PAPERS AND SHORT REPORTS

Influence of intrinsic sympathomimetic activity on respiratory function during chronic β blockade: comparison of propranolol and pindolol

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Abstract

The long term effect of β blockers and the influence of intrinsic sympathomimetic activity on respiratory function were assessed in patients with chronic stable angina pectoris randomised to receive treatment with propranolol (n=21) or pindolol (n=19) for one year. Forced expiratory volume in one second (FEV_1) had fallen by a mean of 240 ml after one year ($p<0.001$) in those treated with propranolol compared with 120 ml in those treated with pindolol ($p<0.05$). The difference between the groups was significant ($p<0.01$). Vital capacity fell significantly only in those treated with propranolol ($p<0.05$ at one year). In those in whom the basal ratio of FEV_1 to forced vital capacity was low (<70%) propranolol, but not pindolol, caused a significant ($p<0.05$) fall in FEV_1 throughout treatment.

Long term administration of pindolol has a less adverse effect on respiratory function than propranolol, which results in a progressive deterioration in respiratory function over one year.

Introduction

β Blockers may have a deleterious effect on respiratory function owing to blockade of the β adrenoceptors in the lung, which are responsible for bronchomotor tone; this results in appreciable bronchoconstriction in susceptible subjects, such as those with chronic obstructive airways disease, in whom the use of β blockers may be restricted,[1,2] and patients with asthma.[2-4] Furthermore, acute bronchospasm may occur in some subjects with no history of asthma, chronic obstructive airways disease, or allergic disorders.[5,6] Some β blockers cause an increase in airways resistance in healthy subjects.[7] Using a body plethysmograph, MacDonald *et al* and McNeill and Ingram showed that a single dose of intravenous propranolol may increase airway resistance.[8,9]

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Propranolol, a non-selective β blocker without intrinsic sympathomimetic activity, is the β blocker most commonly incriminated as having such respiratory effects.[2-4] Few studies have reported the long term effect of propranolol on patients with non-asthmatic chronic obstructive airways disease, and the results have been conflicting.[10-12] Most controlled studies have been based on single doses of β blocker given either intravenously or orally.[13-15] Data on long term treatment have usually resulted from open, uncontrolled investigations,[16,17] and so its effect has not been established. β Blockers with intrinsic sympathomimetic activity are thought to have a less detrimental effect on ventilation compared with "pure" β blockers, such as propranolol. The role of intrinsic sympathomimetic activity in moderating bronchoconstriction induced by β blockers, however, is not clear.[18] We undertook this study to establish the effect of long term oral administration of β blockers on respiratory function in a group of patients with angina pectoris and to assess the potential benefits of intrinsic sympathomimetic activity.

Patients and methods

Forty consecutive men with chronic stable angina (New York Heart Association class II or III) were recruited to the study from a cardiac clinic. A diagnosis of reversible myocardial ischaemia was confirmed by exercise electrocardiography. Patients were excluded if they suffered from reversible airways obstruction, a known allergic disorder, diabetes mellitus, heart block, or renal failure. Before recruitment the patients either had been responding inadequately to treatment or had not been receiving any. All treatment was withdrawn over two weeks, and after a further two weeks without taking any drugs the patients were randomly allocated on a single blind basis to treatment with propranolol 40 mg thrice daily (n=21) or pindolol 2·5 mg thrice daily (n=19) for two weeks, the dosages increasing thereafter to 80 mg and 5 mg, respectively, thrice daily. The drugs were formulated as indistinguishable opaque gelatin capsules. Glyceryl trinitrate was the only other routine drug permitted throughout the study.

Respiratory function was assessed two, six, 12, 26, and 52 weeks after the start of treatment and results analysed without knowledge of the drug being taken. Airways diameter was estimated indirectly by measuring forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) with a Morgan rolling seal dry spirometer (model b), which has a reproducibility better than 2%; the resultant ratio of FEV_1: FVC was then

calculated. All measurements were taken after the patients had rested seated for three minutes after an overnight fast. Measurements were taken at 0930-1100, two to three hours after the last oral dose of β blocker, as this is the time when peak blood concentrations occur.[19] On each occasion the patient had been present in the laboratory for at least 45 minutes to allow for equilibration to occur. There is no consensus over the number of measurements of each variable that need be taken when measuring respiratory function.[20] In the present study we used the mean of three satisfactory attempts after a single training attempt, each attempt being separated by one minute. The spirometer was calibrated daily, before any measurement. As a dry spirometer was used the volumes indicated on the chart paper were corrected to standard temperature and pressure according to the ambient temperature.

Statistical analysis—For each variable changes within the groups were assessed by two way analysis of variance. If the F value obtained indicated a significant change post hoc comparisons were made using Student's paired *t* test and a Wilcoxon signed rank test (for non-normally distributed data), comparing values at two, six, 12, and 52 weeks with basal values. Differences between the groups were tested using both Student's unpaired *t* test and a Mann-Whitney test. The most conservative significance values from these tests are reported.

Results

The two groups of patients were similarly matched in terms of age, body weight, height, and mass index (table I). Table II shows the results of respiratory function tests. Basal respiratory function was similar in the two groups, although those taking propranolol had a slightly lower FEV_1 (NS).

TABLE I—*Characteristics of patients recorded at first hospital visit, before treatment. (Values expressed as means (SD) or as numbers (%) of patients)*

	Patients receiving pindolol (n=19)	Patients receiving propranolol (n=21)	p Value
Age (years)	54·1 (9·75)	52·8 (5·95)	NS
Quetelet index ($\times 10^3$) (kg/cm^2)	2·45 (0·30)	2·49 (0·29)	NS
Height (m)	1·75 (0·07)	1·74 (0·06)	NS
Weight (kg)	75·2 (9·96)	75·1 (10·42)	NS
Heart rate (beats/min)	68 (8·6)	71 (10·3)	NS
Systolic blood pressure (mm Hg)	128 (17·7)	134 (28·8)	NS
Diastolic blood pressure (mm Hg)	73 (13·9)	79 (15·0)	NS
No (%) of current smokers (≥ 10/day)	7 (37)	8 (38)	
No (%) of ex-smokers	8 (42)	5 (24)	
No (%) with previous myocardial infarction	6 (32)	6 (29)	

In those treated with pindolol mean FEV_1 had fallen by 120 ml after 52 weeks' treatment ($p<0·05$). When results were expressed as a percentage of the value predicted for age (using nomograms[21]) there was a highly significant fall in mean FEV_1, from 89·5% to 85·6% at 52 weeks ($p<0·01$). No significant changes occurred in other variables, although the ratio of FEV_1:FVC fell slightly, reflecting the fall in FEV_1.

In those treated with propranolol the fall in FEV_1 was significant at two weeks ($p<0·05$) and increased sequentially to a mean of 240 ml at 52 weeks ($p<0·001$). A similar significant reduction occurred when FEV_1 was expressed as a percentage of the predicted value. A significant fall in FVC occurred at 52 weeks ($p<0·05$), and although the ratio of FEV_1:FVC did not change this reflected similar decreases in FEV_1 and FVC. The difference in the mean fall in FEV_1 at 52 weeks achieved with pindolol compared with propranolol (127 *v* 241 ml) reached significance ($p<0·01$) (table III). Similarly, the fall in FVC in patients taking propranolol was significantly greater ($p<0·01$) at 26 and 52 weeks than that in patients taking pindolol, although the resultant change in FEV_1:FVC ratio was not significantly different.

Pindolol caused a significant reduction in FEV_1 and FEV_1:FVC at 52 weeks only when the basal value of FEV_1:FVC was 70% or more (table IV). Propranolol caused a similar reduction in FEV_1 regardless of whether the basal value was less or greater than 70%, although the reduction was more significant at 12 and 52 weeks in those with basal ratios of 70% or more.

TABLE III—*Mean reductions in FEV_1 compared with basal values*

	Weeks after start of treatment				
	2†	6†	12†	26†	52†
Pindolol	52	55	99	92	127*
Propranolol	134*	171*	211***	208**	241***

Difference within group: *$p<0·05$, **$p<0·01$, ***$p<0·001$. Difference between groups: †$p<0·01$.

Discussion

This study found a progressive deterioration in respiratory function during long term β blockade in patients with no history of reversible airways disease. This phenomenon was most pronounced with propranolol, which had a significantly greater effect on FEV_1 than pindolol. In addition, FVC became progressively smaller during treatment with propranolol, but did not change during treatment with pindolol. There was no significant difference in an individual patient's response to each β blocker according to basal values of FEV_1 and FVC, propranolol having a consistently detrimental effect while pindolol caused only small reductions in FEV_1 and FEV_1:FVC.

Although propranolol caused a progressive and highly significant reduction in FEV_1 (table III), it is not clear whether a reduction of 240 ml in FEV_1 (at 52 weeks) is clinically important as none of the patients reported increasing breathlessness or wheeze with this drug. It is also possible that the deterioration in respiratory function might progress beyond one year in a cumulative fashion, resulting in a worsening of symptoms. This effect of long term oral administration of propranolol in patients with chronic obstructive airways disease would probably result in symptomatic deterioration in pulmonary function in patients who did not initially have symptoms. Though the drug did not cause a rapid and dramatic clinical exacerbation in our patients, it did cause a definite and sustained increase in airways obstruction compared with pindolol.

The significantly greater deterioration in variables of respiratory function presumed to reflect changes in large airway calibre that we found with propranolol compared with an agent with intrinsic sympathomimetic activity has been mentioned previously.[22] Patakas

TABLE II—*Mean (SD) results of respiratory function tests*

	Basal	Weeks after start of treatment: 2	6	12	26	52
			Patients treated with pindolol			
FEV_1 (l)	3·16 (0·830)	3·11 (0·824)	3·11 (0·831)	3·06 (0·832)	3·07 (0·826)	3·04 (0·782)*
FEV_1 (% predicted)	89·5 (19·01)	87·5 (18·80)	87·7 (18·45)	86·4 (19·43)	86·8 (18·89)	85·6 (17·88)**
FVC (l)	4·6 (0·819)	4·6 (0·876)	4·66 (0·875)	4·59 (0·856)	4·6 (0·860)	4·6 (0·874)
FVC (% predicted)	100·7 (14·16)	99·5 (13·90)	101·7 (12·92)	100·3 (14·74)	100·5 (14·08)	100·5 (14·75)
FEV_1:FVC	68·1 (9·79)	67·6 (8·92)	67·2 (9·06)	67·0 (9·36)	66·9 (9·50)	66·7 (9·29)
			Patients treated with propranolol			
FEV_1 (l)	3·07 (0·585)	2·93 (0·590)*	2·9 (0·579)*	2·87 (0·579)***	2·86 (0·570)**	2·88 (0·612)***
FEV_1 (% predicted)	87·1 (14·84)	83·5 (14·40)	82·4 (14·98)**	81·6 (14·89) ***	81·6 (14·44) ***	80·6 (14·98) *
FVC (l)	4·42 (0·717)	4·37 (0·746)	4·38 (0·776)	4·31 (0·739)	4·27 (0·766)	4·23 (0·772)*
FVC (% predicted)	97·9 (14·10)	96·6 (14·20)	97·0 (14·78)	95·3 (14·31)	94·4 (13·41)	93·5 (13·58) *
FEV_1:FVC	67·1 (9·02)	67·1 (8·79)	67·0 (8·70)	66·9 (8·56)	67·0 (8·61)	66·8 (7·67)

FEV_1 = Forced expiratory volume in one second. FVC = Forced vital capacity. *$p<0·05$, **$p<0·01$, ***$p<0·001$ compared with basal values.

TABLE IV—*Mean (SD) results of respiratory function tests classified according to basal value of FEV_1:FVC*

		Basal	Weeks after start of treatment: 2	6	12	26	52
			Pindolol group				
FEV_1:FVC ≥70%	FEV_1 (l)	3·73 (0·56)	3·71 (0·57)	3·67 (0·63)	3·64 (0·66)	3·65 (0·55)	3·54 (0·58)*
	FEV_1 (% predicted)	101·4 (13·35)	99·9 (15·47)	98·6 (15·12)	98·0 (18·10)	98·1 (12·55)	95·3 (14·08)
	FEV_1:FVC	76·7 (3·62)	73·6 (4·22)	74·1 (3·92)	75·7 (4·11)	75·0 (3·31)	72·3 (2·78)*
FEV_1:FVC <70%	FEV_1 (l)	2·63 (0·662)	2·57 (0·620)	2·61 (0·665)	2·58 (0·619)	2·55 (0·677)	2·58 (0·663)
	FEV_1 (% predicted)	78·8 (17·19)	76·4 (14·24)	77·9 (15·87)	75·9 (14·43)	76·2 (15·93)	77·0 (16·94)
	FEV_1:FVC	60·4 (6·28)	61·1 (6·06)	59·4 (7·32)	58·6 (8·08)	59·6 (8·08)	59·4 (6·57)
			Propranolol group				
FEV_1:FVC ≥70%	FEV_1 (l)	3·35 (0·47)	3·19 (0·58) *	3·18 (0·52)*	3·13 (0·49)	3·21 (0·49)	3·14 (0·52)**
	FEV_1 (% predicted)	93·0 (10·70)	88·3 (12·70)*	88·6 (12·49)*	86·9 (12·49)**	89·3 (10·42)	87·8 (11·41)**
	FEV_1:FVC	75·1 (3·98)	71·8 (4·34)*	72·0 (5·73)*	72·1 (4·61)*	72·6 (4·96)	71·5 (5·02)
FEV_1:FVC <70%	FEV_1 (l)	2·82 (0·582)	2·71 (0·526)	2·63 (0·559)*	2·63 (0·567)*	2·54 (0·445)*	2·54 (0·564)*
	FEV_1 (% predicted)	81·6 (16·42)	79·2 (15·03)	76·7 (15·33)*	76·7 (16·19)*	74·7 (14·41)*	74·0 (15·25)*
	FEV_1:FVC	64·4 (5·16)	63·1 (7·99)	60·8 (6·01)*	61·5 (5·78)	62·8 (9·91)	62·5 (7·20)

FEV_1=Forced expiratory volume in one second. FVC=Forced vital capacity.
*p<0·05; **p<0·01 compared with basal values.

et al, however, when studying respiratory function after single oral doses of propranolol (40 mg) and pindolol (2·5 mg) in asthmatic patients, confirmed that propranolol has a bronchoconstrictive effect on large and small airways but found that pindolol, although it did not have a significant effect on large airway calibre, caused a significant bronchoconstriction of the small airways.[23] They suggested that pindolol remains potentially dangerous in asthmatic patients because of this effect on small airways.

Most previous studies have examined the effect of single oral or intravenous doses of β blockers, usually in patients with reversible airways obstruction. Studies evaluating the effect of β blockers on respiratory function in patients receiving long term treatment for hypertension or angina pectoris are rare. Several studies have examined exclusively non-selective agents without intrinsic sympathomimetic activity. Two such studies of intravenous propranolol found an increase in airways resistance after only a few minutes.[10,24] The consensus is that these agents result in a predictable deterioration in respiratory function in the short term.[25,26]

Several studies have evaluated the role of intrinsic sympathomimetic activity on respiratory function. Benson *et al* carried out an acute study in 12 asthmatic subjects who received placebo, propranolol (100 mg), pindolol (5 mg), acebutolol (300 mg), and atenolol (100 mg) and showed that propranolol caused the greatest reduction in FEV_1.[27] Others have confirmed the benefit of intrinsic sympathomimetic activity.[28] One disadvantage of agents with intrinsic sympathomimetic activity compared with cardioselective drugs was shown in a study of the effect of metoprolol and acebutolol on eight asthmatic subjects.[29] FEV_1 and peak expiratory flow rate were reduced significantly by both drugs, but after an infusion of terbutaline a dose dependent increase in the two variables occurred, although the increase was partly inhibited by acebutolol compared with atenolol. Thus if airways obstruction does occur it is less likely to be reversed by a β_2 agonist if the β blocker is not relatively β_1 selective.

Thus there is agreement that non-selective agents without intrinsic sympathomimetic activity cause potentially harmful changes in respiratory function in patients with asthma and possibly also in those with irreversible chronic obstructive airways disease and even healthy subjects. Cardioselectivity tends to reduce the bronchoconstrictive effect, as does intrinsic sympathomimetic activity.

The available evidence suggests that no β blocker is entirely safe in patients with chronic obstructive airways disease. If possible an alternative drug should first be considered. Bronchoconstriction after administration of a β blocker is most pronounced in those with reversible bronchial obstruction. β Blockers with intrinsic sympathomimetic activity or cardioselectivity have a less pronounced effect on pulmonary function and so should be preferred in cases in which a β blocker is thought desirable despite the presence of respiratory impairment.

Ideally, it would be advantageous to develop a β blocker with no adverse effects on respiratory function—that is, a completely cardioselective agent. This, however, would not be possible as it has been established that β_1 and β_2 receptors are not completely separated in different organs, as was postulated by Lands *et al*.[30]

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