
The effects of inhaled formoterol on the autonomic nervous system in adolescents with asthma

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Background: The safety of long-acting beta-2-adrenergic agonists is increasingly questioned by physicians. Although formoterol is frequently used in childhood, its effects on the autonomic cardiovascular system have not been studied.

Objective: To investigate the effects of inhaled formoterol on autonomic nervous system using heart rate variability in adolescents with persistent asthma.

Methods: Electrocardiography of 20 asthmatic adolescents (12–20 years) was monitored for 5 specific days. The first day served as basal measurement, and the 2nd and 3rd days reflected the effects of a single and 2 doses of formoterol, respectively. From days 4 to 29, patients received regular treatment with formoterol/budesonide and were monitored on days 30 and 31 to evaluate the development of cardiac and respiratory tolerance after single-dose and 2 doses of formoterol, respectively. Electrocardiographs were analyzed for heart rate, heart rate variability (both time and frequency domain parameters), and spirometry tests were performed.

Results: Inhalation of single-dose formoterol increased heart rate and decreased heart rate variability parameters (ratio of the normal-to-normal [NN] intervals changing in excess of 50 ms to total of NN intervals [pNN50], total power [TP][ms], TP[ln]) compared with the corresponding baseline values during the first 12 hours of the day. The heart rate variability parameters (pNN50, TP[ms], TP[ln], root mean square of differences between adjacent NN intervals) during the first 12 hours were increased on the 30th day compared with the 2nd day and decreased on the 31st day compared with the 30th day.

Conclusion: Single-dose formoterol inhalation decreases cardiovagal responsiveness and increases the sympathetic tone in cardiac autonomous control, and regular use of formoterol causes development of tolerance to these effects. However, additive doses of formoterol cause loss of this tolerance.

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INTRODUCTION

Sympathetic and parasympathetic regulation of heart rate (HR) in patients with asthma differs from that in normal individuals, even in normal conditions in which the patient is free of an asthma attack.¹ The parasympathetic system dominates, and the heart rate variability (HRV) is significantly lower in asthmatic patients compared with healthy control subjects.^{1–3} Investigation of the autonomic nervous system in asthmatic patients is important, because the cholinergic nerves are the most important part of the bronchoconstrictory pathway.^{4–7}

Heart rate variability (HRV) is a noninvasive diagnostic method used for the assessment of autonomic cardiovascular function. Indexes of the HRV reflect the cardiac autonomic

tone.^{8,9} Among these parameters, the standard deviation of differences between adjacent normal-to-normal (NN) intervals (SDSD), root mean square of differences between adjacent NN intervals (RMSSD), ratio of the number of NN intervals changing in excess of 50 milliseconds to total NN intervals (pNN50), and high frequency (HF) mainly reflect parasympathetic activity, whereas low frequency (LF) reflects both sympathetic and parasympathetic activity, and LF/HF reflects the autonomic balance. Total power (TP), which is the variance of total NN intervals (in millisecond [ms] and normal logarithm [ln]) and standard deviation of all NN intervals (SDNN) reflect the whole variability.

Change in the HRV pattern provides an early and sensitive indicator of compromised health.^{9,10} A high variability in HR is a sign of good adaptability reflecting well-functioning autonomic control mechanisms. Conversely, lower variability is often an indicator of abnormal and insufficient adaptability of the autonomous nervous system.^{9,10} Decreased HRV has emerged as an indicator of risk related to adverse events in normal subjects¹⁰ and patients with a wide range of diseases.^{11–16}

Long-acting β_2 -adrenergic agonists (LABAs) are widely used as an add-on therapy to inhaled corticosteroids (ICS) for

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patients with moderate to severe asthma. Many studies have demonstrated the benefits of adding a LABA to the treatment in adults and children with uncontrolled asthma, including improvement in lung function, protection against asthma exacerbations, and relief of asthma symptoms.^{17,18} However, the introduction of the LABAs salmeterol and formoterol prompted questions regarding the possibility of safety issues. The adverse effects are rare and include tachycardia, palpitation, tremor, peripheral vasodilatation, hyperactivity, and some metabolic effects. The association between the use of LABAs and the increased risk of acute exacerbations and cardiac side effects in patients with asthma is controversial.^{18–24} Although the use of LABAs in patients with asthma may be a potential cause of cardiac side effects, by no means is this thought to be a likely trigger. The short- and long-term effects of salbutamol and salmeterol on HRV in children with asthma were studied previously.^{25–28} Initiation of β_2 -adrenoceptor agonist treatment increases HR and decreases HRV and potassium concentrations, whereas continued use may increase the risk of adverse cardiovascular events.²⁹ β_2 -Adrenergic agonists increase sympathetic cardiovascular activity in children with asthma.^{25–27} In previous studies, acute salbutamol inhalation decreased sympathetic modulation in the cardiovascular autonomic balance,^{26,28,30} and a 2-week salbutamol treatment increased baseline LF variability and LF/HF ratio when compared with the placebo.

To our knowledge, the long-term effects of formoterol on HRV have not been reported in adults or children. The aim of this study was to assess the long-term effects of formoterol on HRV in adolescents with asthma by using both frequency and time domain measures of HRV and to document whether tolerance to the effects of formoterol on cardiovascular responses develops.

METHODS

Patients

Twenty adolescents (mean age, 14.4 ± 0.5 ; range, 12–20 years) with a diagnosis of asthma who were followed in the Pediatric Allergy and Asthma Unit of Hacettepe University Faculty of Medicine were studied. Asthma was diagnosed according to the American Thoracic Society guidelines.³¹ The patients were evaluated for a period of 31 days. Holter monitoring and spirometry tests were performed on the 1st (Basal day [BD]), 2nd (Single-dose day [SDD]), 3rd (Additive-dose day [ADD]), 30th (Single-dose tolerance day [SDTD]) and 31st (Additive-dose tolerance day [ADTD]) days. All the adolescents had persistent asthma, and none of them had been receiving any drug, including asthma drugs such as oral steroids, long-acting beta-2 agonists, leukotriene receptor antagonists, theophylline, or cromolyn during the last month, but ICSs were permitted. Patients with diabetes mellitus, renal, cardiovascular, gastrointestinal, and central and peripheral nervous system disorders or any diseases that might have influenced autonomic function were excluded. All patients had physical examinations and were questioned about their

medical history as pertains to any cardiovascular disease or medication. Blood pressure, blood tests including hemogram and biochemical analysis, thyroid function tests, urinalysis, electrocardiographic analysis, and echocardiography evaluation were all within normal limits. Consumption of caffeine-containing foods such as tea, cola, or chocolate, heavy physical exercise, and short-acting beta-2 agonists were not permitted for 24 hours before the Holter monitoring. Characteristics of the study population are given in Table 1. Written informed consent was obtained from the parents of all patients and from the adolescents. The study protocol was approved by the Ethics Committee of Hacettepe University (No: LUT 05/11-6, 27.01.2005).

Study Design

First, all patients were trained regarding the use of a Turbuhaler, and their skills were tested by a Turbuhaler usage trainer. The compliance of the patients to the therapy was tested with diaries, and the diaries were checked each week to determine whether the patients obeyed the drug intake directives. No problem with compliance occurred.

On the 1st day of the study, the patients performed a basal flow-volume spirometry test at 9 AM by a dry rolling spirom-

Table 1. Characteristics of the Study Population

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Sex (F/M)	9/11
Age (year) ^a	14.4 ± 0.5
Age range (year)	12–20
FEV1 (%) ^a	98.9 ± 3.9
FEV1 > 80%	17
Reversibility with formoterol (%) ^a	3.6 ± 0.7
IgE (IU/L) ^a	135.1 ± 38.3
Eosinophil (%) ^a	3.8 ± 0.6
Eosinophil number ^a	290.0 ± 48.7
Atopy (n)	13
Asthma severity	
Mild persistent	19
Moderate persistent	1
Follow-up time (year) ^a	6.9 ± 1.0
No. of patients with emergency room admission within last year	4
No. of patients with hospitalization within last year	0
Controller medication	16
ICS ^b	
Budesonide	15
Fluticasone	1
OCS	0
LTRA	0
Combined ^c	0
Combined medication (Before last month)	11

Abbreviations: ICS, inhaled corticosteroids; OCS, oral corticosteroids; LTRA, leukotriene receptor antagonist.

^a Mean $\pm$ standard error of the mean.

^b Mean ICS dosage: 393.3 ± 37.1 μ g/day.

^c Inhaled corticosteroids + formoterol/salmeterol.

eter (2130 Spirometer; Sensor Medics Co, Yorba Linda, California) and then 24-hour Holter monitoring was done by ELATEC Holter system (Ela Med Inc, Arvada, Colorado) (basal HRV).

On the 2nd day, each patient was given a 4.5 µg formoterol Turbuhaler (Oxis Turbuhaler, Astra Zeneca; Luton, Bedfordshire, United Kingdom) at 9 AM and performed flow-volume spirometry just before and 15 minutes after the formoterol inhalation. Holter monitoring also started just before the drug intake and continued for 24 hours (single-dose HRV).

On the 3rd day of the study, patients were given 4.5 µg formoterol Turbuhaler at 9 AM and at 12 noon, and flow-volume spirometry was performed just before and 15 minutes after each formoterol inhalation. Twenty-four-hour Holter monitoring started before the first dose of the drug intake at 9 AM (additive-dose HRV).

Between days 4 and 29, patients regularly used combined 4.5 µg formoterol and 160 µg budesonide as a Turbuhaler treatment twice per day at 12-hour intervals (Symbicort TurbuhalerK) because of safety concerns. During this period, Holter monitoring was not done, and patients were told not to take the evening dose on the 29th day.

On the 30th day, patients had taken a single dose of 4.5 µg formoterol Turbuhaler at 9 AM, and flow-volume spirometry was performed just before and 15 minutes after the formoterol inhalation. Holter monitoring started before the drug intake and continued for 24 hours (single-dose tolerance HRV).

On the 31st day, patients had taken 4.5 µg formoterol Turbuhaler at 9 AM and at 12 noon, and flow-volume spirometry was performed just before and 15 minutes after each formoterol inhalation. Twenty-four-hour Holter monitoring started before the first dose of the drug intake at 9 AM (additive dose tolerance HRV) (study diagram, Fig 1).

We performed the 1st day measures to obtain the basal HRV and spirometry values. The aim of the 2nd day measurement was to show the effect of single-dose formoterol on forced expiratory volume in 1 second (FEV₁) and on HRV parameters. The aim of the 3rd day measurements was to determine any extra effect of an additive formoterol dose on HRV and FEV₁. We compared the 2nd day and 30th day measurements of HRV and FEV₁ and those of the 30th day and 31st day to see whether any tolerance effect of formoterol

(with single or add-on doses) occurred on bronchodilatory and cardiovascular responses after 4 weeks of treatment with formoterol.

Holter monitoring and HRV analysis

The ambulatory electrocardiograms (ECGs) were recorded by 3-channel analog recorders and analyzed using the ELATEC Holter system (Ela Med Inc, Arvada, CO) for 24 hours on the 1st, 2nd, 3rd, 30th, and 31st days of the study period as mentioned in the study protocol. All Holter recordings were obtained at rest, and the patients were not allowed to perform any extra work except for their routine daily performance. The recordings were analyzed with specialized computer software called ELATEC Holter software. All recordings were also visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artifact were automatically and manually excluded from the analysis. Both the time domain and frequency domain parameters of HRV were performed.

The mean HRs and corrected QT values also were evaluated for 12 daytime hours, 12 nighttime hours, and for 24 hours on the days in which the Holter monitoring was done.

In addition to mean HRs, LF/HF and RMSSD measurements were compared hourly for 12 daytime hours on the 1st, 2nd, 3rd, 30th, and 31st days of the study period to differentiate the hours primarily responsible for the differences obtained from the 12-hour daytime measurements.

Statistics

Normality tests of variables were assessed by 1-sample Kolmogorov-Smirnov test. Normally distributed variables were compared by Paired-Samples T test (t test in dependent groups), and non-normally distributed variables were compared by Wilcoxon test. Statistical significance was considered for *P* values below .05. All analyses were performed using the SPSS 11.5 software program (Chicago, Illinois).

RESULTS

In the spirometry tests, FEV₁ parameters were compared, and basal FEV₁ (% predicted ± standard error of the mean [SEM]) values were not different on BD and SDTD. The differences before and after the formoterol inhalation were found to be significant on the SDD and SDTD (96.2 ± 4.4 vs 99.8 ± 4.1 and 98.5 ± 4.2 vs 102.1 ± 3.78; *P* < .01), on the ADD (98.5 ± 4.0 vs 100.3 ± 3.8; *P* = .02), and on the ADTD (100.2 ± 3.8 vs 102.5 ± 3.5; *P* = .04) after the first doses, and also on the ADTD after the second dose of formoterol (102.1 ± 4.2 vs 104.7 ± 4.0; *P* < .01).

The 12-hour daytime analysis showed an increase in mean HR on the SDD compared with the BD (*P* = .03), and an increase was also found on the ADTD compared with the BD (*P* = .05). On the SDTD, the mean HR was lower than that of the SDD (*P* = .05). Mean HR comparisons revealed no statistical significance for the 12-hour nighttime and 24-hour Holter monitorings (Fig 2).

Changes in HRV parameters were seen in the 12-hour daytime analysis in both frequency domain and time domain

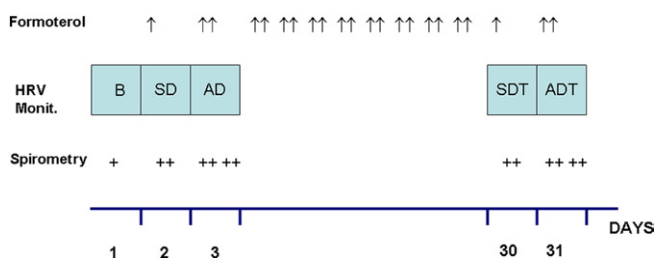


Figure 1. Flow chart of the study. B, basal; SD, single dose; AD, additive dose; SDD, single dose tolerance; ADT, additive dose tolerance.

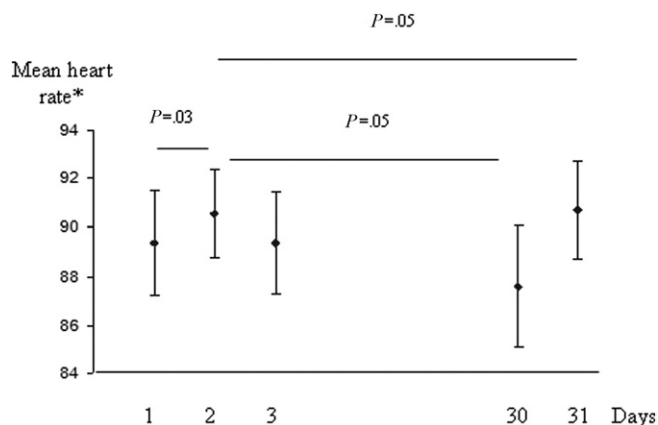


Figure 2. 12-Hour daytime mean heart rates for 31 days *($\pm$ standard error of the mean).

parameters (Table 2). The SDSD of HRV decreased significantly on the ADTD compared with the SDTD ($P = .02$). The SDNN showed a significant decrease on the ADTD compared with the SDTD ($P = .04$). The pNN50 was decreased on SDD compared with BD ($P = .03$) and on ADTD compared with SDTD ($P = .02$). Conversely, pNN50 increased on SDTD compared with the SDD ($P = .02$), and the analysis of the RMSSD showed a borderline increase on SDTD compared with the SDD ($P = .05$) (Fig 3).

Among the frequency domain parameters of HRV, a decrease in TP(ms) was seen on SDD compared with BD ($P = .03$), and an increase on SDTD compared with SDD ($P = .04$) were seen. A decrease was also found in TP(ln) values on SDD compared with BD ($P = .02$) and on ADTD compared with SDTD ($P = .05$). The TP(ln) increased on SDTD compared with SDD ($P = .05$). The LF measurements on SDTD were decreased compared with SDD ($P = .03$). No

change occurred in HF and LF/HF parameters throughout the study period (Fig 4).

None of the parameters used in HRV analysis revealed a statistically significant difference in either 12-hour nighttime or 24-hour Holter monitorings.

Mean QTc records after formoterol intake for 3 hours were compared, and SDTD mean QTc was found to be decreased when compared with SDD (0.17 ± 0.01 vs 0.20 ± 0.02 ; $P = .03$).

To evaluate the hours at which the formoterol effect starts and ends, we analyzed daytime measures hourly for HR, LF/HF ratio, and RMSSD. Mean LF/HF ($\pm$ SEM) increased in the 5th hour of the 2nd day and in the 6th hour of the 3rd day compared with the 1st day ($*P < .05$). Mean RMSSD ($\pm$ SEM) decreased in the 1st hour of the 2nd day and in the 5th, 6th, and 7th hours of the 3rd day compared with the 1st day; and in the 2nd and 3rd hours of the 31st day compared with the 30th day. The RMSSD increased in the 3rd hour of the 30th day compared with the 1st day and the 7th hour of the 30th day compared with the 2nd day ($*P < .05$).

DISCUSSION

In the current study, we showed the long-term effects of formoterol inhalation on respiratory function and on the cardiac autonomic system. One of the strong aspects of the study was the use of 24-hour Holter recordings to exclude the external effects; in addition, the use of both time domain and frequency domain parameters of HRV enabled the comparison of different parameters. Dose-response characteristics of formoterol were also studied by giving additive doses on the 3rd and 31st days. Formoterol improved respiratory function, and this effect on the bronchial tree persisted throughout the study period and was not lost. A single dose of formoterol inhalation increased mean HR and decreased HRV (pNN50, TP[ms], TP[ln]). However, tolerance occurred by the begin-

Table 2. HRV Parameters during the Study Period

Parameter	1 st day (Basal day)	2 nd day (Single dose)	P^*	3 rd day (Additive dose)	P^{**}	30 th day (Single dose tolerance)	P^{***}	31 st day (Additive dose tolerance)	P^{****}
SDSD	115.5 $\pm$ 5.4	115.5 $\pm$ 6.3	NS	118.7 $\pm$ 6.6	NS	121.1 $\pm$ 6.2	NS	113.4 $\pm$ 6.6	.016
SDNN	83.5 $\pm$ 6.0	86.4 $\pm$ 5.5	NS	89.8 $\pm$ 6.2	NS	91.3 $\pm$ 5.4	NS	84.8 $\pm$ 5.1	.037
pNN50	20.9 $\pm$ 2.5	18.2 $\pm$ 2.7	.028	18.9 $\pm$ 2.8	NS	20.9 $\pm$ 2.9	.017	16.7 $\pm$ 2.7	.020
RMSSD	54.3 $\pm$ 4.9	54.4 $\pm$ 6.5	NS	54.3 $\pm$ 6.2	NS	55.4 $\pm$ 5.4	.049	51.9 $\pm$ 6.6	NS
TP(ln)	8.57 $\pm$ 0.09	8.44 $\pm$ 0.11	.015	8.49 $\pm$ 0.11	NS	8.52 $\pm$ 0.11	.048	8.43 $\pm$ 0.13	.047
TP(ms)	5,746 $\pm$ 563	5,093 $\pm$ 552	.028	5,486 $\pm$ 613	NS	5,565 $\pm$ 580	.035	5321 $\pm$ 711	NS
LF	35.6 $\pm$ 1.8	38.4 $\pm$ 2.6	NS	35.4 $\pm$ 1.5	NS	35.3 $\pm$ 1.5	.032	35.7 $\pm$ 1.5	NS
HF	20.8 $\pm$ 1.8	20.3 $\pm$ 1.9	NS	20.4 $\pm$ 1.8	NS	19.2 $\pm$ 1.4	NS	19.4 $\pm$ 1.7	NS
LF/HF	2.07 $\pm$ 0.25	2.31 $\pm$ 0.34	NS	2.09 $\pm$ 0.29	NS	2.07 $\pm$ 0.21	NS	2.25 $\pm$ 0.29	NS

(Mean $\pm$ SEM). Comparison between. * 2nd and 1st days, ** 3rd and 2nd days, *** 30th and 2nd days, **** 31st and 30th days. The standard deviation of differences between adjacent NN intervals (SDSD); SD of all normal-to-normal intervals (SDNN [milliseconds]); Ratio of the number of normal-to-normal intervals changing in excess of 50 milliseconds to total normal-to-normal intervals (pNN50); the root mean square of differences between adjacent normal-to-normal intervals (RMSSD [milliseconds]). Total power (TP), variance of total NN intervals (in millisecond [ms] and normal logarithm [ln]); low frequency (LF); high frequency (HF); and ratio of LF/HF.

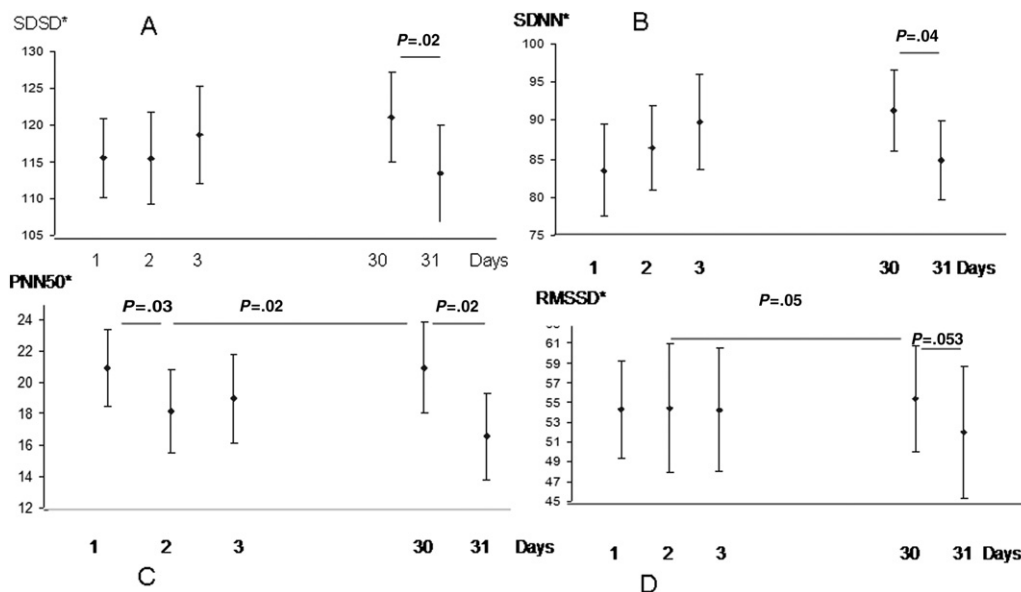


Figure 3. Changes in the time domain HRV parameters during 12-hour daytime period for 31 days $\ast(\pm$ standard error of the mean).

ning of the 2nd day of treatment; in other words, the adverse effect of formoterol on cardiac HRV did not persist. In addition, the tolerance was lost after additive doses of formoterol (SDSD, SDNN, pNN50, TP[ln]). Formoterol inhalation did not have any prolongation effect on the QTc interval. Formoterol showed its effects on HRV within the first hours of the daytime measurements, which is in accordance with the pharmacodynamics of the drug. The beta-2 agonists increase the sympathetic tone while decreasing the parasympa-

thetic tone. The additional doses of formoterol in tolerant patients may explain the increased cardiac autonomic side effects observed in patients using LABAs.

The long-term effects of formoterol on HRV were not reported previously in adults or children.^{18, 20–24} The results of the previous studies concerning the effects of beta-2 agonists on HRV are controversial. Jartti et al.²⁵ found that a 4-week salmeterol treatment in children with asthma increased sympathetic dominance, decreased HRV, and improved pulmonary function,

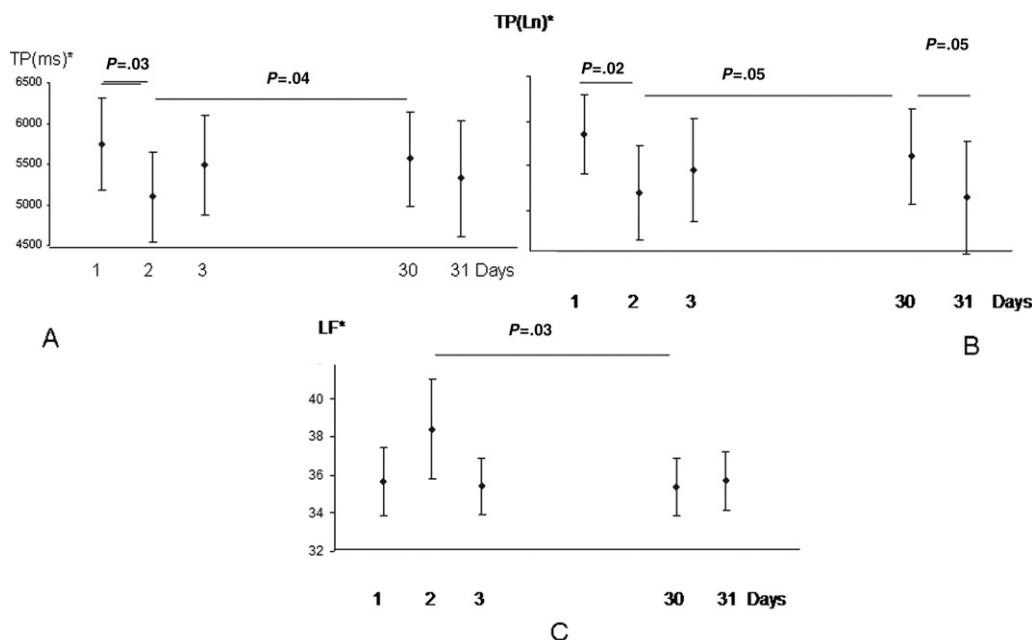


Figure 4. Changes in the frequency domain HRV parameters during 12-hour daytime period for 31 days $\ast(\pm$ standard error of the mean).

and a tolerance developed to the cardiovascular response.²⁵ In another study, the same group found that 2-week salbutamol treatment decreased HRV, and tolerance to this effect developed.²⁶ Similarly, Eryonucu et al³⁰ found that HRV decreased and sympathetic tone increased with acute use of salbutamol and terbutaline in adults with asthma. However, the results of studies evaluating the short-term effects of salmeterol and formoterol³² and the long-term effects of salmeterol usage in adults with asthma³³ did not show any change in HRV.

We found that a single-dose inhaled formoterol caused an early increase in respiratory function and HR and a decrease in HRV. All these effects supported the hypothesis of sympathetic predominance in these patients. Beta-2 agonists decrease parasympathetic activity while increasing sympathetic activity.^{26, 27, 30} In addition, this effect disappeared in the following hours, consistent with the pharmacodynamics of the drug. An additive dose of formoterol on the 3rd day did not make any difference either in heart rate or in HRV when compared with the BD measurements. The increase in FEV₁ after formoterol inhalation persisted, although no increase in FEV₁ occurred after the additional dose of formoterol. This latter effect can be explained by the characteristics of our patients, because most of them had mild to moderate asthma and their respiratory functions were near normal; thus, a significant increase in FEV₁ was not seen. All these findings showed that no tolerance to the bronchodilatory effects of formoterol occurs; however, even in the early periods, a tolerance to the cardiac effects of the drug is seen. Our findings were consistent with the findings of some previous studies,^{25, 26, 30} while contradicting others.^{32, 33} The later studies were performed in adult patients; thus, the greater dose per kilogram may have contributed to the development of the tolerance to cardiac effects in our adolescents.

Our SDTD (30th day) findings (increase in TP[ln], TP[ms], pNN50, and RMSSD and decrease in LF compared with BD) showed that early effects of formoterol on HRV and HR do not persist, and a tolerance to the early effects develops. These results were parallel to those reported by Jartti et al.^{25, 26} In contrast, Lotvall et al³³ reported that 3, 6, 9, and 12 months of salmeterol treatment did not make any difference in salbutamol response in HR and blood pressure in adults with asthma. In the current study, the development of tolerance in adolescents may be related with the greater dose per kilogram in this age group, greater protection of the autonomic system in children and adolescents,^{4, 6} or the increased mucosal permeability when compared with adults. Moreover, the increased parasympathetic response in adults may be related to the persistence of asthma or the prolonged use of beta-2 mimetics.

The hourly analysis of HRV showed some differences (decrease in LF/HF, increase in RMSSD) recorded within the first hours, which showed the effect of formoterol on the cardiac system that is consistent with the pharmacodynamics of the drug. In addition, parasympathetic dominance was seen in the preceding hours (decreased HR, decreased LF/HF, increased RMSSD). Parasympathetic dominance occurs in children with asthma, despite the fact that autonomic balance is relatively preserved in children compared with adults with asthma.^{4, 6, 30}

We also evaluated the effect of an extra dose of formoterol on HRV after 4 weeks of regular usage of formoterol with budesonide. Twelve-hour daytime measures showed that ADTD (31st day) SDDSD, pNN50, SDNN, and TP(ln) measures were decreased when compared with those of the SDTD (30th day), and HR increased. This means that the cardiac effects of formoterol and early period additive doses of formoterol were well tolerated regardless of the cumulative dose and therapy period; addition of an extra dose after a long-term fixed dose may cause the recurrence of the cardiac autonomic side effects. Many forms of formoterol on the market consist of doses over 4.5 µg, as was used in this study. Thus, increasing doses, as was seen with the additive dose, increase the risk of cardiac side effects. Though beyond the scope of this study, Mann et al³⁴ demonstrated an increase in mortality with higher than recommended doses of formoterol, specifically seen in a study of children. Thus, understanding the potential cardiac sequelae of escalation in LABA doses is important. However, we suggest that cardiac effect is only 1 of the theories associated with the use of LABAs.

In our study, evaluation of the Holter recordings did not show any prolongation in QTc interval. With new pharmacological agents, the effects of the agent on cardiac functions and rhythm are also evaluated because of safety concerns. Formoterol was shown to be safe with respect to QTc prolongation in therapeutic dosages, although at very high dosages (over 10 times the therapeutic dosage), it may cause long QTc.^{35, 36}

As is the case for most studies, this study has some limitations. First, the compliance of the patients to the therapy was tested with diaries, which is a parameter dependent on patients' statements. The uncontrolled and unblinded nature of the study is another limitation. In addition, mathematical manipulation of RR-interval spectral power must be grounded solidly on physiologic principles to avoid the interference of nonneural mechanisms on HRV-like respiratory pattern and physical activity.^{37, 38} We tried to minimize these effects by allowing patients to perform only routine daily activities. We also used both time and frequency domain parameters of HRV to minimize confounding influences.

To our knowledge, this is the first study evaluating the long-term effects of formoterol on HRV in children and adults by using both frequency and time domain parameters of HRV. In addition, the effects of additive doses of formoterol, in the early period and after 4 weeks of therapy, on HRV, QTc interval, and respiratory functions were also evaluated.

In conclusion, formoterol increases respiratory function, and this effect on the bronchial tree persists. Thus, formoterol additive doses may be effective in acute asthmatic attacks to relieve the symptoms. A single dose of formoterol inhalation increases mean HR and decreases HRV; tolerance to this cardiac effect occurs with chronic use of the therapy. However, additive doses of formoterol cause loss of the development of tolerance. Despite the need for further studies to clarify the clinical significance of the findings, additional doses of formoterol in tolerant patients may be considered for at least some of the cardiac side effects observed in patients using LABAs.

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