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Effect of Inhalational Salbutamol on Electrophysiology of Heart in Children

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ABSTRACT

Back ground
Hypoglycaemia is a prominent cause for QT-interval prolongation and evokes the pro-arrhythmogenic. Salbutamol, a β2-adrenoreceptor agonist also causes QT-interval prolongation. The present study was conducted to investigate the acute electrophysiological effects of salbutamol (selective β2- agonists), administered by nebulization in children and to provide a further insight into the possible cardiovascular effects of inhaled salbutamol.

Materials and Methods
30 children from outpatient department of Indira Gandhi Medical College and Research Institute, Kadirkamam, Puducherry, were enrolled for the study. The ECG was taken before and after the salbutamol nebulization. The criteria such as Heart rate (HR1&HR2),PR interval (PR1&PR2), QRS duration (QRS1&QRS2), corrected QT interval (QTC1&QTC2), P axis (Paxis1&Paxis2), QRS axis (QRS axis1&QRS axis2), T axis (Taxis1&T axis) were analysed and statistically evaluated.

Results
The present study showed that the single regular dose of salbutamol nebulization significantly increased the heart rate, decreased the PR interval, decreased the P axis, and decreased the T axis. But there were no significant changes in QRS duration, QTC interval or QRS axis.

Conclusion
Our study allows us to speculate that the significant tachycardia, shortening of the PR interval (decrease in the AV nodal conduction time), decrease in the T wave axis may facilitate the induction of premature atrial beats and ventricular arrhythmias in patients receiving salbutamol nebulisation.

Keywords:
heart rate variability, inhaled β2-agonist, Hypoglycaemia, arrhythmogenic, QT-interval prolongation

1. Introduction

The heart has a unique electrophysiological property of generating rhythmical electrical impulses. To conduct the electrical impulses rapidly throughout the heart and to cause rhythmical contraction , the heart has a specialised system of generating two types of action potential, 1.Nodal cell action potential, 2. Non – nodal cell action potential[1]. Nodal cell action potential are referred to as "slow response action potential which are characteristic of action potential found in the sinoatrial node and atrioventricular node. These action potentials display automaticity (or) pacemaker activity and therefore undergo spontaneous depolarisation. Non – nodal cell action potentials are referred to as "fast response" action potentials, which are characteristic of atrial and ventricular myocyte and the fast conducting purkinje system in the ventricles. These action potentials are initiated by the pacemaker activity and causes rhythmical contraction of the atrium and ventricles. Cells within the sinoatrial node (SA node) are the primary pacemaker site in the heart. Pacemaker activity is spontaneously generated by the SA nodal cells and their rate can be modified significantly by external factors such as

1. Autonomic nerves by their sympathetic and parasympathetic innervations[2].
2. Drugs like Digitalis, Quinidine, Procainamide, Disopyramide, Phenothiazine, Tricylic antidepressants etc can prolong the QT interval (prolong the duration of ventricular depolarisation and ventricular repolarisation)[3].

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3. Hormones especially thyroid hormones and catecholamines. (Thyroid hormones increase the number of β receptors on nodal tissues in SA and AV node of the heart and also increases the sensitivity of β receptors to catecholamines. Catecholamines increase cardiac excitability and contractility)[4].
4. Ions like sodium, potassium and calcium (Increase or decrease in various ionic concentrations in plasma may affect the electrophysiological properties of the heart) [2].
5. Ischemia/Hypoxia (may affect entire myocardium due to poor perfusion and oxygenation)[1].
The atrial and ventricular myocardium consist of β_1 and β_2- adrenergic receptors[5-8]. It has been demonstrated that β_2-adrenergic receptors constitute about 20 to 40 % of the total number of β receptors in the human heart and play a significant role in physiologic and pathologic conditions[7-8]. It has also been demonstrated that the autonomic nervous system and especially its sympathetic component play an important role in the development of cardiac arrhythmias[9-11]. The increased sympathetic activity and the consequent enhanced catecholamine release result in the activation of myocardial adrenergic receptors, which mediate its arrhythmogenic effects[9-12]. The most common respiratory symptoms for attending the paediatric outpatient and emergency department in children are due to wheeze, dyspnoea, chest tightness and shortness of breath. The common causes for wheezing in children include wheeze associated lower respiratory infection (WALRI), hyperreactive airway diseases (HRAD), bronchial asthma etc.
Inhaled β2 adrenoceptor agonists are the most effective known bronchodilators[13]. The most commonly used selective β_2 agonist is salbutamol. Salbutamol is the cornerstone of rescue therapy for acute asthma attacks and is widely used for its proven efficacy and safety[14,15]The most common mode of administration of salbutamol is by nebulization. Apart from the well known side effects of salbutamol like fine tremors, tachycardia, palpitation, dry mouth, muscle spasm and anxiety, serious cardiac events like arrhythmias, cardiac arrest and acute cardiac death have also been documented[16-22] EleftheriosM.kallergis et al have documented that inhaled β2 agonists results in significant changes of cardiac electrophysiological properties. Salbutamol enhances atrioventricular(AV) nodal conduction and decreases AV nodal, atrial, and ventricular refractoriness in addition to its positive chronotropic effects. These alterations could contribute to the generation of spontaneous arrhythmias[13].
Coskun S, et al have found out that standard doses of nebulized salbutamol in acute asthmatic attack are associated with high QTd (QT dispersion) values[23]. This might increase the incidence of cardiac arrhythmia at high doses in asthmatics[24-26]. Such doses of salbutamol are commonly given by nebulizer during acute asthmatic attacks[27]. A number of previous reports have described a relationship between inhaled β_2-agonist (salbutamol) use and increased cardiovascular morbidity and mortality. Despite the large number of clinical studies showing a relationship between inhaled β2-agonist treatment and cardiovascular risk, only few reports have systematically investigated the effects of β2-agonist inhalation on the electrophysiology of heart in children.
As sufficient data does not exist concerning the acute cardiac electrophysiological effects of β2 agonists in children, particularly inhaled β2 agonists, the present study investigated the electrophysiological characteristics of nebulized salbutamol in children.

2. Materials and Methods

Children with wheeze associated lower respiratory tract infections (WALRI), hyperreactive airway diseases, bronchial asthma patient who presented to the paediatric outpatient department of Indira Gandhi Medical College and Research Institute, Kadirkamam, Puducherry, formed the

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study population (n=130) during February 2013 to July 2013. All patients met the American Thoracic society criteria for asthmain which asthma is a clinical syndrome characterised by paroxysmal coughing, wheezing and dyspnoea caused by the hyperresponsiveness of the tracheobronchial system to different stimuli resulting in airway obstruction[96] based on ECG's. One ECG was taken before and after the salbutamol nebulization. The SPSS statistical software package program(version 19) was used to perform all statistical calculations.

3. Results

The patient population included 130 children. There were 74 males and 56 females between 1 year and 12 years of age (mean,6±3yrs). The weight of the children was in between 8 kg to 39 kg(mean,21.21±8.92).The height of the children was in between 73 cms and 150 cms (mean,111.89±21.82). The BMI was calculated and the value was in between 14.58 and 17.80 (mean,16.15±0.8). All the children were 100% immunised. Table 1 displays the baseline demographic characteristics of the patient population like weight in kg, height in cms, BMI(kg/m^2).

Table 1. Baseline Demographic Characteristics Of The Patient Population
{Age,weight in kg,height in cms,BMI(Body mass index) =weight in kg/(height in metres)^2 }

		Minimum	Maximum	Mean	Std. Deviation
Age (yrs)		1.00	12.00	6.0269	3.4084
Weight(kg)		8.00	39.00	21.2154	8.92691
Height(cm)		73.00	150.00	111.8923	21.82639
BMI		14.58	17.80	16.1492	0.80925

Table 2. Tests of significance of difference in means by paired t test before and after salbutamol nebulization.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HR1	116.62	130	20.283	1.779
	HR2	126.02	130	21.817	1.913
Pair 2	PR1	128.79	130	25.240	2.214
	PR2	123.96	130	29.451	2.583
Pair 3	QRS1	78.25	130	36.391	3.192
	QRS2	78.07	130	33.484	2.937
Pair 4	QTC1	466.76	130	49.352	4.328
	QTC2	468.18	130	53.393	4.683
Pair 5	PAXIS1	36.47	130	33.606	2.947
	PAXIS2	25.30	130	34.924	3.063
Pair 6	QRSAXIS1	62.01	130	23.181	2.033
	QRSAXIS2	63.27	130	21.220	1.861

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Pair 7	TAXIS1	22.24	130	35.266	3.093
	TAXIS2	12.72	130	27.229	2.388

Abbrevations

HR1-heart rate(before nebulization) ,HR 2-heart rate(after nebulization), PR 1-PR interval(before nebulization) ,PR2- PR interval(after nebulization), QRS1-QRS duration(before nebulization), QRS2- QRS duration(after nebulization), QTC1-Corrected QT interval(before nebulization), QTC2- Corrected QT interval(after nebulization), P AXIS1-P Axis value(before nebulization), P AXIS 2- P Axis value(after nebulization), QRS AXIS1- QRS AXIS1(before nebulization), QRS AXIS2- QRS AXIS2(after nebulization), T AXIS1- T AXIS1(before nebulization), T AXIS2- T AXIS2 (after nebulization)

Table 3. Electrophysiological Effects of salbutamol(ECG parameters before and after nebulization and the significant p value)

		Sig. (2-tailed)
Pair 1	HR1 - HR2	.000
Pair 2	PR1 - PR2	.036
Pair 3	QRS1 - QRS2	.817
Pair 4	QTC1 - QTC2	.746
Pair 5	PAXIS1 - PAXIS2	.004
Pair 6	QRSAXIS1 - QRSAXIS2	.371
Pair 7	TAXIS1 - TAXIS2	.008

Table 2 and Table 3 showed the ECG parameters of subjects at baseline (before) and immediately after Salbutamol nebulization (within 5 to 15 minutes). From the analysis of the ECG parameters before and after Salbutamol nebulisation, the present study revealed that Salbutamol nebulisation produced significant changes in the cardiac electrophysiological parameters mentioned below. There was a significant increase in the heart rate after salbutamol nebulization. Salbutamol nebulisation increased the heart rate from 116.62±20.283 (before nebulization) to 126.02±21.817 (after nebulization) (p=0.000). There was a significant decrease in the PR interval from 128.79±25.24 ms (before nebulization) to 123.96±29.451 ms (after salbutamol nebulisation) (p=0.036). There was a significant decrease in the P axis parameter from 36.47±33.60 degrees (before nebulization) to 25.30±34.92 degrees (after salbutamol nebulisation) (p=0.004).There is a significant decrease in the T axis parameter from 22.24±35.26 degrees (before nebulization) to 12.72±27.22 degrees (after salbutamol nebulisation) and value was statistically significant (p = 0.008). There was a slight decrease in the QRS interval after salbutamol nebulisation from the

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baseline value but the difference was not statistically significant (p=0.817). There was a slight increase in the QTC interval after salbutamol nebulisation from the baseline value but it was not statistically significant (p=0.746). There was a slight increase in the QRS axis parameter after salbutamol nebulization but the value was not statistically significant (p=0.371).

4. Discussion

Despite the widespread use of β2-agonists, their safety has been questioned. Several studies have reported an increased incidence of cardiac arrhythmias in patients treated with these agents.[16-22].There are studies which are found to have an increased cardiovascular death with the use of oral and nebulized β2-agonists[20-22]. Although no causal relationship has been demonstrated, the possible arrhythmogenic effects of these drugs place them under considerable suspicion. Clarifying the effects of β2-agonists on electrophysiological parameters could provide a significant insight into the potential arrhythmogenic role of these agents. This study has evaluated the cardiac electrophysiological effects of a single, regular dose of an inhaled β2-agonist(salbutamol) in children. Salbutamol was selected, as it is one of the most widely used inhaled β2-agonists and would ensure improved correlation with standard clinical practice. The main finding of this study was that the inhalation of a standard dose of the β2-agonist salbutamol resulted in significant changes of cardiac electrophysiological properties. From our study we found that inhalation of a single regular dose of salbutamol nebulization significantly increased the heart rate, decreased the PR interval, decreased the P axis, and decreased the T axis. But there was no significant change in QRS duration, QTC interval or QRS axis.

Salbutamol nebulization produces a significant increase in heart rate because it is a β_2 sympathomimetic drug[97] Sympathomimetic drugs mimic the action of endogenous catecholamines. Salbutamol stimulates β-adrenergic receptors in the human heart which results in enhanced catecholamines release at the sympathetic nerve endings[53]. Catecholamines (especially norepinephrine) binds to β_1 receptors, which increases the intracellular cyclic AMP that in turn increases the calcium channels. Hence the membrane is rapidly depolarised to the firing level and the depolarisation phase of the action potential becomes steeper, which results in positive chronotropic effect .Thus heart rate increases significantly[2]. Increase in sympathetic stimulation causes enhanced automaticity, increased conduction velocity and decreased action potential duration. This causes cardiac cells to fire more rapidly, respond to signals more rapidly and recover more quickly[1].

There was a significant decrease in the PR interval after salbutamol nebulization. This may be due to the following reasons, 1.Due to increase in heart rate(tachycardia) itself since PR interval is shortened at fast heart rates and prolonged at slower heart rate[2].2.PR interval may be shortened due to decrease in the AV(atrioventricular) conduction time. PR interval reflects the AV (atrioventricular) conduction time. The AV conduction time includes the time taken for the atrial depolarisation, the conduction delay in the AV node and the time required for the impulse to traverse the conduction system before ventricular depolarisation begins.

Since PR interval is decreased in our study, it could be due to decreased AV conductio time. This indirectly implicates that the duration of atrial depolarisation, the duration of conduction delay in the AV node and the time required for the impulse to traverse the conduction system before ventricular depolarisation begins are all shortened. Since the time of atrial depolarisation is reduced, atrial premature beats can occur. If the conduction delay occurring at the AV node before excitation spreads to the ventricles is shortened, the decremental conduction will not take place. The AV nodal delay allows contraction of the atria to be completed before the ventricle

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starts contracting and provides safety for the ventricles. When SA node discharges more rapidly due to decreased AV nodal conduction time, all impulses are allowed to excite ventricles. Hence extreme ventricular tachycardia will occur. This suggests that a decrease in the PR interval can lead to both premature atrial beats and ventricular arrhythmias which will lead to serious cardiovascular effects if not diagnosed. If the PR interval is normal, it indicates that the impulse is following normal conduction pathways. Short PR intervals (less than 0.12 second) also indicate that the impulse originated somewhere other than the SA node. This variation is associated with junctional arrhythmias and preexcitation syndromes which produces fatal cardiovascular outcomes.

Our study shows no statistically significant changes in QRS duration, QTC interval or QRS axis. The QRS complex is the electrical wave that signals the depolarization of the myocardial cells of the ventricles. If the duration is greater than 0.12 seconds, it indicates an abnormal intraventricular conduction velocity . Since the QT interval shortens at fast rate and lengthens at slow heart rate, QT interval must be corrected in accordance to the heart rate (QTC).using Bazett's formula[28]. The above electrophysiologic effects of salbutamol are in accordance with the known cellular effects of the β-adrenergic stimulation (shortening of the action potential duration in the nodes and in the atrial muscle, increase in upstroke velocity of the action potential in the AV node, and no effect on the upstroke velocity of the action potential in the His-Purkinje system or ventricular myocardium) [98]. Therefore, our findings could be explained by the direct activation of β2-adrenergic receptors. It has indeed been increasingly recognized that β1- and β2-adrenergic receptors coexist in the human heart[5-8,99-101]. β2-adrenergic receptors constitute 20 to 30% and 30 to 40% of the total number of β-adrenergic receptors in human ventricles and atria, respectively[8]. In addition, salbutamol, being a selective β2-agonist, would not be expected to stimulate β1-adrenergic receptors under the conditions applied. Furthermore, salbutamol in our study produced a greater electrophysiological changes in atrial tissue compared with the ventricular tissue. These differential involvement on atrial and ventricular electrophysiological changes could be explained by the different density of β2-adrenergic receptors in atrial and ventricular myocardium, suggesting that the effects of salbutamol were mediated by direct activation of these receptors[8] .

In our present study we have found that there was a significant decrease in the P axis parameter after salbutamol nebulization **.**The mean frontal P wave axis in an electrocardiogram (ECG), reflects the atrial orientation in the thorax. Several investigators have studied the correlation of spirometry with a standard 12-lead electrocardiogram (ECG). In studies correlating ECGs with spirometry, the best discriminant for airway obstruction was the mean frontal vector of the P wave [28-35]. There is "verticalization" of the P axis with progressive hyperinflation. This is because the orientation of the atria changes with progressive hyperinflation as their inferior surface rests on the diaphragm[36]. When the diaphragm descends, rotational forces on the atria cause changes in the P wave axis. Hyperinflation may be seen early and even with mild airway obstruction and might serve as a reliable marker of air-trapping. The vertical orientation of the P axis would be reversed or decreased with a bronchodilator, as airway obstruction and hyperinflation were relieved. In our present study we also found that there was a decrease in the P axis, which could be due to the effect of salbutamol, which had relieved the airway obstruction and hyperinflation due to the obstructive airway disease. Our findings are also supported by the study conducted by Krishnan et al, on theelectrocardiographic prediction of hyperinflation in children. He found out that a verticalP axis vector due to hyperinflation would be present in childreneven with mild airway obstruction and might serve as a reliable marker of air-trapping. The vertical orientation of the P axis in the ECG would be reversed with a bronchodilator. When

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airway obstruction and hyperinflation were relieved after nebulization, there was a decrease in the P axis. Interestingly, there was no significant change in QRS axis, suggesting that atrial and not ventricular orientation is altered[37]. There is a significant decrease in the T wave axis after salbutamol nebulisation. T wave is the most unstable component of the ECG recording. Changes in the T wave deflection occur with hyperventilation, heavy meals, anxiety, changes in body position[3].T wave changes are frequently suggestive of coronary insuffiency. Any tachycardia may result in coronary insuffiency, which manifest as ST segment depression and T wave inversion in those leads where the QRS complexes are dominantly upright[3,38]

The decrease in the T wave axis in our study may be due to the following reasons, 1.stimulation of the β2 adrenergic receptors in the ventricular myocardium by the sympathomimetic drug salbutamol. Salbutamol shortens the action potential duration of ventricular repolarisation and thereby decreases the T wave axis. This further enhances the conditions for cardiac re-entry and cardiac arrhythmias. 2. The decrease in the T wave axis may be due to myocardial ischemia caused by salbutamol nebulisation because inhaled β2 agonists increase the heart rate due to systemic absorption of the drug. This shortens the diastole, thereby increasing the myocardial oxygen consumption and reducing the time for coronary artery perfusion [38.] It can also lead to a worsening of hypoxemia due to changes in the ventilation perfusion ratio within the lungs [44].This may lead to a reduction in the subendocardial blood flow[45] The combination of hypoxemia ,and use of β2 adrenergics and tachycardia might increase the myocardial work load favouring myocardial ischemia[38]. Myocardial ischemia occurs due to decreased blood supply and the ischemic region myocardial cells undergo rapid repolarisation due to fast opening K+ channels[2]. Hence there was a decrease in the T wave axis after salbutamol nebulisation in our study.

Our findings are supported by M D Lowe and his co-workers in their study on β2 adrenergic receptors mediate important electrophysiological effects in human ventricular myocardium. According to their study salbutamol shortened the action potential duration at repolarisation phase and produced important electrophysiological responses mediated through β_2 receptors in human ventricular myocardium which increased the risk of arrhythmia[39]. All these findings of our study are also supported by the study conducted on asthmatic children by LZ Zanoni et al .In their study in acute exacerebrations of asthma there were coexistence of hypercapnia, hypoxemia, tachycardia and ECG features of myocardial ischemia which were associated with the potential risk of severe cardiac arrhythmias[43].

Our findings of T wave axis are also supported by Biberman and his co-workers that adrenergic stimulation either therapeutically or by endogenous catecholamine release might result in asynchronous repolarisation of the myocardium.Hyperventilation and therapeutic sympathomimetic stimulation (salbutamol nebulisation) would certainly explain the appearances of ischaemia in the first few hours of an attack of asthma[51]. The results of our study demonstrated that salbutamol, a selective β2-agonist, administered by nebulizer has significant electrophysiological effects on the atrium, nodes, and ventricle in children. The dosages administered reflected the regular recommended clinical dose, emphasizing that our findings are of particular importance since there is significant correlation with the everyday clinical practice. Larger doses of salbutamol, such as those used in asthmatic exacerbations, could lead to even more pronounced changes in myocardial conduction and refractoriness.

Existing data on the effects of β2-agonists, especially those administered in an inhaled form, on myocardial electrophysiologic properties are negligible. In a previous experimental study, inhaled metaproterenol, a β2-agonist, resulted in significant enhancement of AV node conduction and a decrease of cardiac tissue refractoriness in dogs[52]. In a recent human study, salbutamol produced similar effects but was administered IV[104]. In general, our findings are in agreement with the

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results of the above-mentioned studies. There are, however, some significant differences. First, our study evaluated the acute effects of inhaled, selective β2-agonist (salbutamol) on electrophysiological properties of heart in children. Secondly, the administration mode of salbutamol correlates well with everyday clinical conditions. Especially, in our study the proportional decrease of atrial refractory period after salbutamol inhalation was greater than the decrease of ventricular refractory period, which is consistent with the different density of β2-adrenergic receptors in atrial and ventricular myocardium[8].

Our study is supported by the study conducted by Eleftherios M. Kallergis, which concluded that inhaled salbutamol results in significant changes of cardiac electrophysiological properties. Inhaled salbutamol results in significant changes of cardiac electrophysiological properties. Salbutamol enhances atrioventricular (AV) nodal conduction and decreases AV nodal, atrial, and ventricular refractoriness in addition to its positive chronotropic effects. These alterations could contribute to the generation of spontaneous arrhythmias [13] It has been demonstrated by Zipeset al, Kaumann AJ et al and Han J et al that the autonomic nervous system and especially its sympathetic component play an important role in the development of cardiac arrhythmias. [9-11]The increased sympathetic activity and the consequent enhanced catecholamine release result in the activation of myocardial adrenergic receptors, which mediate its arrhythmogenic effects.[9-12]

Our finding is further supported by the study conducted by LeylaCekici et al,on short term effects of inhaled salbutamol on autonomic cardiovascular control in healthy subjects concluded that inhalation of a single inhaled β2-agonist (salbutamol) resulted in significant haemodynamic changes with significant increase in heart rate[38]. It has also been documented that standard doses of nebulized salbutamol in acute asthmatic attack is associated with high QTd values[23] .This might increase the incidence of cardiac arrhythmia at high doses in asthmatics[24-26] .Such doses of salbutamol are commonly given by nebulizer during acute asthmatic attacks[27].

A study was conducted by Del Rio -Navarro B and his co-workers, on metabolic and electrocardiographic effects of salbutamol in pediatric asthmatic patients and demonstrated that QTC interval was significantly enlarged but had no clinical meaning [54]. We also documented that there is a slight increase in QTC interval after salbutamol nebulization, but it was not statistically significant. M.D. Lowe et al conducted a study on the effects of β_2 adrenergic stimulation on ventricular repolarisation in vivo. According to this study it has been observed that β_2 receptors mediate important electrophysiological effects in human ventricular myocardium. It also provided further insight into the mechanism that increased sympathetic activity increases arrhythmia risk .This study also supports our study findings [39].

There is further evidence that salbutamol increases the episodes of ventricular tachycardia in patient with heart failure[40].Apart from the beneficial effects, nebulised salbutamol shows electrocardiographic changes such as flattening of T wave, depression of ST segment, or prolongation of QT interval , all dependent on the doses administered[41,42]

5. Conclusion

The present study found that salbutamol nebulisation was able to modulate the cardiac electrophysiological properties by altering the heart rate and PR interval. Further, those effects were the results of β2-adrenergic stimulation due to arrhythmias. Since salbutamol nebulization provides effective bronchodilatation, it is warranted in the treatment of acute attacks characterised by expiratory obstruction in infants and young children. It is suggested that further studies are required to clarify to what extent the electrophysiologic effects of salbutamol

contribute to the generation of spontaneous arrhythmias before extrapolating our findings to all human subjects.

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Conflict of Interest
The authors declare no conflict of interest.

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