within 6 hours after being obtained. Automated

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cell counters were used to determine the TLC count values. "Sysmex XN-2000™ Hematology System" (Sysmex Company), as well as the evaluation of peripheral blood smears stained with Leishman's solution for a differential leucocytic count to determine eosinophils, erythrocyte sedimentation rate (ESR).

At 0h of clinical presentation, C reactive protein (CRP) was estimated using a test kit (Cromatest). Antibodies to human CRP are coated on the AVITEX- CRP latex particles. Within 2 minutes of mixing the latex suspension with serum containing elevated CRP levels on a slide, clear agglutination was observed.

All patients were subjected to postero-anterior (PA) radiography of Chest with full inspiration. All patients had standard 12-lead ECG recordings taken. Electrocardiograms were recorded on 12-channel equipment at a paper speed of 25mm/s and a standardization of 10mm/mV. Electrocardiograms were recorded after stabilization of patients and repeated if palpitation or chest pain were present. Echocardiographic examinations were performed for cases who developed arrythmia using an echocardiography system that is commercially available (Vivid 7, GE Vingmed Ultrasound, Horten, Norway or (EPIQ 7, Philips Ultrasound Systems, Koninklijke Philips N.V., Amsterdam, the Netherlands; E9) with a multi-frequency transducer, and harmonic imaging as appropriate.

Ethical Consideration:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (IRB #9727-23-8-2022). All parents of patients who participated in the study provided written informed consent. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows. IBM Corp., Armonk, New York) version 23.0. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and non-parametric data as median and range. Student's t test was used to compare two groups of variables that are regularly distributed, whereas Mann-Whitney U test is used to compare two groups of variables that were not normally. P value ≤0.05 was considered to be statistically significant.

RESULTS

Table 1 summarized the age and gender of the studied patients.

Table (1): Demographic characters of the studied patients (n. 56).

Variables	Mean (SD)/ N. (%)	
Age per years		
Mean ± SD	9.2 ± 2.7	
Range	9 (5-13)	
Sex (n. %)		
Males	27	48.2
Females	29	51.8

Table 2 summarizes sinus tachycardia and prolonged QT interval of the studied patients.

Table (2): Electrocardiography abnormality in the studied patients.

Variable	n.	%
Sinus tachycardia	18	32.1%
Prolonged QT interval	3	5.3%

Table 3 showed that there was no relation between personal characters and occurrence of sinus tachycardia in studied group.

Table (3): Personal characters and occurrence of sinus tachycardia in studied groups.

Variables	Asthmatic children		Test	P-value
	With Sinus tachycardia (n. 18)	Without Sinus tachycardia (n. 38)		
Age per years (Mean ± SD)	8.8 ± 2.9	9.4 ± 2.6	0.806	0.424
Gender n. (%)				
Females	10 (55.6)	19 (50)	0.15	0.69
Males	8 (44.4)	19 (50)		
Other atopy n. (%)				
Yes	10 (55.6)	13 (34.2)	2.3	0.13
No	8 (44.4)	25 (65.8)		
Family atopy n. (%)				
Yes	14 (77.8)	21 (55.3)	2.6	0.1
No	4 (22.2)	17 (44.7)		

t: t test, χ 2 :Chi-square test, P>0.05 no significant.

Table 4 showed that there was relation between asthma grade and occurrence of sinus tachycardia in studied group.

Table (4): Relation between occurrence of arrhythmia and asthma exacerbation severity.

Variables	Asthmatic children				Test	P-value
Asthma grade	With Sinus tachycardia n. 18		Without Sinus tachycardia n. 38			
	No.	%	No.	%		
Grade2	20	64.5	11	35.5	0.84	0.66
Grade3	17	68	8	32		

χ^2 : Chi-square test, P>0.05 no significant.

Table 5 showed that there was significant association between sinus tachycardia with increase heart rate.

Table (5): Relation between vital signs and occurrence of sinus tachycardia in studied groups.

Variables	Asthmatic children		Test	P-value
	With Sinus tachycardia n. 18	Without Sinus tachycardia n. 38		
Systolic blood pressure(mm hg) Mean ± SD	113 ± 4.8	114 ± 4.9	0.064	0.95
diastolic blood pressure(mm hg) Mean ± SD	76 ± 4.9	75.5 ± 5.04	0.8	0.427
Respiratory rate per minute Mean ± SD	27 ± 4.02	28 ± 2.9	0.313	0.755

t: t test, P>0.05 no significant, *P<0.05 significant.

Table 5 showed that there was significant decreased hemoglobin level in children with sinus tachycardia compared to other asthmatic children. Otherwise there was no difference of other CBC parameters and occurrence of sinus tachycardia in studied groups. There was no difference between vital signs and occurrence of sinus tachycardia in studied groups.

Table (6): Relation between CBC picture, ABG and occurrence of sinus tachycardia in studied groups.

Variables	Asthmatic children		Test	P-value
	With Sinus tachycardia n. 18	Without Sinus tachycardia n. 18		
CBC picture				
Hemoglobin (g/ml) Mean ± SD	9.8 ± 1.3	11.7 ± 1.2	2.46	0.019*
Neutrophil median(range)	3.3 (0.6-19.7)	4.2 (1.1-23.3)	U 1.94	0.051
Lymphocyte Median(range)	4.2 (2.2-6.3)	4.4 (1.1-9)	U 0.45	0.648
ABG				
Co2 Mean ± SD	32.2 ± 3.7	36.2 ± 5.9	1.498	0.140
Hco3 Mean ± SD	21.1 ± 4.8	22.7 ± 3.4	1.504	0.138
ABG Mean ± SD	7.4 ± 0.04	7.4 ± 0.03	0.218	0.828

t: t test, U: Mann Whitney U test, P>0.05 no significant, *P<0.05 significant.

Table 7 showed that there was no difference in serum electrolytes and occurrence of sinus tachycardia in studied group. There was no relation between kidney function and occurrence of sinus tachycardia in studied group.

Table (7): Relation between serum electrolyte, kidney function and occurrence of sinus tachycardia in studied group.

Variables	Asthmatic children		Test	P-value
	With Sinus tachycardia n. 18	Without Sinus tachycardia n. 38		
Serum electrolyte				
Sodium (Mean ± SD)	137.1 ± 3.05	136.5 ± 2.1	0.701	0.490
Potassium (Mean ± SD	3.8 ± 0.5	4 ± 0.47	1.667	0.101
Calcium (Mean ± SD)	9.6 ± 1.3	9.1 ± 0.69	1.628	0.109
Magnesium (Mean ± SD)	2.2 ± 0.35	2.08 ± 0.25	1.298	0.206
Phosphorus (Mean ± SD)	3.8 ± 0.53	4.1 ± 0.49	1.93	0.48
Kidney function				
Urea Median (range)	13 (6.4-23)	13.9 (4.6-23)	0.23	0.82
Creatinine Mean ± SD	0.54 ± 0.13	0.57 ± 0.12	0.51	0.66

t: t test, P>0.05 no significant, *P<0.05 significant.

Table 8 showed that there was no relation between treatment of bronchial asthma and occurrence of sinus tachycardia in studied group.

Table (8): Relation between treatment and occurrence of sinus tachycardia in studied group.

Variables	Asthmatic children				χ^2	P-value
	Sinus tachycardia n. 18		Without Sinus tachycardia n. 38			
	No.	%	No.	%		
Ipratropium nebulizer	18	100.0	38	100.0	-	-
Budesonide nebulizer	18	100.0	38	100.0	-	-
salbutamol nebulizer	18	100.0	38	100.0	-	-
Corticosteroid	18	100.0	38	100.0	-	-
Mg SO4 Neb	6	33.3	18	47.4	0.98	0.32

χ^2: Chi-square test, P>0.05 no significant.

DISCUSSION

Regarding demographic data, the current study showed that there were 27 (48 %) males and 29 (52%) females, the mean age of all patients was 9.2 (SD 2.7) years and ranged from 5 to 13 years.

In agreement with the current study, **Mpairwe *et al.*** [8] enrolled 562 children with asthma and revealed that there were 52% females and 48% males with mean age of 11.4 (range 5-17) years.

Sinus Tachycardia: Our study reported sinus tachycardia in 18 (32%) of hospitalized asthmatic children. **Dabour *et al.*** [9] investigated the risk of arrhythmia in asthmatic children. Their study revealed that 20% of the studied asthmatic children have sinus tachycardia and it is the only type of arrhythmia in this study. Nineteen (95%) patients received both inhaled salbutamol and ipratropium and 1 (5%) patient received ipratropium only.

Adimadhyam *et al.* [10] concluded that compared to non-users, adolescents and young adults with asthma had a higher risk of arrhythmia when using inhaled ipratropium.

Khalilian *et al.* [11] study investigated the impact of a 2-agonist on heart rate and QTc to evaluate any possible arrhythmogenic concerns. They reported significant increase in HR after use of inhaled β2-agonist (salbutamol)**.**

The traditional mainstay of acute asthma therapy is inhaled, short-acting, beta-2 adrenergic agonists, whereas long-term management of moderate to severe asthma involves the use of inhaled, selective beta-2 adrenergic agonists in conjunction with inhaled glucocorticoids [12]**.**

Salbutamol causes bronchodilation by activating 2-adrenergic receptors, which causes bronchial smooth muscle to relax through the action of cyclic adenosine monophosphate (cAMP) [13]**.**

Salbutamol is a selective 2 agonist, but studies have demonstrated that they also exert effects on 1 receptor in the myocardium, which contains both 1- and 2-

adrenergic receptors. When used in excess, 2-agonists may lose their receptor specificity and produce tachycardia, heart ischemia, and arrhythmias [13].

A second effect of 2-agonists is the relaxation of vascular smooth muscle, which results in peripheral vasodilation and tachycardia [14].

Long QT syndrome: The most common cause of syncope in children and sudden death is long QT syndrome. The individual is susceptible to "Torsades de Pointes," which can develop into ventricular fibrillation and result in unexpected death [15].

Most long QT syndromes are brought on by changes in the genes that produce the myocyte ion channels. Long QT syndrome can be congenital or acquired, with the latter condition typically brought on by drugs such domperidone, erythromycin, and clarithromycin, all of which are frequently prescribed to children [15]. Also, electrolyte disturbances as hypokalemia, hypomagnesemia and hypocalcemia may cause prolongation of QTc [16].

In the present study, there were 3 (5%) cases with prolonged QT interval. Two patients in grade II and one patient in grade III.

In their study to describe electrocardiographic findings in Children with Severe Asthma, **Kern *et al.*** [17] detected prolongation of QT c in 15% patients.

In their study, **Khalilianand and Colleagues** reported prolongation of QTc in 88.5% of patients after use of β2-agonist. Moreover, one patient had prolonged QTc (greater than 450 milliseconds) [11].

Kotby *et al.* [18] examined the relationship between the QTc interval and the severity of the attack and the bronchodilators utilized in acute asthma attacks. They reported a longer QTc interval in 13% of kids with moderate to severe asthma, which is consistent with our findings. The number of bronchodilators utilized increased the QTc interval, but not statistically significantly.

The Na+/K+-ATPase pump in skeletal muscle is largely 2-stimulated by salbutamol, which transfers potassium intracellularly and results in hypokalemia [19]. A well-known risk factor for cardiac arrhythmia and QTc prolongation is hypokalemia [13].

Also, ipratropium bromide had showed a significantly higher risk of QT prolongation [20].

In our study, 1 out of 3 patients with long QTc had hypokalemia and all 3 patients received inhaled salbutamol, ipratropium and corticosteroid.

Relation between arrhythmia: The current study showed that there was no relation between occurrence of arrhythmia with age and sex in asthmatic children.

This comes in agreement with the adults' study by **Chan *et al.*** [21] who revealed that there was no significant association between the incidence of arrhythmia with age and sex.

According to the current study, there is no link between occurrence of arrhythmia with history of other atopic diseases and family history of atopy.

A recent meta-analysis by **Zeng *et al.*** [22] demonstrated that patients with atopic diseases have a higher risk of developing atrial fibrillation, particularly those with asthma.

Regarding vital signs, the current study showed no relation between occurrence of arrhythmia and both Blood pressure and oxygen saturation in asthmatic children. However, **Taha *et al.*** [4] in adults showed that there was significant association between hypertension and arrhythmia in adult asthmatic patients. The difference between this result and our study may be due to difference in age group as in adult patients, hypertension, coronary heart disease and diastolic dysfunction are more prevalent.

Also, **Saito *et al.*** [23] showed that there was significant association between heart rate variability and oxygen saturation. The difference between this result and our study may be due to absence of hypoxia in our patients.

Regarding the grade of asthma, the current study showed that 55% of children had grade II, and 45% of them had grade III of asthma severity. We also revealed that arrhythmia had occurred in both groups of severity and it was more prevalent in grade III group with no statistical difference.

Grymonprez *et al.* [24] and **Konecny *et al.*** [25] indicated that the incidence of arrhythmia was strongly connected with the frequency of exacerbations and severity of chronic obstructive pulmonary disease (COPD). COPD patients experienced varying degrees of dilated left atrium and systemic inflammatory response. Moreover, aberrant ventricular and atrial dilatation causes cardiac muscle injury and systolic dysfunction, all of which increase the risk of arrhythmia [26]. Non adherence to asthma prophylaxis was present in majority of our patients; most of them were in grade III severity. The associations between non -adherence and both poor disease control and more severe disease are clearly stated in different literatures.

Cepelis *et al.* [6] shown that there was an Arrhythmia risk and asthma control levels are correlated, with people with uncontrolled asthma having the highest arrhythmia risk. The current study showed that there was significant decrease hemoglobin level in children with sinus tachycardia compared to other asthmatic children. Otherwise, there is no difference of other CBC parameters and occurrence of sinus tachycardia in asthmatic children. Anemia is a well- known risk factor for sinus tachycardia. In the presence of anemia, asthma treatment cause more increase in heart rate.

Regarding the relation between serum electrolyte and occurrence of sinus tachycardia, our study showed no significant relation. One patient with long QTc had hypokalemia and other 2 cases had normal K level.

Regarding effect of treatment used for asthma on occurrence of arrhythmia, we cannot rely on statistical analysis in our study as all patients had received the same categories of treatment making no use for statistical tests.

CONCLUSION

Asthmatic children were at increased risk of developing sinus tachycardia. There were significant association between sinus tachycardia with increased heart rate, and reduced hemoglobin level. In order to underline our findings, we advise further research using bigger patient populations and longer follow-up intervals. Serial electrocardiographic recordings for hospitalized asthmatic patients were a must for early detection and management of arrhythmia. As bronchodilators may be arrhythmogenic, care must be taken when using them.

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