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Inhaled β2-Adrenoceptor Agonists

Cardiovascular Safety in Patients with Obstructive Lung Disease

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Abstract

Although large surveys have documented the favourable safety profile of β2-adrenoceptor agonists (β2-agonists) and, above all, that of the long-acting agents, the presence in the literature of reports of adverse cardiovascular events in patients with obstructive airway disease must induce physicians to consider this eventuality. The coexistence of β1- and β2-adrenoceptors in the heart clearly indicates that β2-agonists do have some effect on the heart, even when they are highly selective. It should also be taken into account that the β2-agonists utilised in clinical practice have differing selectivities and potencies. β2-agonist use has, in effect, been associated with an increased risk of myocardial infarction, congestive heart failure, cardiac arrest and sudden cardiac death. Moreover, patients who have either asthma or chronic obstructive pulmonary disease may be at increased risk of cardiovascular complications because these diseases amplify the impact of these agents on the heart and, unfortunately, are a confounding factor when the impact of β2-agonists on the heart is evaluated. Whatever the case may be, this effect is of particular concern for those patients with underlying cardiac conditions. Therefore, β2-agonists must always be used with caution in patients with cardiopathies because these agents may precipitate the concomitant cardiac disease.

Inhaled β2-adrenoceptor agonists (β2-agonists) are widely used in the treatment of asthma and chronic obstructive pulmonary disease (COPD) because they improve airflow limitation and exercise tolerance and, consequently, health-related quality of life.[1] However, there is concern about their safety; in particular, they can induce an increase in heart rate, an increase in contractile force, a decrease in peripheral vascular resistance with increased pulse pressure and an increase in cardiac output, as well as changes in serum potassium and magnesium levels,[2-4] which are factors that may affect conduction pathways in the heart and increase the risk of sudden cardiac death.[5-11] All of these effects are due to the presence of β-adrenoceptors in the heart.

1. β-Adrenoceptors and the Heart

Cardiac β-adrenoceptors are important regulators of cardiac function, and respond to neuronally re-

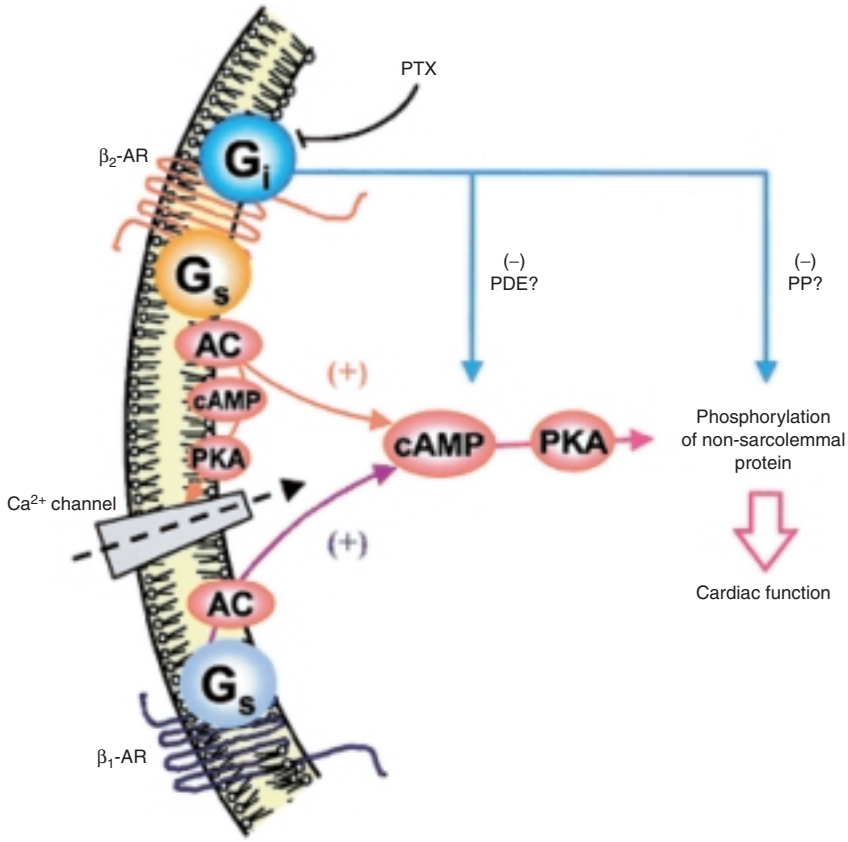

Fig. 1. Dual coupling of cardiac β_2-adrenoceptor (AR) to the stimulatory G protein (G_s) and inhibitory G protein (G_i). The β_2-AR–coupled G_i activation functionally localises the G_s-mediated adenylyl cyclase (AC)–cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signalling complex to the subsarcolemmal microdomain, perhaps by stimulating phosphodiesterase (PDE) or protein phosphatases (PP). In contrast, β_1-AR couples exclusively to G_s protein. Pertussin toxin (PTX) pretreatment prevents the β_2-AR-mediated G_i activation (reproduced from Xiao et al.,[15] with permission).

leased and circulating catecholamines. Their stimulation results in positive cardiotonic and chronotropic responses, cardiac myocyte growth and cardiac toxicity.[12,13] β-Adrenoceptors are, in fact, coupled via the stimulatory G protein (G_s) to the effector enzyme adenylyl cyclase, which converts the substrate magnesium adenosine triphosphate to cyclic adenosine monophosphate (cAMP), with the subsequent activation of protein kinase A (PKA). cAMP is a positively cardiotonic and chronotropic second messenger and is a strong promoter of cellular growth.

Even though the β_1-adrenoceptors are classically described as the key participants in triggering and regulating cardiac contractility, stimulation both of β_1- and of β_2-adrenoceptors leads to positive inotropy via coupling to adenylyl cyclase and the generation of cAMP.[14] However, in contrast to the β_1-adrenoceptor, β_2-adrenoceptors can also couple to the inhibitory G-protein (G_i), at least in murine and rat cardiomyocytes[15] (figure 1). Whether this holds true also for the human heart is still to be elucidated. Bristow et al.[14] demonstrated that the proportions of β_1- and β_2-adrenoceptors in normal hearts were 77% and 23%, respectively. Functional β_1- and β_2-adrenoceptors coexist on both atria and both ventricles. In the human heart, the β_1 **:** β_2-adrenoceptor ratio is about 60–70% **:** 40–30% in the

atria and about 70–80% : 30–20% in the ventricles.[13] Interestingly, Rodefeld et al.[16] have shown that in human sinoatrial nodes, β-adrenoceptor densities were about 3-fold higher than in the adjacent atrial myocardium. Although the β1-adrenoceptor subtype predominates, the β2-adrenoceptor density was about 2.5-fold higher in the sinoatrial node than in the right atrial myocardium. β2-Adrenoceptors are also present on the adrenergic nerve terminals in the heart, where they facilitate norepinephrine (noradrenaline) release.[17]

Despite the fact that β1-adrenoceptors predominate in human myocardium, the functional responses mediated by β1- and β2-adrenoceptors are not necessarily different. This may be because human cardiac β2-adrenoceptors are more effectively coupled to adenylyl cyclase than are the β1-adrenoceptors.[18] There is solid documentation of direct β2-adrenoceptor-mediated positive cardiotonic and chronotropic effects in humans *in vivo* using β2-agonists such as terbutaline or salbutamol (albuterol).[18] Interestingly, the positive cardiotonic effects of high doses of terbutaline and salbutamol are slightly antagonised by β1-selective antagonists such as bisoprolol or atenolol. It has been suggested that activation of prejunctional β2-adrenoceptors (which have been demonstrated to exist in human heart), leading to enhanced norepinephrine release, may contribute to the cardiac effects of β2-adrenoceptor agonists, at least at higher doses.[18]

In the heart, β-adrenoceptor stimulation provides the most powerful mechanism to augment cardiac contractility in response to a 'fight-or-flight' situation. However, prolonged exposure of the β-adrenoceptors to an agonist leads to a decrease in receptor responsiveness (i.e. desensitisation). This process is mediated either by a negative feedback regulation by PKA or, alternatively, by the G-protein-coupled receptor kinase (GRK) family (GRK1–6), in particular GRK2, which is also known as β-adrenoceptor kinase 1 (βARK1).[19] The rate at which a β-agonist drives receptor desensitisation parallels its intrinsic efficacy,[20] indicating that the active conformation of the receptor, which couples with the downstream signal transduction pathway, is also recognised by the cellular desensitisation machinery.[21] The intrinsic efficacies of commonly used β2-agonists are listed in table I.

In the failing heart, the respective proportions of β1- and β2-adrenoceptors are 60% and 38%.[14] This decrease in the proportion of β1-adrenoceptors and relative increase in the proportion of β2-adrenoceptors has been postulated to be a result of selective down-regulation of the β1-adrenoceptors, with little or no change in the expression of β2-adrenoceptors.[14] It is a protective mechanism that counteracts the deleterious effects induced by chronic sympathetic activation.[14] Cardiac β-adrenoceptor stimulation can evoke programmed cell death (apoptosis), with β1-adrenoceptors (via the G_s protein) inducing proapoptotic effects, and β2-adrenoceptors (via the G_i protein) inducing antiapoptotic effects, at least in rat cardiomyocytes.[26] It must be emphasised that in the failing human heart, G_i levels are increased. Therefore, one can speculate that this increase in G_i levels would be

Table I. Summary of some pharmacological properties of selected β2-adrenoceptor agonists[21-25]

β2-Adrenoceptor agonist	Affinity for β2-adrenoceptor (K_i, nmol/L)	Efficacy at β2-adrenoceptor[a]	Potency at β2-adrenoceptor[b]	Selectivity ratio (β2 : β1-adrenoceptor)	Intrinsic efficacy (%)	Approximate onset of action (min)	Approximate duration of action
Isoprenaline	200	(100)	(1)	1 : 1	100	2–5	<20 min
Salbutamol	2500	86	0.55	1 : 1375	4.9	2–3	4–6h
Fenoterol	ND	100	ND	1 : 120	42	2–4	4–6h
Terbutaline	ND	65–85	ND	ND	ND	2–4	4–6h
Salmeterol	53	63	8.5	1 : 85 000	<2.0	30	>12h
Formoterol	76	100	20	1 : 120	20	2–3	>12h

a Relative to isoprenaline as 100%.

b Relative to isoprenaline.

ND = no data available.

protective for the human heart because it would enhance the antiapoptotic effects of β_2-adrenoceptor stimulation.[27] It is obvious that the failing heart becomes more dependent on β2-adrenoceptor stimulation for cardiotonic support. However, the activation of these receptors may also alter cardiac electrical stability, increasing the propensity for the onset of malignant arrhythmias in the diseased heart. In the failing heart, β-adrenergic signal transduction is reduced secondary to desensitisation-related changes in β_1-adrenoceptors, in G_i, in the enzyme responsible for modulating receptor activity by phosphorylation (βARK), and even in the expression of the adenylyl cyclase enzyme itself.[28] In the end-stage failing heart, 50–60% of the total signal transducing potential is lost but substantial signalling capacity remains.[13]

It is noteworthy that aging is associated with a sustained increase in the level of serum norepinephrine and a diminished β-adrenergic response to catecholamines.[29,30] The mechanism underlying this age-dependent reduction in cardiac β-adrenoceptor function is not completely understood. It is likely that this age-related decline in β-adrenergic response in the non-failing human heart is primarily due to a selective down-regulation of β_1-adrenoceptors, as seen in patients with heart failure.[31] Other supposed mechanisms are decreased agonist binding of β_1-adrenoceptors, uncoupling of β_2-adrenoceptors and abnormal G protein-mediated signal transduction. However, unlike in heart failure, there is no evidence of increased βARK activity or up-regulation of G_i proteins[32]. Aging is also not associated with any change in myocardial excitation-contraction coupling.

2. Effects of β_2-Adrenoceptor Agonists on Cardiac Function

The presence of β_2-adrenoceptors in the heart explains why β_2-agonists can induce a number of adverse effects that potentially impact on cardiac function. These effects are usually considered to be mild.[33] Nonetheless, Lemaitre et al.[34] have suggested that, in patients with asthma, an increased risk of primary cardiac arrest is associated with high use of metered-dose inhaled β_2-agonists, as well as with the use of nebulised β_2-agonists. Moreover, in patients with cardiovascular disease, an initial prescription of an inhaled β_2-agonist has been associated with a 7-fold increase in the risk of myocardial infarction.[35]

It remains unknown whether the use of all inhaled β_2-agonists leads to an increased risk of incident heart failure or whether it may affect the risk of hospitalisation among patients with existing heart failure. Coughlin et al.[36] described a 3-fold increased risk of idiopathic cardiomyopathy associated with the use of oral or nebulised β_2-agonists. Martin et al.[37] described a similar finding of a 3-fold risk of nonfatal heart failure associated with the long-acting, oral β_2-agonist bambuterol but not with inhaled salmeterol. Neither of these studies demonstrated a dose-response relationship between inhaled β_2-agonists and the risk of heart failure. In addition, neither study examined all-cause mortality as an endpoint. In any case, it has been shown that full β_2-agonists would elicit a greater response than partial agonists. In fact, in dose-response studies, strong agonists have been demonstrated to be capable of causing more severe adverse effects, such as greater tachycardia and reductions in serum potassium levels, than weak partial agonists.[38-40]

2.1 Interferences with Rhythm

Acute salbutamol inhalation decreases cardiovagal nervous responsiveness, increases sympathetic dominance in the cardiovascular autonomic balance, and has a tendency to decrease baroreflex sensitivity, in addition to improving pulmonary function.[41] Moreover, it decreases parasympathetic drive and increases sympathetic modulation of the cardiovascular autonomic balance.[37] These effects explain why 2 weeks of salbutamol treatment increased the baseline low frequency variability and low frequency/high frequency variability ratio of R–R intervals on ECG when compared with placebo.[41]

A recent meta-analysis of randomised, placebo-controlled trials of β_2-agonist treatment in patients with obstructive airway disease[42] reported that a single dose of a β_2-agonist caused an increase in

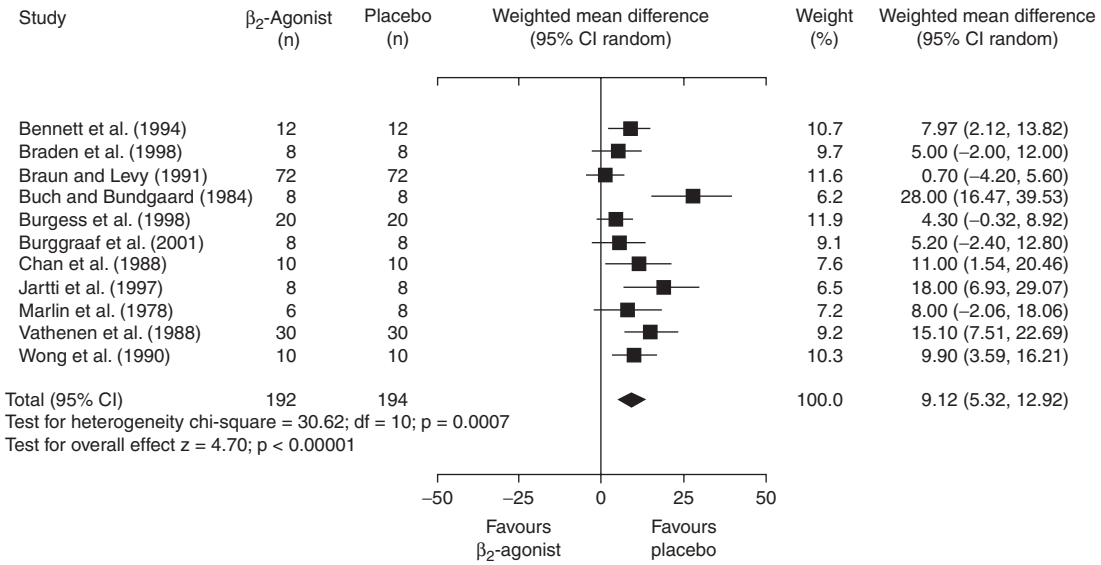

Fig. 2. Cardiovascular effects of β2-adrenoceptor agonist (β2-agonist) use. Heart rate, beats per minute (treatment minus placebo) in single-dose trials (Bennett et al.,[44] Braden et al.,[45] Braun and Levy,[46] Buch and Bundgaard,[47] Burgess et al.,[48] Burggraaf et al.,[49] Chan et al.,[50] Jartti et al.,[40] Marlin et al.,[51] Vathenen et al.[52] and Wong et al.[4]) [reproduced from Salpeter et al.,[42] with permission]. **df** = degrees of freedom.

heart rate of 9.12 beats per minute [bpm; 95% CI 5.32, 12.92) [figure 2], and also a reduction in serum potassium level of 0.36 mmol/L (95% CI 0.18, 0.54), compared with placebo. For trials lasting from 3 days to 1 year, the relative risk for sinus tachycardia alone was 3.06 (95% CI 1.7, 5.5). Effectively, mild tachycardia is common when patients are first exposed to β2-agonists, even the most recently available, highly β2-adrenoceptor-specific agents.[43] At least in part, tachycardia may result from dilation of the peripheral vasculature, which reduces venous return, resulting in activation of sympathetic nervous system reflexes and increased cardiotonic and chronotropic effects. β2-Agonists may also stimulate β2-adrenoceptors in the cardiac muscle itself, in both the left ventricle and the right atrium, thus directly increasing heart rate.

All of the older adrenergic agents, such as isoprenaline (isoproterenol) and epinephrine (adrenaline), increase heart rate.[53] Among the newer short-acting β2-agonists, fenoterol increases heart rate to a significantly greater extent than salbutamol[4,54-56] or terbutaline.[4,57] It is worth mentioning that fenoterol has been reported to be as likely to cause tachycardia as isoprenaline.[58] The impact on heart rate is dose-related for all agents.[4,52,56,59-61]

Fortunately, tolerance to the cardiac-stimulatory effects of β2-agonists develops rapidly,[52] even in response to high-dose isoprenaline.[62] Very few patients experience tachycardia, which is more likely to be seen in infrequent rather than frequent users.

Heart rate increases are reflected in adverse-event reports of palpitations but arrhythmias are reported far less frequently.[43] Rhythm disturbances may occur more frequently with fenoterol than salbutamol.[55] Terbutaline use in patients with COPD results in ectopic activity but no evident arrhythmias.[63] Measurable changes can be recorded in ECG parameters, such as the corrected QT (QTc) interval and the Q–S_2 interval,[54] but the clinical significance of these changes is still under debate. Recently, it has been documented that catecholamines can induce T-wave lability in congenital long QT syndrome.[64]

Torsade de pointes in a patient on usual-dose β2-agonist therapy has been described.[65] It was attributed to hypokalaemia and QTc prolongation in-

duced by the β_2-agonist. Hypokalaemia occurs with β_2-adrenergic stimulation as a result of intracellular movement of potassium into the skeletal muscle.[43] In patients with obstructive airway disease, serum potassium levels could be still further decreased with the use of corticosteroids and diuretics, and the cardiac effects of hypokalaemia could be aggravated by underlying hypoxaemia.[35,66] It is intriguing that both hypoxaemia and fenoterol cause myocardial repolarisation abnormalities in humans, in terms of increased QTc dispersion (interlead variability in QTc interval), but that only fenoterol increases the QTc interval.[67] This may be relevant in the aetiology of arrhythmias in patients with acute severe asthma where β_2-agonist therapy and hypoxaemia coexist. Although prolongation of the QTc interval has been associated with cardiac dysrhythmias, rare case reports of troublesome arrhythmias suggest that some patients may have a low threshold for ventricular arrhythmias, even in the absence of a prolonged QTc interval.[68]

Salmeterol and formoterol, two long-acting β_2-agonists, are now considered the mainstay of treatment in both asthma[69] and COPD.[70] Some studies have evaluated the cardiac impact of these agents in healthy individuals showing, for example, a safety profile for formoterol that was comparable to that of short-acting β_2-agonists, with very small adverse effects on the heart rate and QTc interval that were without clinical consequence[71] even when very high doses were administered.[72] Bennett and Tattersfield[2] compared the time course and dose-response relationships of the systemic effects of salmeterol 100, 200 and 400μg with those of salbutamol 600, 1200 and 2400μg. Both salmeterol and salbutamol caused dose-dependent changes in heart rate, QTc interval and plasma potassium levels. The onset of cardiac effects was rapid for both drugs, whereas changes in potassium levels occurred more gradually with salmeterol. The relative dose potencies of salmeterol compared with salbutamol for changes from baseline in QTc interval and plasma potassium levels were 7.1 (95% CI 3.9, 14.4) and 8.2 (95% CI 5.7, 12.6), respectively. Salmeterol was associated with steeper dose-response curves for heart rate and plasma glucose level than was salbutamol; therefore, relative dose potency values could not be calculated.

Bremner et al.[54] compared the cardiac effects of formoterol, salbutamol and fenoterol. On study days, patients inhaled five doses of either formoterol 24μg, salbutamol 400μg or fenoterol 400μg at 30-minute intervals. All agents significantly increased heart rate and the QTc interval, and decreased the $Q–S_2$ interval and plasma potassium levels compared with placebo, but fenoterol had a significantly greater maximum effect on heart rate, QTc and $Q–S_2$ interval. Formoterol and fenoterol caused a similar maximum reduction in plasma potassium level, greater than that due to salbutamol. In a head-to-head comparison, salmeterol 100, 200 and 400μg and formoterol 24, 48 and 96μg caused rapid dose-related increases in heart rate that were evident 1 minute after inhalation.[73] During the first 10 minutes, the increase in heart rate was slightly greater with formoterol than with the corresponding doses of salmeterol, but salmeterol subsequently caused a greater increase, with a peak between-treatment difference in effect on heart rate 2–4 hours after dose administration. A further increase in heart rate occurred with both drugs, reaching a maximum 5–6 hours after dose administration. The highest absolute values were seen following the highest doses of salmeterol. Dose-related effects were apparent 7 hours after the highest dose of formoterol and after 8 hours with salmeterol. QTc showed an early dose-related increase with both drugs, in keeping with the changes in heart rate. Plasma potassium levels showed a dose-related decrease following both drugs; this occurred more rapidly with formoterol; however, drug-related effects were still present at 8 hours after salmeterol, but not formoterol, administration. The relative dose potencies over 4 hours for formoterol compared with salmeterol for heart rate, QTc interval and plasma potassium level were 4.1 (95% CI 3.0, 5.6), 7.0 (95% CI 2.9, 64) and 5.8 (95% CI 4.1, 8.6), respectively.

In patients with asthma, Kemp et al.[74] found that salmeterol doses from 12.5 to 100μg caused only a 2–5 bpm increase in heart rate compared with place-

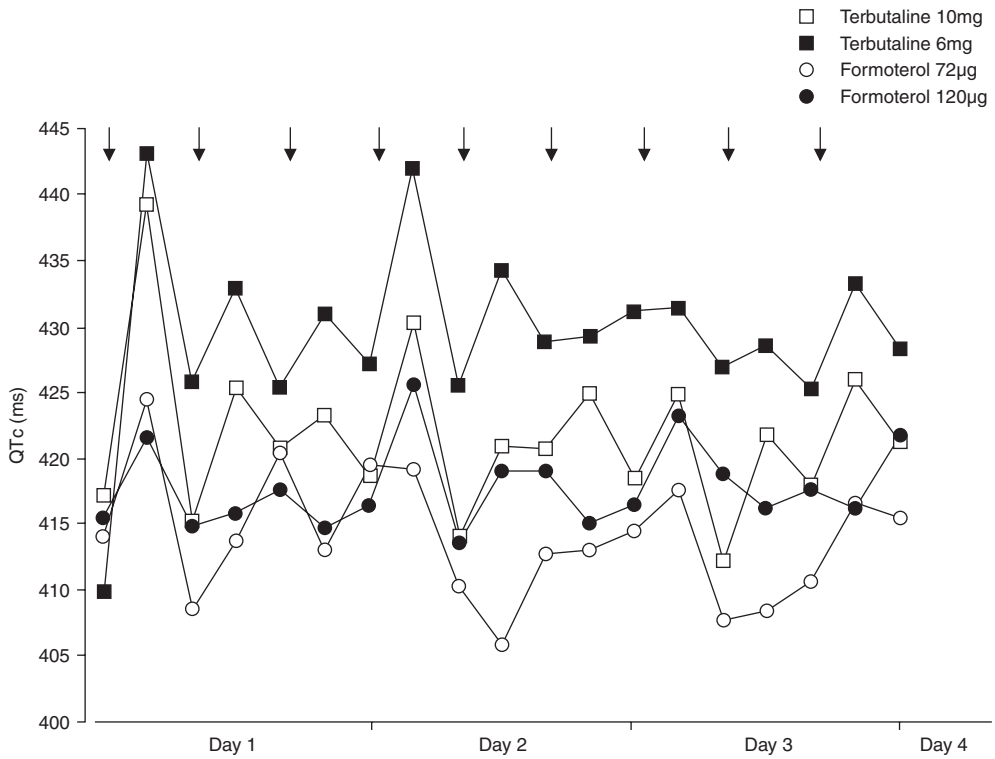

Fig. 3. Mean QT interval corrected for heart rate (QTc) values before, during the 3 treatment days and after treatment (day 4) in patients receiving formoterol 72 or 120µg and terbutaline 6 or 10mg via Turbuhaler®. The arrows represent the dose administration times (reproduced from Totterman et al.,[79] with permission from European Respiratory Society Journals Ltd).

bo. Of those patients given the highest dose of salmeterol (100µg), 13–17% had ventricular premature beats (vs 4–9% of patients given placebo, salbutamol or lower doses of salmeterol) and 17% reported palpitations. Burgess et al.[48] reported that in patients with mild-to-moderate asthma there was no difference between the maximum effects of formoterol 12µg and placebo on heart rate, blood pressure, electromechanical systole ($Q–S_2$ interval), the electrocardiographic QTc interval and plasma potassium; the 24µg dose significantly decreased plasma potassium levels (−0.2 mmol/L) compared with placebo. The two highest doses (48 and 96µg) affected most of the variables, with the 96µg dose having a significantly different effect to placebo on heart rate (9 bpm), $Q–S_2$ interval (−11ms), QTc (17ms) and plasma potassium level (−0.5 mmol/L).

Holter monitoring and echocardiograms of 17 children given salmeterol 200 µg/day did not show any cardiac adverse effects.[75] Studies using Holter monitoring in healthy and asthmatic adults have similarly not given any cause for concern.[76-78]

High β_2-agonist exposure as a result of repeated inhalations of formoterol 6 µg/dose resulted in fewer chronotropic, cardiotonic and electrophysiological effects than the same number of doses of terbutaline 0.5 mg/dose, when both were delivered via Turbuhaler® **1**[79] in stable asthmatic patients (figure 3). The differences in effect between formoterol 72µg and terbutaline 6mg, for both mean change in cardiac frequency over 3 days (−6.2 bpm; 95% CI −9.1, −3.3) and QTc interval (−9.3ms; 95% CI −16, −2.6), were statistically significant. The differences between formoterol 120µg and

1 The use of trade names is for product identification purposes only and does not imply endorsement.

terbutaline 10mg in effects on cardiac frequency (−8.2 bpm; 95% CI −11.1, −5.3) and QTc interval (−20.6ms; 95% CI −27.2, −14.1) were also statistically significant.

Long-acting β_2-agonists have also been used extensively in high-risk asthma patients. Lanes et al.[80] found no increase in incidence rates for emergency care, hospitalisation or intensive care unit stays among asthmatic patients receiving salmeterol. In an emergency room study, high doses of formoterol (total dose 90μg) had less effect than terbutaline (total dose 10mg) on heart rate and serum potassium levels.[81] The mean heart rate response was 93.5 versus 101.7 bpm, and serum potassium levels decreased from 4.02 to 3.89 mg/L with formoterol versus 4.22 to 3.76 mg/L with terbutaline. However, it is noteworthy that, in the US, SMART (Salmeterol Multi-Center Research Trial) was prematurely discontinued as a result of a small but significant increase in asthma-related deaths in patients receiving salmeterol versus those receiving placebo.[82] Subgroup analyses suggested the risk of asthma-related death may be greater in African American patients than in Caucasians. Since SMART has not been published, it is not possible to describe the real cause of these deaths, however, considering what was observed in the placebo group, it is possible to argue that they may have been linked to the impact of salmeterol on the heart rather than to reduced control of asthma. However, it must be highlighted that African American participants had more severe asthma at entry and were likely to have been undertreated with inhaled corticosteroids. Moreover, it is well known that the regular use of β_2-agonists can result in tolerance to their bronchodilator and non-bronchodilator effects, and may lead to an increase in asthma exacerbations and deaths.[42]

Patients with COPD are at increased risk for sinus tachycardia, although premature atrial complexes, atrial fibrillation, premature ventricular complexes and ventricular tachycardia are often reported.[83] Nonetheless, long-acting β_2-agonists have a good safety record in COPD. Goldkorn et al.[84] were unable to find any clinically important or statistically significant changes in heart rate, QTc interval, T-wave height or plasma potassium level associated with the use of formoterol 120μg or salbutamol 2000μg in a small group of patients with moderate-to-severe COPD. Ferguson et al.[85] reviewed 17 studies involving 1443 patients who received placebo and 1410 patients who received salmeterol 50μg twice daily, and found no increase in cardiovascular adverse effects with salmeterol compared with placebo (table II). Holter data revealed no episodes of sustained ventricular tachycardia and no clinically significant differences in 24-hour heart rate, ventricular and supraventricular ectopic events, qualitative ECGs, QT intervals or vital signs between the salmeterol treatment group and the placebo group. Similar findings emerged when patients were stratified according to age (≥65 vs <65 years) and the known presence of cardiovascular disease. However, in a study of 12 high-risk patients with COPD who had pre-existing cardiac arrhythmias and hypoxaemia (alveolar oxygen partial pressure <60mm Hg), significant increases in mean heart rate relative to placebo were reported after single doses of formoterol 12 or 24μg, or salmeterol 50μg.[86] The greatest effect was observed with formoterol 24μg. Notable limitations of this study were the small number of patients evaluated and that no baseline Holter monitoring was

Table II. Incidence of cardiovascular events in 1443 patients who received placebo and 1410 patients who received salmeterol 50μg twice daily (bid), by age and concurrent cardiovascular (CV) condition at baseline[a] (reproduced from Ferguson et al.,[85] with permission)

Patient characteristics	Placebo[a]	Salmeterol 50μg bid[a]
Age[b]		
<65y	737/48 (7)	711/49 (7)
≥65y	706/61 (9)	699/64 (9)
≥75y	124/13 (10)	128/14 (11)
Without concurrent CV condition[c]	862/44 (5)	823/48 (6)
Concurrent CV condition[c]	580/65 (11)	587/65 (11)
treated[d]	166/25 (15)	145/23 (16)
not treated	414/40 (10)	442/42 (10)

a Values given as no. of patients/no. of CV events (% patients).
b Placebo group, n = 1443; salmeterol group, n = 1410.
c Placebo group, n = 1442; salmeterol group, n = 1410.
d Treated with antiarrhythmic and/or bradycardic agents.

Table III. Risk of myocardial infarction associated with metered-dose inhaler (MDI) β_2-adrenoceptor agonist (β_2-agonist) use among patients with cardiovascular disease according to frequency and recency of use (reproduced from Au et al.,[35] with permission from the *American Journal of Respiratory and Critical Care Medicine*, official journal of the American Thoracic Society, © American Thoracic Society)

Category of use	Controls[a] (n = 1140)	Cases[b] (n = 678)	OR, adjusted for matching factors [OR (95% CI)]	OR, adjusted for matching factors and other factors[c] [OR (95% CI)]
Never users[d]	1000	556	1.0 (reference)	1.0 (reference)
One-time users[d]				
no prescription in past 3mo	49	39	1.42 (0.91, 2.2)	1.21 (0.76, 1.93)
one canister prescription in past 3mo (new users)	4	17	7.67 (2.54, 23.2)	7.32 (2.34, 22.8)
Greater than one-time users[d]				
no prescription in past 3mo	39	29	1.39 (0.84, 2.29)	1.14 (0.67, 1.93)
one canister prescribed in past 3mo	10	12	1.99 (0.84, 4.68)	1.78 (0.73, 4.33)
several canisters prescribed in past 3mo	38	25	1.23 (0.73, 2.07)	1.28 (0.74, 2.23)

a Subjects with a history of cardiovascular disease.

b Subjects with an incident myocardial infarction.

c Adjusted for matching factors (age, gender, index year and treated hypertension), smoking status, diabetes mellitus, angina, transient inschaemic attack, congestive heart failure and cardiovascular disease.

d Never users were defined as patients who never received a β_2-agonist MDI canisters in the 2y prior to reference date; one-time users were defined as patients who received exactly one MDI β_2-agonist prescription in the previous 2y; new users were defined as patients who received exactly one MDI β_2-agonist prescription in the 3mo prior to the index date; and greater than one-time users were defined as patients who received two or more MDI β_2-agonist prescriptions in the previous 2y.

OR = odds ratio.

conducted. Few differences were noted between the salmeterol and placebo groups, and the incidence of supraventricular and ventricular premature beats were similar in both groups. Several studies, which have involved patients with acute exacerbations of COPD who were often older than 65 years, have been unable to document a significant impact of a higher than customary dose of formoterol or salmeterol on heart rate. Only minor changes have been observed after the inhalation of salmeterol 100μg or formoterol 48μg.[87-90]

All of these findings are interesting but it must be highlighted that most, if not all, of the physiological outcome studies that have examined the cardiovascular effects associated with β_2-agonists were performed in small numbers of patients. So although one interpretation is that there were no clinically meaningful events, this would be largely incorrect because of the lack of power. In clinical trials, the null hypothesis is usually structured such that finding a difference would disprove the null. However, the converse (i.e. functional equivalency testing) is not necessarily true. In other words, if there is no difference in event rates, one cannot legitimately say that a medication is better, worse or equivalent unless the power of the study has been specified.

2.2 Risk of Myocardial Infarction

A case-control study has suggested that new, single-time use of inhaled β_2-agonists in individuals with existing cardiovascular disease increases the risk of myocardial infarction, while there is no increase in risk for more frequent users of inhaled β_2-agonists and those without cardiovascular disease[35] (table III). A further study, using data collected as part of a large, ongoing study of quality improvement in Department of Veterans Affairs Medical Centers in the US, examined the relationship between inhaled β_2-agonists delivered by metered-dose inhalers (MDIs) and the risk of hospital admission for a subsequent acute coronary event.[91] In comparison with patients who had not filled a β_2-agonist prescription during the 90 days prior to their index date, those who had received a β_2-agonist MDI canister were at greater risk of an acute coronary syndrome. This risk increased in a dose-dependent fashion. Of the 6463 patients for whom the authors had complete information on

covariates, the adjusted odds ratios (ORs) for acute coronary syndrome associated with having received MDI canisters were: 1.38 (95% CI 0.86, 2.23) for one to two canisters, 1.58 (95% CI 1.01, 2.46) for three to five canisters, and 1.93 (95% CI 1.23, 3.03) for six or more canisters. The increased risk of an acute coronary syndrome persisted after adjusting for age and cardiovascular risk factors, including hypertension, diabetes mellitus and smoking history.

According to Au et al.,[35] possible explanations for these findings include the fact that β_2-agonists prescribed for obstructive lung disease may precipitate myocardial ischaemia and infarction as a direct adverse effect. Also, β_2-agonists prescribed for airflow obstruction may cause hypoxaemia by increasing ventilation/perfusion heterogeneity, and thereby precipitate myocardial infarction. Finally, β_2-agonists given for airflow limitation or nonspecific chest symptoms may have precipitated a dysrhythmia, leading to myocardial infarction. The noncausal associations include β_2-agonists prescribed for nonspecific respiratory symptoms or chest discomfort that represents undiagnosed angina, which is a major risk factor for myocardial infarction. In addition, it is possible that β_2-agonists were prescribed for airflow obstruction and, despite treatment, the airflow obstruction caused hypoxaemia and precipitated myocardial infarction. Finally, β_2-agonists may be prescribed for a respiratory illness that is itself associated with an increased risk of myocardial infarction.[92]

There is also another possible explanation. It has been suggested that the β_1-adrenoceptor may play an important role in the pathogenesis of myocardial infarction.[93] Occupancy of β_1-adrenoceptors is a possible cause of the adverse effects of β_2-agonists, particularly at high dosages.[94] The naturally occurring Arg389Gly polymorphism of the β_1-adrenoceptor, which results in an increased response to agonist stimulation,[95] has been documented to be associated with an increased risk of acute myocardial infarction.[96] Unfortunately, no study has explored whether there is a link between an increased risk of an acute coronary syndrome, use of β_2-agonists, and the Arg389Gly polymorphism.

However, some studies have discounted the possibility that inhaled β_2-agonists induce myocardial infarction. Rossinen et al.,[97] performed a trial of the influence of inhaled salbutamol on myocardial ischaemia, arrhythmias and heart rate variability, as assessed by Holter monitoring, in 24 patients with coronary artery disease and clinically stable asthma or COPD; they observed that myocardial ischaemia, heart rate variability and ventricular arrhythmias remained unaltered with doses of salbutamol of up to 5mg.

The study by Suissa et al.[98] provides more solid documentation of the lack of a link between treatment with β_2-agonists and the occurrence of myocardial infarction. These authors, using the Saskatchewan Health Services databases, examined a population-based cohort of all patients aged over 55 years who were newly diagnosed with COPD, and found that short-acting β_2-agonists, in any form, did not increase the risk of acute myocardial infarction, although there was a trend towards a small increase in risk of myocardial infarction of 11% for every ten canisters dispensed within the previous year for frequent or high-dose users of β_2-agonists. First-time use, in particular, also did not increase the risk of myocardial infarction (figure 4). Suissa et al.[98] believe the more plausible explanation for the increased risk observed by Au et al.[35] soon after one-time use of β_2-agonists is misdiagnosis of angina or other respiratory symptoms associated with an imminent myocardial infarction as asthma or COPD. The isolated prescription of an inhaled β_2-agonist, interpreted as 'first-time use', was probably prompted by such symptoms in a patient who did not have asthma or COPD. On the contrary, the small increase in risk of myocardial infarction that the authors recorded in patients with greater utilisation of these medications can probably be justified by the fact that these patients had more severe COPD with more profound airflow limitation, which is itself an explanation for the increased risk.[99]

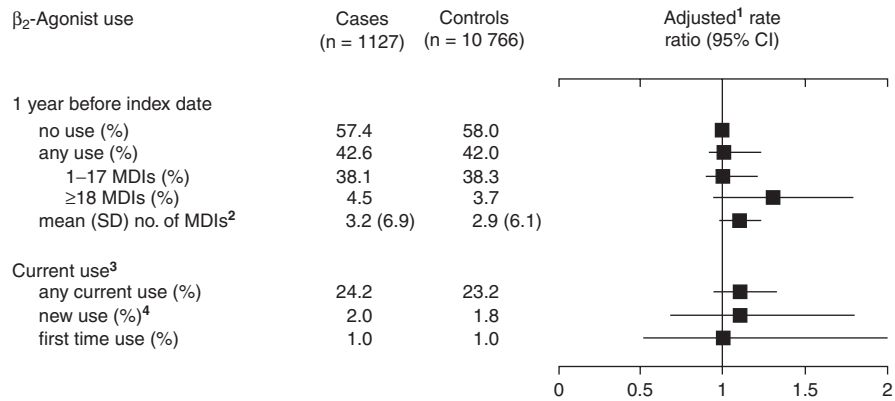

Fig. 4. Adjusted rate ratio of fatal and non-fatal acute myocardial infarction for inhaled β2-adrenoceptor agonist (β2-agonist) use during the year before the index date.[98] **1** Adjusted (after age matching) for sex, number of prescriptions for oral corticosteroids, nasal corticosteroids, inhaled corticosteroids, oral β2-agonist, nebulised β2-agonist and xanthines in the year before the index date, and presence of cardiovascular risk factors (angina pectoris, hypertension, congestive heart failure, arrhythmia, hyperlipidaemia and diabetes mellitus) in the year before the index date. **2** Rate ratio per additional ten metered-dose inhalers (MDIs) of inhaled β2-agonist. **3** Use of inhaled β2-agonist in the 2 months before the index date. **4** Current use of inhaled β2-agonist with no other β2-agonist use of any form during the year before the index date.

2.3 Heart Failure

Some reports suggest the presence of an association between β2-agonists and the risk of chronic heart failure (CHF).[36,100] The Washington, DC, Dilated Cardiomyopathy Study compared 129 patients newly diagnosed with idiopathic dilated cardiomyopathy and 258 randomly dialed neighbourhood controls.[36] They demonstrated an association between idiopathic dilated cardiomyopathy and a history of emphysema or chronic bronchitis (OR 4.4; 95% CI 1.6, 12.4), asthma (OR 1.9; 95% CI 0.9, 4.2), use of oral β2-agonists (OR 3.4; 95% CI 1.1, 11), and use of β2-agonist inhalers or nebulisation (OR 3.2; 95% CI 1.4, 7.1). A total of 20% of the cases had a reported history of β2-agonist inhaler use compared with 6.7% of the controls. More recently, the ACQUIP (Ambulatory Care Quality Improvement Project)[98] found no association between the use of inhaled β2-agonists and the risk of heart failure (1–2 canisters per month, OR 1.3 [95% CI 0.9, 1.8], ≥3 canisters per month, 1.1 [95% CI 0.8, 1.6]). However, among the cohort with a history of CHF, there appeared to be a dose-response association between the amount of inhaled β2-agonists and the risk of hospitalisation for CHF (1–2 canisters per month, adjusted OR 1.8 [95% CI 1.1, 3], ≥3 canisters per month, adjusted OR 2.1 [95% CI 1.2, 3.8]). The increase in risk among patients with existing CHF was independent of their history of COPD, corticosteroid use, β-adrenoceptor antagonist (β-blocker) use, ACE inhibitor use, myocardial ischaemia and cardiovascular risk factors. This is an important finding because many elderly patients with underlying cardiovascular diseases such as CHF have concomitant obstructive airway disease. The ABCHF (Asthma, β-Agonists, and the Development of Congestive Heart Failure) Study[101] also failed to confirm an independent association between asthma, β2-agonist use and the later development of idiopathic dilated cardiomyopathy (figure 5). Although heart failure and asthma can occur simultaneously, wheezing resulting from pulmonary congestion, or 'cardiac asthma', was the most likely cause of nonrandom misclassification bias in the determination of asthma in prior studies. However, there appears to be a link between familial idiopathic dilated cardiomyopathy and asthma, warranting further study.

The observation that β2-agonists may exacerbate heart failure is supported by physiological observations. β1-Adrenoceptors are down-regulated and desensitised among patients with left ventricular

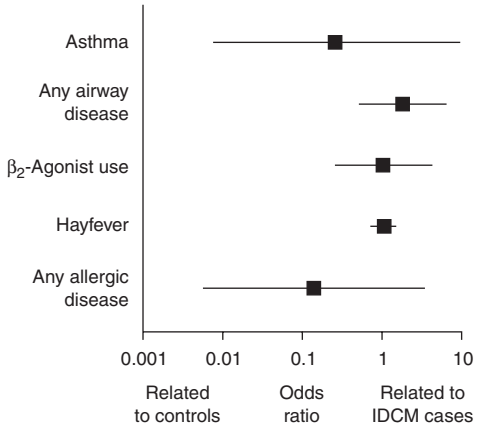

Fig. 5. Selected multivariate relative odds of various asthma and allergic exposures among cases and controls. With adjustment for confounders, multivariate analysis revealed no significant relations between asthma, airway disease β_2-adrenoceptor agonist (β_2-agonist) exposure and duration, and the later development of idiopathic dilated cardiomyopathy (IDCM) [reproduced from Sengstock et al.,[101] © 2002, with permission from Elsevier].

systolic dysfunction, and β_2-adrenoceptors, although desensitised, are found in normal numbers and represent a higher proportion of total β-adrenoceptors.[102,103] Among patients with heart failure, β_2-agonists augment cardiac function but, with regular exposure to β_2-agonists, myocardial β_2-adrenoceptors become desensitised and down-regulated.[104,105] Moreover, long-term β-adrenoceptor stimulation elevates G_i expression.[15] The coupling of β_2-adrenoceptors to G_i proteins negatively regulates the G_s-mediated contractile response in the heart of many mammalian species.[15] Recently, the Ile164 polymorphism of the β_2-adrenoceptor, which leads to a dysfunctional receptor, has been shown to be associated with decreased exercise tolerance and a 5-fold increased risk of death among patients with CHF.[106-109] The possibility that long-term β-adrenergic stimulation induces myocardial, but not systemic, expression of tumour necrosis factor-α, interleukin (IL)-1β and IL-6[110] is another important finding. In fact, evidence suggests that proinflammatory cytokines are capable of modulating cardiovascular function by a variety of mechanisms, including promotion of left ventricular remodelling,[111] induction of contractile dysfunction[112] and uncoupling of myocardial β-adrenoceptors.[113]

Despite the possibility that β_2-agonists might exacerbate heart failure, Ng et al.[114] explored whether long-term inhaled salmeterol therapy (100μg twice daily) improved pulmonary function, without augmentation of neurohormonal systems or ventricular ectopy, in symptomatic heart failure patients with a left ventricular ejection fraction of <40%. Salmeterol significantly increased the mean rate-pressure product by 5% (salmeterol 8878 ± 1560 vs placebo 8414 ± 1440 bpm × mm Hg; $p = 0.04$) and the forced expiratory volume in 1 second, without having measurable effects on neuroactivation or ventricular ectopy.

3. Asthma and Chronic Obstructive Pulmonary Disease as Confounding Factors

Unfortunately, both asthma and COPD amplify the impact of β_2-agonists on the heart and are confounding factors when the impact of these agents on the heart is evaluated.

Hypoxia caused by respiratory insufficiency is a central problem in asthmatic patients. The whole patient is affected by the sequelae of hypoxia, the most prominent organs being the heart and the brain.[115] In the heart, arrhythmias arise because of metabolic deficiencies; these are interpreted as originating directly from the excitatory muscle tissue, which is sensitive to acidosis. It has been documented that patients with a history of asthma are more prone to develop cardiac arrhythmias while receiving QTc interval-prolonging drugs such as β_2-agonists (adjusted OR 9.9; 95% CI 1, 100).[116] A study demonstrated an almost 2-fold greater prevalence of asthma among long QT syndrome-affected patients with respect to their family members who were either unaffected or had borderline QTc intervals (7% vs 4%; $p < 0.001$). The gradual increase in the occurrence of asthma with QTc prolongation raises a question about a possible genetic link between the two diseases. Furthermore, the presence of asthma as a long QT syndrome comorbidity is independently associated with an increased risk of cardiac events after adjustment for QTc interval duration, heart rate and sex. Asthma contributes to a

higher risk of cardiac events, even during early childhood (when asthma is usually clinically silent), and also before the initiation of β-mimetic therapy, indicating a possible predisposing genetic mechanism underlying the association between asthma and long QT syndrome.[117]

In patients with COPD, the activity of the cardiac sympathetic nerves may be affected by recurrent hypoxaemia, hypercapnia, changes in airway tone, increased intrathoracic pressure as a result of airway obstruction, and large fluctuations in heart rate and blood pressure due to increased respiratory effort.[116] The existence of left ventricle myocardial sympathetic nervous alterations as a result of generalised sympathetic autonomic nervous system overactivity has been suggested.[118] Moreover, ischaemic heart disease, right ventricular hypertrophy and arrhythmias are relatively common in patients with chronic symptoms of COPD.[119-121] Patients with hypoxaemic COPD, in particular, have been reported to have subclinical autonomic neuropathy associated with a prolonged QTc interval and an associated risk of ventricular arrhythmias.[121] It is evident that patients with COPD may be at increased risk of cardiovascular complications.

4. Conclusions

Large surveys have documented the safety of β2-agonists, particularly long-acting agents, at therapeutic dosages, and that the risk of cardiac adverse effects is usually related to abuse or use in clinical settings where there are possible contraindications to treatment. Despite this, the existence in the literature of reports on adverse cardiovascular events in patients with obstructive airway disease who are receiving β2-agonists must induce physicians to consider the possibility of this eventuality. The coexistence of β1- and β2-adrenoceptors in the heart clearly indicates that β2-agonists do have some effect on the heart, even when they are highly selective. This is of particular concern for those patients with underlying cardiac conditions.[42]

β2-Agonists are included in all guidelines for the treatment of asthma and COPD, as there is a solid body of evidence that supports their use. Nonetheless, many of the findings that we have described in this article raise the question of whether the use of β2-agonists is really appropriate in general, and in particular in patients with underlying cardiac conditions. It is our firm opinion that at the doses recommended for therapeutic use, β2-agonists can be safely used in patients without any underlying cardiac pathology.[85,122] However, in patients with cardiovascular disease, the prescription of an inhaled β-agonist must always be undertaken with caution as these agents may precipitate the concomitant cardiac disease.[35]

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