The acute effects of inhaled salbutamol on the beat-to-beat variability of heart rate and blood pressure assessed by spectral analysis

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Aims We wanted to study the effects of a 600 µg inhaled salbutamol dose on the cardiovascular and respiratory autonomic nervous regulation in eight children suffering from bronchial asthma.

Methods In this randomized, double-blind, placebo-controlled, crossover study we continuously measured electrocardiogram, finger systolic arterial pressure (SAP) and flow-volume spirometry at baseline as well as 20 min and 2 h after the drug inhalation. The R–R interval (the time between successive heart beats) and SAP variabilities were assessed by using spectral analysis. Baroreflex sensitivity was assessed by using cross-spectral analysis.

Results Salbutamol significantly decreased the total and low frequency (LF) variability of R–R intervals as well as the high frequency (HF) variability of R–R intervals and of SAP. Salbutamol significantly increased the LF/HF ratio of R–R intervals and of SAP, minute ventilation, heart rate and forced pulmonary function in comparison with placebo. The weight of the subjects significantly correlated positively with baroreflex sensitivity and negatively with heart rate after the salbutamol inhalation.

Conclusions We conclude that the acute salbutamol inhalation decreases cardiovascular vagal nervous responsiveness, increases sympathetic dominance in the cardiovascular autonomic balance, and has a tendency to decrease baroreflex sensitivity in addition to improved pulmonary function.

Keywords: salbutamol, autonomic nervous system, heart rate variability, blood pressure variability, bronchial asthma

Introduction

Salbutamol, a selective β_2 -adrenoceptor agonist is used widely as a bronchodilator in the treatment of asthma and other reversible obstructive airway diseases. The adverse effects, which are quite rare after an administration by inhalation, are primarily due to the activated cardiovascular, neuronal and metabolic β -adrenoceptors caused by the drug absorption into the systemic circulation [1]. Thus, the principal adverse effects include tachycardia, palpitation, tremor, peripheral vasodilatation, hyperactivity and various metabolic effects. The association between the use of β_2 -adrenoceptor agonists and the increased risk of fatal or near fatal asthma is controversial [2, 3]. All these findings suggest that β_2 -adrenoceptor agonists may markedly interfere with cardiovascular and respiratory autonomic nervous regulation. The effects of stable bronchial asthma on cardiovascular autonomic regulation is negligible in children [4].

To our knowledge there are no reports published about the acute effects of β_2 -adrenoceptor agonist medication on the beat-to-beat variability of R–R intervals, oscillations of blood pressure or baroreflex sensitivity. These measures have been proven to be valuable in the studies how various neurological, respiratory and cardiovascular diseases, as well

as drug treatment affect the sympathetic and parasympathetic control of cardiorespiratory organ functions [4–11]. Therefore, we investigated how the acute administration of salbutamol affects the cardiorespiratory autonomic regulation of prepubertal children suffering from bronchial asthma.

Methods

Study subjects

Eight children with diagnosed bronchial asthma [five males and three females, mean age (s.d.) 10.5 (0.8) years, height 143 (8) cm, weight 39 (9) kg] participated in the study after a written informed consent was obtained from their parents. The similar demography diminishes the physiological variation caused e.g. by age [12–14] or obesity [13]. Sex has been reported to be unimportant in this context [14]. Before commencing the study each subject was physically examined. Children with diabetes mellitus, cardiovascular, gastrointestinal, urinary tract, central or peripheral nervous system disease were excluded from the study.

The children were recruited from the paediatric asthma register of Turku University Hospital. Asthma was diagnosed on the basis of a clinical history and verified intermittent, reversible airway obstruction. Pulmonary function (mini-Wright peak flow meter, Clement Clarke International Ltd,

England), symptoms and medication were monitored daily for a 1-week period prior to the tests. Only children with stable asthma [the peak expiratory flow variability ratio, (evening value–morning value)/evening value $\times 100\%$, was $<20\%$ during the observation period] were included in the study to avoid confusion produced by acute phase of the disease [11]. In addition, the subjects had not taken any β_2 -adrenoceptor agonists regularly for 4 weeks, and the children were without any sympathomimetic medication for 4 days prior to the tests. Five children regularly received inhaled corticosteroids and two inhaled disodium cromoglycate. None used oral β_2 -adrenoceptor agonists or theophylline. There was no tea, cola-drink or chocolate intake or heavy physical exercise 24 h prior to the study or heavy meal within 2 h and no coffee intake at all.

Study design

The study protocol was approved by the ethics committee of the Turku University Hospital. The study followed a randomized, double-blind, placebo-controlled crossover design. The subjects visited the laboratory three times: an introductory visit to familiarize the volunteer with the test procedure, and two test visits with 1-week intervals. The studies were done between 16.00h and 21.00h to avoid circadian variation of measured parameters [15].

Study drug

A 600 μg inhaled salbutamol dose (salbutamol aerosol, Salbuvent[®], Leiras, Finland) or a placebo dose (placebo aerosol, Leiras, Finland) was used in the study. The 600 μg dose was given by administering a 200 μg dose three times with 5 min intervals and utilising a spacer device (volume 270 ml, Rondo[®], Leiras, Finland) [16]. The subjects inhaled the drug slowly after full expiration and then hold breath for 10 s [17]. The mouth was rinsed immediately after the inhalation to minimize the proportion of a swallowed drug dose [18].

Methods

We measured forced pulmonary function as well as continuous signals of electrocardiogram, finger systolic arterial pressure and flow-volume spirometry before as well as 20 min and 2 h after the study drug inhalation. Sample size, drug dose and observation time were based on the pilot study with overnight Holter monitoring ($n=3$). In the present study subject rested on a bed in a supine position for 15 min to stabilize haemodynamics before the autonomic nervous system function tests. The tests were performed in the following order: 1. A 5 min recording at supine rest during spontaneous breathing. 2. One minute deep breathing test at supine rest in which subject breathed six consecutive deep breathing cycles of 10 s duration (5 s inspiration and 5 s expiration). 3. A 5 min study at supine rest was repeated using a controlled breathing rate (>0.20 Hz in all the subjects). This was defined on the basis of the average breathing frequency of the first study and paced using a sound signal given by a microcomputer sound generator. The fixed respiratory rate was kept constant in all the

following measurements at both cardiopulmonary test visits. 4. A 5 min study in upright position during fixed respiratory rate was done after standing up and stabilization of haemodynamics.

A continuous precordial three channel electrocardiogram was obtained via a cardioscope (Olli Monitor 432, Kone Instrument Division, Finland). A continuous noninvasive arterial blood pressure signal was recorded from the left middle finger kept at heart level using an Ohmeda 2300 BP Monitor (Ohmeda, Inc., U.S.A.). A flow-volume spirometer signal (M901, Medikro Oy, Finland) was recorded to calculate pulmonary air flow and volume changes. The analogue outputs of the monitors were connected to an analogue interface (M9401 Transducer Interface, Medikro Oy, Finland) of an IBM PC/AT compatible microcomputer equipped with an extended cardiovascular autonomic function test software package (Cafts, Medikro Oy, Finland) developed for computing heart rate, blood pressure, air flow and air volume variabilities. The signals were analogue-to-digital converted with a temporal resolution of 200 Hz. The software package utilizes a modified algorithm for QRS detection followed by interpolation of R peaks by second order polynomial fitting [19]. The R–R intervals were detected with a temporal resolution of 2 ms and then systolic, mean, diastolic arterial and pulse pressure were estimated for each R–R interval. Continuous signals of electrocardiogram, blood pressure and respiration were synchronized for time domain (Figure. 1) and spectral analysis. Blood pressure at the level of brachial artery was measured before each cardiovascular test (Sphygmomanometer/printer BP-203 M II, Instrumentarium, Finland).

Analysis

R–R interval and finger systolic arterial pressure variability as well as tidal volume and minute ventilation were computed from user-defined stationary data. Samples of 200 R–R intervals were selected because of the requirement of stationary signals and because some children had difficulties to stay still for a long time. The time series of R–R intervals and SAP and air flow signal were subject to spectral analysis of signal variability. Fast Fourier transformation was used for the spectral analysis. Total variabilities for the R–R interval vector and SAP signal were generated after linear detrending of the signals and the respective variability spectra were integrated over frequency in three frequency bands (very low frequency band <0.07 Hz, low frequency (LF) band from 0.07 Hz to 0.15 Hz and high frequency (HF) band from 0.15 Hz to 0.50 Hz). Because the selected timeseries consisted 200 R–R intervals, very low frequency oscillations (<0.07 Hz) could not be properly analysed and were therefore excluded. Sympathovagal balance was assessed by LF/HF ratio for the R–R interval and systolic arterial pressure (SAP) spectra. Baroreflex sensitivity was assessed utilising fast Fourier transformation-based cross-spectral analysis. The parameter was defined as the square root of the ratio the total variability of R–R intervals/the total variability of SAP. The frequency bands chosen were those in which SAP changes occur prior to R–R interval changes with a coherence coefficient >0.5 [20]. During the deep

Figure 1 R-R interval, finger systolic arterial pressure (SAP), respiratory flow and tidal volume variabilities before and 20 min after 600 μ g salbutamol inhalation in supine rest in a 10 year-old asthmatic girl. Note particularly markedly decreased R-R interval variability, slightly decreased SAP variability, increased respiratory flow rates and increased average tidal volume after the salbutamol inhalation.

breathing test the minima and maxima of the R-R intervals were detected and the respective expiratory/inspiratory ratios were computed. The maximal tidal volumes of the corresponding deep breathing cycles were also computed.

The normal distribution of the variables was confirmed using Shapiro-Wilks' W test and homogeneity of variances using Levene's test. The differences between placebo and salbutamol treatments, carry-over effects, and period effects

were analysed by *t*-test for independent samples [21] and the correlations were calculated with Pearson product-moment correlation (Statistica for Windows, release 4.5, StatSoft Inc., USA). The variabilities were transformed to ten-base logarithmic values to normalize data distribution. Statistical significance was established at the level of $P < 0.05$.

Results

Heart rate and heart rate variability

The salbutamol inhalation increased heart rate from 72 beats min^{-1} to 90 beats min^{-1} [95% confidence interval (95% CI) for mean treatment differences, salbutamol *vs* placebo, 12 to 24] in supine position and from 91 beats min^{-1} to 101 beats min^{-1} (7 to 13) in standing position when compared with placebo treatment (salbutamol *vs* placebo, $P < 0.001$ for both, Table 1). The weight of the children correlated negatively with heart rate in upright position 20 min after the salbutamol inhalation ($r = -0.84$, $P < 0.01$) and also at supine rest 2 h after the salbutamol inhalation ($r = -0.73$, $P < 0.05$).

The total variability of R-R intervals decreased from 4.02 ms^2 to 3.51 ms^2 (95% CI, -0.96 to -0.04) and the HF variability of R-R intervals from 3.87 ms^2 to 3.34 ms^2 (-0.99 to -0.07) after salbutamol during fixed respiratory rate at supine rest (salbutamol *vs* placebo, $P < 0.05$ for both, Figure 2). In the upright position the drug inhalation decreased the total variability of R-R intervals from 3.49 ms^2 to 3.29 ms^2 (-0.30 to -0.10 , $P < 0.001$) and the LF variability of R-R intervals from 2.77 ms^2 to 2.63 ms^2 (-0.27 to -0.01 , $P < 0.05$) 20 min after the inhalation

(Table 1). Salbutamol increased the LF/HF ratio of R-R intervals from 0.74 ms^2 to 0.83 ms^2 (0.04 to 0.14) during fixed respiratory rate at supine rest ($P < 0.05$, Figure 2).

Blood pressure and blood pressure variability

Blood pressure at the level of brachial artery level did not change significantly (Table 2). However, the HF variability of SAP decreased from 2.32 mmHg^2 to 2.03 mmHg^2 (-0.51 to -0.07) and the LF/HF ratio of SAP increased from 0.80 mmHg^2 to 0.93 mmHg^2 (0.02 to 0.24) after salbutamol inhalation during fixed respiratory rate at supine rest ($P < 0.05$ for both, Table 2).

Baroreflex sensitivity

The baroreflex sensitivity had tendency to decrease after salbutamol in upright position (placebo *vs* salbutamol, 20 min measurements $P = 0.08$ and 2 h measurements $P = 0.09$, Table 3). However, it was dependent on the weight of the children 20 min after the salbutamol inhalation in upright position ($r = 0.73$, $P < 0.05$).

Pulmonary function and ventilation

Forced expiratory flow in 1 s increased from 89% predicted to 103% (95% CI, 6 to 22, $P < 0.01$), peak expiratory flow from 82% to 92% (2 to 18, $P < 0.05$), mean expiratory flow when 50% of the forced expiratory volume remained in the lung from 70% to 97% (10 to 44, $P < 0.01$) and mean expiratory flow when 25% of the forced expiratory volume remained in the lung from 54% to 84% (23 to 37,

Table 1 The effect of inhaled salbutamol on heart rate and R-R interval variability.

	Drug	Baseline	20 min	2 h
<i>Supine position</i>				
Heart rate (beats min^{-1})	S	75 $\pm$ 3	90 $\pm$ 4***	85 $\pm$ 4**
	P	72 $\pm$ 4	72 $\pm$ 4	76 $\pm$ 4
Expiratory/inspiratory ratio	S	1.61 $\pm$ 0.06	1.46 $\pm$ 0.06	1.58 $\pm$ 0.07
	P	1.57 $\pm$ 0.06	1.56 $\pm$ 0.05	1.53 $\pm$ 0.08
<i>Upright position</i>				
Heart rate (beats min^{-1})	S	93 $\pm$ 4	102 $\pm$ 4**	101 $\pm$ 4***
	P	92 $\pm$ 5	90 $\pm$ 4	91 $\pm$ 4
Total variability (ms^2)	S	3.29 $\pm$ 0.09	3.29 $\pm$ 0.12***	3.30 $\pm$ 0.16
	P	3.54 $\pm$ 0.18	3.49 $\pm$ 0.13	3.46 $\pm$ 0.15
LF variability (ms^2)	S	2.54 $\pm$ 0.09	2.63 $\pm$ 0.10*	2.61 $\pm$ 0.17
	P	2.78 $\pm$ 0.16	2.77 $\pm$ 0.11	2.74 $\pm$ 0.14
HF variability (ms^2)	S	2.89 $\pm$ 0.13	2.99 $\pm$ 0.14	2.95 $\pm$ 0.17
	P	3.15 $\pm$ 0.22	3.03 $\pm$ 0.22	3.05 $\pm$ 0.19
LF/HF ratio	S	0.89 $\pm$ 0.04	0.89 $\pm$ 0.03	0.89 $\pm$ 0.04
	P	0.89 $\pm$ 0.05	0.94 $\pm$ 0.05	0.91 $\pm$ 0.03

Data are expressed as mean $\pm$ s.e. mean ($n = 8$). Variabilities are expressed as 10-base logarithm values. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ between salbutamol and placebo. P = placebo, S = salbutamol, LF = low frequency and HF = high frequency.

Figure 2 The total (a), LF (b) and HF variability (c) as well as the LF/HF ratio of R-R intervals (d) in supine position at baseline as well as 20 min and 2 h after 600 μg salbutamol (▲) and placebo (■) inhalation. Data are expressed as mean (s.e. mean). Variabilities are expressed as 10-base logarithmic values. * $P < 0.05$ salbutamol vs placebo ($n = 8$).

$P < 0.0001$) after the salbutamol inhalation (Table 4). The average maximal tidal volume in the deep breathing test also increased from 70% of vital capacity to 83% (5 to 21) after the drug administration ($P < 0.01$). Minute ventilation also increased from 10.1 l min^{-1} to 12.8 l min^{-1} (0 to 5) after salbutamol in the upright position during fixed respiratory rate ($P < 0.05$). The other adverse effects of the salbutamol treatment in our children were tremor, palpitation, cough, headache and peripheral vasodilatation, all of which were considered mild.

Discussion

Our study demonstrated that a fairly large therapeutic single dose (600 μg) of inhaled salbutamol has profound effects on cardiovascular autonomic regulation in prepubertal children suffering from bronchial asthma. The analysis of heart rate and blood pressure oscillations showed that the treatment

markedly decreased the total and LF variability of R-R intervals as well as the HF variability of R-R intervals and of SAP. The drug increased the LF/HF ratio of R-R intervals and of SAP. The weight of the subjects correlated positively with baroreflex sensitivity and negatively with heart rate after the salbutamol inhalation. The effects on pulmonary function and minute ventilation are wellknown [1, 22–24].

It was interesting to note that the acute salbutamol inhalation markedly decreased the total, and particularly the HF variability of R-R intervals. This attenuation of respiratory sinus arrhythmia evidences a vagal withdrawal [6, 7]. The rhythmical changes in the vagal activity have been suggested to be caused by the net effect of the central integration of the afferent inflow from systemic arterial baroreceptors, low-pressure receptors in the heart and possibly the stretch receptors of the lung [25]. No dose-response characteristics of the variability indices are yet

Table 2 The effect of inhaled salbutamol on the blood pressure at the level of brachial artery and on the finger systolic arterial pressure variability.

	Drug	Baseline	20 min	2 h
<i>Supine position</i>				
Systolic blood pressure (mmHg)	S	111 ± 3	121 ± 4	119 ± 3
	P	111 ± 4	115 ± 4	116 ± 4
Diastolic blood pressure (mmHg)	S	56 ± 2	60 ± 2	61 ± 2
	P	59 ± 1	60 ± 2	62 ± 1
LF variability (mmHg ²)	S	1.79 (0.12)	1.90 (0.15)	1.96 (0.11)
	P	1.75 (0.15)	1.87 (0.15)	1.76 (0.16)
HF variability (mmHg ²)	S	2.28 (0.10)	2.03 (0.07)*	2.22 (0.10)
	P	2.33 (0.12)	2.32 (0.11)	2.20 (0.11)
LF/HF ratio	S	0.79 (0.06)	0.93 (0.03)*	0.88 (0.05)
	P	0.75 (0.04)	0.80 (0.03)	0.80 (0.06)
<i>Upright position</i>				
Systolic blood pressure (mmHg)	S	117 ± 3	123 ± 3	125 ± 3
	P	119 ± 2	126 ± 5	127 ± 5
Diastolic blood pressure (mmHg)	S	63 ± 3	62 ± 2	66 ± 2
	P	61 ± 3	64 ± 3	66 ± 1
LF variability (mmHg ²)	S	2.18 ± 0.13	2.16 ± 0.06	2.25 ± 0.10
	P	2.33 ± 0.10	2.24 ± 0.11	2.11 ± 0.07
HF variability (mmHg ²)	S	2.52 ± 0.08	2.61 ± 0.05	2.62 ± 0.07
	P	2.63 ± 0.09	2.60 ± 0.08	2.49 ± 0.07
LF/HF ratio	S	0.86 ± 0.04	0.83 ± 0.02	0.86 ± 0.05
	P	0.89 ± 0.03	0.86 ± 0.03	0.85 ± 0.03

Data are expressed as mean ± s.e. mean ($n=8$). Variabilities are expressed as 10-base logarithm values. * $P<0.05$ between salbutamol and placebo. P=placebo, S=salbutamol, LF=low frequency and HF=high frequency.

Table 3 The effect of inhaled salbutamol on baroreflex sensitivity.

	Drug	Baseline	20 min	2 h
Baroreflex sensitivity, supine (mmHg/ms)	S	19.0 ± 2.7	16.6 ± 1.3	16.2 ± 2.3
	P	26.6 ± 6.2	27.2 ± 5.2	20.7 ± 3.8
Baroreflex sensitivity, upright (mmHg/ms)	S	7.7 ± 1.2	7.9 ± 1.3	7.5 ± 1.6
	P	10.1 ± 3.0	9.1 ± 2.1	9.4 ± 1.7

Data are expressed as mean ± s.e. mean ($n=8$). P=placebo, S=salbutamol.

available. However, we considered the effect marked because it was also evident in the upright position which is physiologically characterized by a lower vagal and higher sympathetic activity. The reduction in the HF variability of R–R intervals was likely to cause the simultaneous diminution in the HF variability of SAP [6]. The decrease in the HF variability of SAP in our study cannot be produced by a decrease in ventilatory activity [26], since both tidal volume and minute ventilation increased after the salbutamol inhalation. The decreased cardiovagal activity also primarily increased the sympathetic dominance in the cardiovascular autonomic balance analysed by the LF/HF ratios of R–R intervals and of SAP. The lack of differences

in the deep breathing test, also a test of vagal control, can be in part explained by the increased average maximal tidal volume after the salbutamol inhalation. Increased tidal volume is known to increase heart rate variability [27] and therefore counteracts the heart rate variability reducing influence of the β_2 -adrenoceptor agonist. The major salbutamol effects on the beat-to-beat cardiovascular regulation were shortlasting, and they had almost disappeared two h after the drug inhalation. However, the drug effects on the sympathovagal balance lasted longer: a significant effect could still be identified at the end of the study 2 h after the drug inhalation.

The arterial baroreflex is important in readjusting acute

Table 4 The effect of inhaled salbutamol on pulmonary function.

	Drug	Baseline	20 min	2 h
Forced expiratory flow in 1 s (% predicted)	S	91 $\pm$ 4	103 $\pm$ 5**	104 $\pm$ 7*
	P	89 $\pm$ 2	89 $\pm$ 3	91 $\pm$ 3
Peak expiratory flow (% predicted)	S	83 $\pm$ 4	92 $\pm$ 6*	95 $\pm$ 7*
	P	84 $\pm$ 4	82 $\pm$ 4	83 $\pm$ 4
Mean expiratory flow 50 (% predicted)	S	73 $\pm$ 6	97 $\pm$ 9**	97 $\pm$ 12**
	P	70 $\pm$ 4	70 $\pm$ 6	69 $\pm$ 4
Mean expiratory flow 25 (% predicted)	S	54 $\pm$ 8	76 $\pm$ 12*	84 $\pm$ 7****
	P	53 $\pm$ 5	53 $\pm$ 6	54 $\pm$ 6
Vital capacity (% predicted)	S	103 $\pm$ 5	107 $\pm$ 7	110 $\pm$ 9
	P	103 $\pm$ 4	101 $\pm$ 4	99 $\pm$ 4
Maximal tidal volume (% vital capacity)	S	67 $\pm$ 6	71 $\pm$ 5	83 $\pm$ 3*
	P	64 $\pm$ 5	72 $\pm$ 4	70 $\pm$ 4
Minute ventilation, supine (l min ⁻¹)	S	8.2 $\pm$ 0.7	9.3 $\pm$ 0.8	9.8 $\pm$ 1.0
	P	8.7 $\pm$ 0.9	9.2 $\pm$ 1.0	8.8 $\pm$ 1.0
Minute ventilation, upright (l min ⁻¹)	S	9.2 $\pm$ 0.7	10.6 $\pm$ 1.2	12.8 $\pm$ 2.0*
	P	10.7 $\pm$ 1.6	10.4 $\pm$ 1.5	10.1 $\pm$ 1.1

Data are expressed as mean $\pm$ s.e. mean ($n=8$) * $P<0.05$, ** $P<0.01$ and **** $P<0.0001$ between salbutamol and placebo.

P=placebo, S=salbutamol.

increases in blood pressure to its original value. This is accomplished by vagal activation and adrenergic inhibition which decrease heart rate and total peripheral vascular resistance [9]. When blood pressure is below a targeted level baroreflex sensitivity attenuates preventing further decrease. It was novel to note that the salbutamol dose decreased the LF variability of R-R intervals, which is related to arterial baroreflex function [7, 9]. The non-significant decrease in baroreflex sensitivity estimated by the cross-spectral analysis may be due to the small number of subjects. However, the preservation of baroreflex function correlated positively with the weight of the test subjects suggesting that attenuation of baroreflex sensitivity may be related to the plasma salbutamol concentrations as the dose was the same. The adverse cardiovascular side-effects depending closely on the drug dosage were also supported by the negative correlation between the heart rate and the weight of the subjects after the salbutamol inhalation. The attenuated baroreflex sensitivity was not caused by decreased blood pressure because no such decrease was found in our study.

The cardiovascular effects were somewhat expected because inhaled salbutamol is largely absorbed into systemic circulation in children [28]. The effects are produced directly by the binding of salbutamol on β -adrenoceptors on and remote from adrenergic nerve terminals but also indirectly by enhancing noradrenaline release after activation of presynaptic β -receptors [29, 30]. In addition, noradrenaline has been suggested to inhibit acetylcholine release from postganglionic cholinergic nerve terminals in canine tracheal smooth muscle [31]. This is probably mediated by pre-synaptic β -receptors and may in part explain the decreased cardiovagal effects. Approximately 5% of the plasma

concentration of salbutamol has also been shown to penetrate the blood-brain barrier in rats suggesting that the stimulation of central β -adrenoceptors may account for some of the drug effects [32].

In conclusion, the acute salbutamol inhalation markedly decreases cardiovagal nervous responsiveness, increases sympathetic dominance in the cardiovascular autonomic balance, and has tendency to decrease baroreflex sensitivity. According to our experience at least some of the undesirable effects are likely to be dependent on the dose kg⁻¹. Further studies are needed to evaluate the effects of β_2 -adrenoceptor agonists on cardiovascular autonomic regulation in adults, because the changes demonstrated in this study are similar to the risks factors known to predispose to malignant ventricular tachyarrhythmias in adults with heart diseases [33, 34].

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References

- 1 Price AH & Clissold SP. Salbutamol in the 1980s. A reappraisal of its clinical efficacy. *Drugs* 1989; **38**: 77–122.
- 2 Spitzer WO, Suissa S, Ernst P, *et al.* The use of beta₂-adrenoceptor agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; **326**: 501–506.
- 3 Mullen ML, Mullen B, Carey M. The association between beta-agonist use and death from asthma. *JAMA* 1993; **270**: 1842–1845.

- 4 Jartti TT, Tahvanainen KUO, Kaila TJ, *et al.* Cardiovascular autonomic regulation in asthmatic children evidenced by spectral analysis of heart rate and blood pressure variability. *Scand J Clin Lab Invest* 1996; **56**: 545–554.
- 5 Tarlo PA, Välimäki I, Rautaharju PM. Quantitative computer analysis of cardiac and respiratory activity in newborn infants. *J Appl Physiol* 1971; **31**: 70–75.
- 6 Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol* 1985; **249**: H867–H875.
- 7 Pomeranz B, Macaulay RJB, Caudill MA, *et al.* Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; **248**: H151–H153.
- 8 Hirvonen HE, Salmi TT, Heinonen E, Antila KJ, Välimäki IA. Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy. *Cancer* 1989; **64**: 801–805.
- 9 Madwed JB, Albrecht P, Mark RG, Cohen RJ. Low-frequency oscillations in arterial pressure and heart rate: a simple computer model. *Am J Physiol* 1989; **256**: H1573–H1579.
- 10 Siimes ASI, Välimäki IAT, Antila KJ, *et al.* Regulation of heart rate variation by the autonomic nervous system in neonatal lambs. *Pediatr Res* 1990; **27**: 383–391.
- 11 Garrard CS, Seidler A, McKibben A, McAlpine LE, Gordon D. Spectral analysis of heart rate variability in bronchial asthma. *Clin Auton Res* 1992; **2**: 105–111.
- 12 Shannon DC, Carley DW, Benson H. Aging of modulation of heart rate. *Am J Physiol* 1987; **253**: H874–H877.
- 13 Hellman JB, Stacy RW. Variation of respiratory sinus arrhythmia with age. *J Appl Physiol* 1976; **41**: 734–738.
- 14 Piha SJ. Cardiovascular autonomic reflex tests: normal responses and age-related reference values. *Clin Physiol* 1991; **11**: 277–290.
- 15 Hartikainen J, Tarkkainen I, Tahvanainen K, Mäntysaari M, Länsimies E, Pyörälä K. Circadian variation of cardiac autonomic regulation during 24-h bed rest. *Clin Physiol* 1993; **13**: 185–196.
- 16 Stenius-Aarniala, Kiviranta K, Poppius H. Evaluation of a new spacer device for drug inhalation. *Eur J Clin Pharmacol* 1993; **44**: 153–155.
- 17 Editorial. The proper use of metered dose inhalers. *Chest* 1984; **86**: 342–343.
- 18 Lin C, Magat J, Calesnick B, Symchowicz S. Absorption, excretion and urinary metabolic pattern of ³H-albuterol aerosol in man. *Xenobiotica* 1972; **2**: 507–515.
- 19 Tahvanainen K, Länsimies E, Tikkanen P, *et al.* Microcomputer-based monitoring of cardiovascular functions in simulated microgravity. *Adv Space Res* 1992; **12**: 1227–1236.
- 20 Robbe HWJ, Mulder LJM, Ruddel H, Langewitz WA, Veldman JBP, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension* 1987; **10**: 538–543.
- 21 Jones B, Kenward MG. The 2 × 2 cross-over trial, the analysis using *t*-tests. In *Design and analysis of cross-over trials*. Ed Jones B & Kenward MG, London: Chapman and Hall, 1989: 22–28.
- 22 Leitch AG, Clancy LJ, Costello JF, Flenley DC. The effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men. *Br Med J* 1976; **1**: 365–367.
- 23 Newth CJL, Amsler B, Anderson GP, Morley J. The ventilatory and oxygen costs in the anesthetized rhesus monkey of inhaling drugs used in the therapy and diagnosis of asthma. *Am Rev Respir Dis* 1991; **143**: 766–771.
- 24 Holmgren D, Sixt R. Effects of salbutamol inhalations on transcutaneous blood gases in children during the acute asthmatic attack: from acute deterioration to recovery. *Acta Paediatr* 1994; **83**: 515–519.
- 25 Melcher A. Respiratory sinus arrhythmia in man. A study in heart rate regulating mechanisms. *Acta Physiol Scand* 1976; **Suppl 435**: 1–31.
- 26 Manoach M, Gitter S. On the origin of respiratory waves in circulation I: the role of the chest pump. *Pflug Arch* 1971; **325**: 40–49.
- 27 Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R–R interval power spectra is largely ignored. *J Appl Physiol* 1993; **75**: 2310–2317.
- 28 Penna AC, Dawson KP, Manglick P, Tam J. Systemic absorption of salbutamol following nebulizer delivery in acute asthma. *Acta Paediatr* 1993; **82**: 963–966.
- 29 Scheinin M, Koulou M, Laurikainen E, Allonen H. Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: A Placebo-controlled dose-response study in healthy volunteers. *Br J Clin Pharmacol* 1987; **24**: 645–653.
- 30 Langer SZ. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* 1980; **32**: 337–362.
- 31 Vermiere PA, Vanhoutte PM. Inhibitory effects of catecholamines in isolated canine bronchial smooth muscle. *J Appl Physiol* 1979; **46**: 787–791.
- 32 Caccia S, Fong MH. Kinetics and distribution of the β_2 -adrenergic agonist salbutamol in rat brain. *J Pharm Pharmacol* 1983; **36**: 200–202.
- 33 van Ravenswaaij-Arts CMA, Kollée LAA, Hopman JCW, Stoeltinga GBA, van Geijn HP. Heart rate variability. *Ann Intern Med* 1993; **118**: 436–447.
- 34 Osterziel KJ, Hänlein D, Willenbrock R, Eichhorn C, Luft F, Dietz R. Baroreflex sensitivity and cardiovascular mortality in patients with mild to moderate heart failure. *Br Heart J* 1995; **73**: 517–522.

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