Cardiovascular effects of fenoterol under conditions of hypoxaemia

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Abstract
Background The reason for the association of increased risk of death with fenoterol in patients with asthma in New Zealand is unknown but may relate to its cardiovascular effects. Most deaths from asthma occur outside hospital, where hypoxaemia is likely to be a complicating factor. The cardiovascular effects of fenoterol have been investigated therefore under conditions of normoxaemia and hypoxaemia.

Method Eight healthy men were studied on two occasions. Measurements of heart rate, blood pressure, total electromechanical systole (Qs,I), electrocardiographic QTe interval, cardiac index, stroke volume, and ejection fraction were made under conditions of normoxaemia and hypoxaemia. The order in which treatments were applied was according to a Latin square design.

Results Before inhalation of fenoterol hypoxaemia was associated with a significant increase in heart rate (8 beats/min) and QTe interval (15-6 ms). Under conditions of normoxaemia fenoterol caused a significant increase in heart rate (14-3 beats/min), systolic blood pressure (7-7 mm Hg), stroke volume (27-7 ml), cardiac index (1-6 l/min/m²), ejection fraction (11-48), and QTe interval (32-9 ms) and a fall in Qs,I (–23-2 ms) and diastolic blood pressure (–8-4 mm Hg). Under conditions of hypoxaemia the changes after inhalation of fenoterol were similar to those recorded during normoxaemia; thus the effects of hypoxaemia and fenoterol were additive (heart rate 21-9 beats/min, QTe 43-5 ms with fenoterol and hypoxaemia).

Conclusion The chronotropic and electrophysiological effects of fenoterol were enhanced by conditions of hypoxaemia.

Methods
Subjects
We studied eight healthy, non-smoking male volunteers, aged 27-44 years. All had a normal resting electrocardiogram (ECG). None was taking any medication. The study design was approved by the research ethical committee of the Wellington Area Health Board, and each subject gave written informed consent. Subjects’ height and weight were measured for calculation of the cardiac index.

Investigations and Protocol
Subjects attended the laboratory after fasting on two occasions. They rested supine and breathed air through a non-rebreathing anaesthetic circuit and closely fitting face mask. After 10 minutes baseline recordings of electromechanical systole (Qs) a high speed surface ECG, blood pressure and two dimensional echocardiogram were recorded. The subjects then breathed room air to maintain normal arterial oxygen saturation (Sao2) or an appropriately adjusted nitrogen-oxygen gas mixture to maintain an Sao2 of 90%. The Sao2 was measured continuously by pulse oximetry.
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The order of treatment—that is, whether room air or the hypoxic gas mixture was applied first—was randomised according to a Latin square design and was single blind to the subject. After a further 10 minutes all recordings were repeated.

The subject then inhaled four puffs (800 μg) of fenoterol from a metered dose inhaler via a spacing device. Further recordings were made after a further 15 to 30 minutes while the subjects breathed room air or the low oxygen concentration gas mixture. End tidal carbon dioxide tension (Pco₂) was monitored continuously at the mouth with an infrared analyser (Datex Normocap).

Electromechanical systole (QSₜ) was measured from high speed photographic recordings of the ECG and phonocardiogram as described. QSₜ was corrected for heart rate (QSₜ₁) by using an equation developed in our laboratory. The QT interval was measured from the ECG and corrected for heart rate (QTc) by using the Bazett formula. All the echocardiographic recordings were performed by the same investigator (D McH), who used a Hewlett Packard 770208 ultrasound imaging system. All recordings from a given subject were made in the same position and from the same intercostal space. Measurements of left ventricular dimensions were made according to the guidelines of the American Society of Echocardiography. All tracings were recorded at 100 mm/s and measurements were made to the nearest mm, the mean of six cardiac cycles being used. From the recordings the following were calculated: cardiac output (CO), stroke volume (SV), heart rate (HR), ejection fraction (EF), and mean velocity of circumferential shortening (Vcf). The cardiac index (CI) was calculated from cardiac output and the individual’s height and weight.

**STATISTICAL ANALYSIS**

Data were analysed with SAS statistical package. The analysis was performed on change from control data. The following were determined: (a) the values after breathing room air or the gas mixture before the administration of fenoterol; (b) the values after fenoterol compared with values before the administration of fenoterol; (c) the differences between the fenoterol effect under conditions of hypoxaemia and normoxaemia—fenoterol-hypoxaemia interaction.

**Results**

There were no significant differences between the subjects’ baseline measurements on the two study days. The echocardiographic data represent those of seven subjects as recordings in one subject were inadequate on one study day.

The change from baseline for heart rate, blood pressure, QSₜ₁, and QTc are shown in table 1 and the echocardiographic data and end tidal Pco₂ in table 2. The changes at 40 minutes were similar to those at 25 minutes, so only the latter are shown in the tables.

**HYPOXAEMIA EFFECT**

Hypoxaemia was not associated with a change in end tidal Pco₂. When values were compared with those obtained when subjects were breathing room air for 10 minutes hypoxaemia was associated with a significant increase in heart rate and QTc interval (table 1) and a tendency for the cardiac index to increase, though this change was of borderline statistical significance (p = 0.07).

**FENOTEROL EFFECT**

By comparison with the baseline values fenoterol caused a significant increase in heart rate, systolic blood pressure, QTc interval, cardiac index, stroke volume, ejection fraction, and confidence intervals calculated with the CIA statistical package. The analysis was performed on change from control data. The following were determined: (a) the values after breathing room air or the gas mixture before the administration of fenoterol; (b) the values after fenoterol compared with values before the administration of fenoterol; (c) the differences between the fenoterol effect under conditions of hypoxaemia and normoxaemia—fenoterol-hypoxaemia interaction.

**Table 1** Effect in terms of mean change from control of hypoxaemia and fenoterol (administered after the 10 minute recording) on the cardiovascular measurements

<table>
<thead>
<tr>
<th>Time* (min)</th>
<th>Normoxaemia</th>
<th>Hypoxaemia</th>
<th>Hypoxaemia effect: difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before fenoterol</td>
<td>Fenoterol effect: difference (95% CI)</td>
<td>Before fenoterol</td>
<td>Fenoterol effect: difference (95% CI)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>10</td>
<td>14.3</td>
<td>15.4 (10.0-20.8)</td>
<td>6.9</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>10</td>
<td>7.6</td>
<td>10.0 (6.0-14.0)</td>
<td>3.0</td>
</tr>
<tr>
<td>Systolic</td>
<td>25</td>
<td>-2.4</td>
<td>-1.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic</td>
<td>10</td>
<td>-1.5</td>
<td>-8.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>25</td>
<td>-2.3</td>
<td>-2.3</td>
<td>0.01</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>10</td>
<td>-3.3</td>
<td>-3.3</td>
<td>0.01</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>25</td>
<td>32.9</td>
<td>36.2 (28.3, 44.1)</td>
<td>43.5</td>
</tr>
</tbody>
</table>

*10 min is immediately before administration of fenoterol; 25 min is 15 min after fenoterol.
†Effect of adding fenoterol during normoxaemia.
‡Effect of adding fenoterol during hypoxaemia.
mean velocity of circumferential shortening (tables 1 and 2). It also decreased Qs/I and
diastolic blood pressure significantly. Fenoterol did not affect end tidal Pco₂.

FENOTEROL-HYPOXAEMIA INTERACTION

The effect of fenoterol on heart rate increase was about the same under conditions of hypoxaemia (increase 15·0 beats/min) and normoxaemia (increase 15·4 beats/min). The findings were similar for virtually all of the other cardiovascular and echocardiographic measurements. Thus the joint effect of fenoterol and hypoxaemia was approximately the sum of their independent effects.

Discussion

The chronotropic and electrocardiographic (QTc) effects of hypoxaemia and fenoterol were additive in this study. The increase in heart rate is likely to lead to an increase in myocardial oxygen demand, which could be harmful to a patient. Excessive increase in the QT interval has been associated with an increased risk of ventricular arrhythmias.18

It could be argued that we have exceeded the manufacturer’s recommended dose of fenoterol and that the increase in the QTc interval in this study is not great. In earlier work we showed a direct relation between the dose of β agonists inhaled and their cardiovascular effects.6 17 It is well recognised that asthmatic patients may self administer very high doses of their inhaled β agonist during a severe asthma attack17 and the British Thoracic Society recommended that doses up to 50 puffs of a β agonist from a metered dose inhaler could be used during severe asthma.20 Thus the doses used in this study are likely to underestimate the cardiovascular responses that may occur from the combination of fenoterol and hypoxaemia in the clinical setting.

The circulatory effects of hypoxaemia are complex and depend on its degree and cause and on the individual’s compensatory gaseous changes.2 These vary from an increase in heart rate alone to increases in cardiac output and subsequently to bradycardia and myocardial depression.2, 21

In our study hypoxaemia had no effect on any of the contractile indices, such as Qs/I, a sensitive indicator of a positive inotropic effect,22 or the velocity of circumferential shortening, suggesting that the small increase in cardiac index is more likely to be related to changes in loading than to be a direct inotropic effect. The lack of an inotropic effect after hypoxaemia or the combination of fenoterol and hypoxaemia may be due to the mild degree of hypoxaemia attained in this study; alternatively, it could be due to the fact that the recordings after hypoxaemia were performed when the subjects had become re-oxygenated as the maximum cardiovascular effects during hypoxaemia occur by five minutes.8

The effect of hypoxaemia on the QTc interval in our study has not been reported elsewhere. We have not studied the underlying mechanisms, but it is unlikely to be due to increased sympathetic outflow at the arterial oxygen saturation seen in the study;23 it may be due to reflex mechanisms from chemoreceptor stimulation.

The end tidal Pco₂ was unchanged throughout this study. This is in keeping with the results of previous work, in which the Paco₂ has usually not altered until the PaO₂ is below 8·0 kPa or less than 90% saturated.24

In conclusion, we have shown that when subjects are given fenoterol under conditions of hypoxaemia there are additive electrocardiographic and chronotropic effects. The relation between these changes and the increased risk of death identified with fenoterol remains to be determined.

Table 2  Effect in terms of mean change from control of hypoxaemia and fenoterol (administered after the 10 minute recording) on the hypocardiographic measurements and end tidal carbon dioxide tension (Pco₂)

<table>
<thead>
<tr>
<th></th>
<th>Normoxaemia</th>
<th>Hypoxaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time* (min)</td>
<td>Before fenoterol</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>10</td>
<td>0-6</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>25</td>
<td>1·7</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>25</td>
<td>27-7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>10</td>
<td>1·4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>25</td>
<td>11·4</td>
</tr>
<tr>
<td>Vcf (circ/h)</td>
<td>10</td>
<td>0-01</td>
</tr>
<tr>
<td>Vcf (circ/h)</td>
<td>25</td>
<td>0-39</td>
</tr>
<tr>
<td>End tidal pco₂ (mm Hg)</td>
<td>10</td>
<td>-0·3</td>
</tr>
<tr>
<td>End tidal pco₂ (mm Hg)</td>
<td>25</td>
<td>0·8</td>
</tr>
</tbody>
</table>

*10 min is immediately before administration of fenoterol; 25 min is 15 min after fenoterol.
†Effect of adding fenoterol during normoxaemia.
‡Effect of adding fenoterol during hypoxaemia.
Conversion to SI units: 1 mm Hg ≈ 0·133 kPa.


