β -Blocker Use in Heart Failure Patients with Airways Disease

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ABSTRACT

Background: β -Blockers are often withheld from patients with obstructive airways disease, especially those with reversible airways disease due to fear of inducing bronchospasm. We report our single center experience of cautiously treating such patients who have concomitant chronic heart failure (CHF).

Hypothesis: The use of cardioselective β -blockers under caution and specialist supervision may be tolerable in many CHF patients with obstructive airways disease, resulting in clinical improvement rather than detriment.

Methods: A retrospective case notes analysis was performed on CHF outpatients who had obstructive airways disease and been treated with β -blockers.

Results: A total of 43 patients were identified, with an average ejection fraction of 31.8%; 18 of these patients had fixed obstructive airways disease, 15 patients had reversible obstructive airways disease, 10 patients had a label of obstructive airways disease (but no supporting evidence for the diagnosis in the hospital notes). In all 3 groups, β -blockers had been initiated and maintained without any respiratory event over a median continuous exposure time of 135 days. Limitation of the dose was documented in only 2 patients because of worsening shortness of breath. New York Heart Association (NYHA) class significantly improved for the group with the use of these agents ($p = 0.003$).

Conclusion: A cautious approach (under specialist supervision) to β -blocker use in patients with heart failure and airways disease can result in successful treatment. The implications of withholding these agents may have more serious consequences than their administration.

Introduction

Considering all pharmacological treatments administered in the setting of chronic heart failure (CHF), β -blockade arguably confers unsurpassed prognostic benefit. The deleterious effects of sympathetic nervous system activity was recognized many years ago and in particular, elevated levels of circulating catecholamines were acknowledged to correlate strongly with adverse prognosis.¹ Moreover, elevated catecholamines have been demonstrated to induce apoptosis of cardiomyocytes,² cause myocardial anaerobic glycolysis and acidemia leading to impaired myocyte function,³ and significantly increase the risk of lethal arrhythmias.⁴ Ensuing randomized clinical trials assessing β -blockers in CHF proceeded to demonstrate exceptional mortality and morbidity reduction within relatively short time frames.^{5–9}

One of the continuing fears over prescribing β -blockers is in the setting of obstructive airways disease. Indeed, a background diagnosis of either chronic obstructive pulmonary disease (COPD) or bronchial asthma is a common reason for withholding such treatment.¹⁰ In the United Kingdom, the British National Formulary advises that β -blockers should not be given to patients with asthma or a history of bronchospasm. It does however state that in rare situations, where there is no alternative, a cardioselective β -blocker may be given under “extreme caution and under specialist supervision.” In the setting of CHF, our center considers

that the criteria of “no alternative” is fulfilled and proceeds with cautious treatment. This is on the presumption that withholding treatment may have more serious consequences than giving treatment. In this article, we reflect on our single center experience of β -blocker use in CHF patients who have concomitant obstructive airways disease.

Methods

A retrospective analysis of case notes was performed on patients who had attended the dedicated CHF outpatient department at a large regional cardiac center (Wythenshawe Hospital, Manchester, UK), at any time over an 18 month period (March 2007 to August 2008). Case notes were selected for detailed review if they fulfilled the basic criteria of (1) having a hospital records diagnosis of both chronic heart failure and obstructive airways disease (defined as COPD, COPD with reversibility, or bronchial asthma) and (2) having documentation of β -blocker prescription during our care. After identification of suitable patients, important data was extracted. This included the etiology of heart failure; left ventricular ejection fraction (LVEF) at diagnosis; type of obstructive airways disease; data supporting the diagnosis (including pulmonary function test results [PFTs], reversibility testing etc); type of β -blocker given; what dose of β -blocker had been achieved to date; continuous days demonstrable on β -blocker; New York Heart Association (NYHA) class before β -blocker and at 1,

3, and 6 months following β -blocker initiation; intolerance details; cardiovascular events detailed after initiation; and respiratory events detailed after initiation. All data was extracted and compiled by a cardiology registrar with heart failure clinic experience. To determine if NYHA class significantly changed after β -blocker use, we performed a repeated measures analysis. Statistical significance was considered if p values were <0.05 .

Results

Over the prespecified time period, 43 patients (mean age of 68.1 years, range, 52–78 years) were identified who had a confirmed diagnosis of both chronic heart failure and concomitant obstructive airways disease. In each patient, the diagnosis of CHF had been confirmed by a cardiologist. The average LVEF (measured by 2-D echocardiography, Simpson's biplane method) for the group was 31.8% (standard deviation [SD] ± 9.1). An ischemic etiology had been confirmed in 63.6% of the patients. Treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) was co-administered to 42 of the 43 patients (97.7%) during the study period. Diuretics were taken by 35 patients (81.4%) and aldosterone antagonists by 13 patients (30.2%).

For analysis, we separated patients into 3 respiratory diagnostic groups:

- (1) Group A—Confirmed fixed obstructive airways disease (defined as COPD confirmed by PFTs and without evidence of reversibility after nebulized salbutamol).
- (2) Group B—Confirmed reversible obstructive airways disease (defined as COPD confirmed by PFTs and with evidence of significant reversibility after nebulized salbutamol, or a confirmed respiratory expert diagnosis of bronchial asthma).
- (3) Group C—Patients labeled with obstructive airways disease, but with unknown PFTs/reversibility tests, or the diagnosis had not been made by a respiratory expert.

Chronic obstructive pulmonary disease was considered to be confirmed if the forced expiratory volume (FEV₁) was documented to be less than 70% of predicted. We followed the American Thoracic Society (ATS) and the Global initiative for Obstructive Lung Disease (GOLD) definitions of reversibility, being equivalent to an FEV₁ change $>12\%$ after bronchodilators.¹¹ Demographics for each group can be seen in the Table. In group A there were 18 patients, group B contained 15 patients, and in group C there were 10 patients.

For all patients, bisoprolol and nebivolol were the most commonly used β -blockers (given to 51.2% and 37.2%, respectively). The only other β -blocker prescribed was carvedilol used in 11.6%. In all cases, bisoprolol and nebivolol had been

Table 1. Demographics

	All Patients	Group A	Group B	Group C
Cohort size	43	18	15	10
Mean age (y)	68.1	70.1	70.2	63.9
Ischemic CHF etiology (%)	63.6%	55.6%	60.0%	90.0%
Mean LVEF	31.8%	32.5%	33.6%	27.8%
Bisoprolol treated	51.2%	44.4%	53.3%	60.0%
Nebivolol treated	37.2%	44.4%	33.3%	30.0%
Carvedilol treated	11.6%	11.2%	13.3%	10.0%
Median length of treatment exposure (in days)	135	136	125	174

Patient Demographics: Group A were patients with confirmed fixed chronic obstructive airways disease and no reversibility after inhaled salbutamol. Group B were patients with confirmed chronic obstructive airways disease and significant reversibility after inhaled salbutamol, or a diagnosis of asthma made by a respiratory expert. Group C were patients with a label of chronic obstructive airways disease but no supporting evidence for the diagnosis. Abbreviations: CHF, chronic heart failure; LVEF, left ventricular ejection fraction.

initiated at a dose of 1.25 mg daily, whereas carvedilol was initiated at a dose of 3.125 mg twice daily. No respiratory events, defined as hospital attendance for bronchospasm occurred in any patient over the selected time period. The calculated median continuous time exposure was 135 days (interquartile range [IQR] 257). Data was omitted in 14 patients, whom we could not be confident of overall time exposure (several were discharged from regular follow-up after establishing β -blockade treatment; several had also been taking β -blockers prior to their first attendance at our clinic for undetermined time periods).

At the time of our analysis, the current mean daily dose being given for each β -blocker (or the dose at discharge from clinic) was 4.8 mg for bisoprolol, 3.7 mg for nebivolol, and 21.25 mg for carvedilol. It should be stated that many patients were still likely to undergo future up titration, and therefore these do not represent maximum tolerated doses. Indeed, only 6 patients were documented to have reached their maximum tolerated doses and of these, only 2 were documented to have reached maximum tolerated doses because of a reported worsening of shortness of breath at higher doses. Interestingly, both of these patients had fixed airways obstruction with no evidence of reversibility on PFTs. The remaining 4 patients had relative bradycardia and systemic hypotension documented.

Finally we performed a repeated measures analysis to determine if there was any significant NYHA class change

Figure 1. A graph depicting the change in NYHA class following β -blocker treatment in patients with both obstructive airways disease and chronic heart failure. Abbreviation: NYHA, New York Heart Association.

documented within a 6 month period following β -blocker initiation. Patients were included in this analysis if they were initiated on therapy during the specified time period and had achieved at least 3 months follow-up ($n = 32$). There was a significant reduction in NYHA class demonstrated ($p = 0.003$, mean NYHA at baseline = 2.58, mean NYHA at follow-up (≥ 3 mo, ≤ 6 mo) = 2.08, Figure 1).

Discussion

Withholding β -blockers from patients with CHF is an extremely precarious situation, given the detrimental consequences of heightened adrenergic activity. Although many patients with obstructive airways disease are often excluded from β -blockade treatment due to fears of bronchospasm, it would appear that cardioselective agents can be tolerated by most of these patients, even those with documented reversible airways disease. Whilst supporting safety data of their use in this setting is in relatively short supply, it should be noted that the evidence for detrimental harm is far scarcer.

The evidence for β -blocker induced bronchospasm originates largely from case reports of propranolol use, which followed its introduction several decades ago.^{12,13} However since that time, alternative β -blockers have been developed with enhanced cardioselectivity. Agents with high affinity for β_1 adrenoreceptors include bisoprolol and nebivolol.¹⁴ Both of these agents are also confirmed to offer prognostic benefit to patients with CHF. A meta-analysis performed by the Cochrane group has assessed the safety of cardioselective β -blockers in mild to moderate reversible airways disease.¹⁵ Following the analysis of 29 available clinical trials, these agents were not found to cause adverse respiratory symptoms. After the first administered dose, a small (7%) reduction in FEV₁ was seen. However,

this was not associated with any change of symptoms and importantly, continuing therapy was not associated with a persistent reduction of FEV₁. Furthermore, a significant improvement in the response to inhaled salbutamol was seen with β -blocker treatment. This appears to have led to discussion on whether β -blockers could actually be beneficial for asthmatics.^{16,17} Nevertheless, much of this evidence does not appear to have been translated into clinical practice. Indeed, the recent ESC Heart Failure Task Force Guidelines have continued to state that a history of asthma should be regarded as a contraindication to β -blocker use.¹⁸ This might be a reflection on the fact that only short-term safety evidence is available for cardioselective β -blockers in reversible airways disease. The Cochrane meta-analysis for example, was only able to retrieve trial data of up to 1 month in treatment duration. Therefore, data supporting the long-term safety of cardioselective β -blocker use is lacking in the literature.

In this retrospective analysis, cardioselective β -blockers had all been started at the lowest dose (such as bisoprolol 1.25 mg daily or nebivolol 1.25 mg daily). Patients were typically maintained on this dose for a minimum period of 1 month, before up titrating carefully. We believe this cautious approach may be vital in ensuring both success and safety. Overall, given the fact that β -blockers offer CHF patients substantial prognostic benefit; we would extend a recommendation to carefully consider their use in those with concomitant obstructive airways disease. Outside of CHF, β -blockers have less robust evidence for prognostic benefit (including ischemic heart disease and hypertension). An argument may legitimately exist therefore to seek alternatives in these situations.

It should be highlighted, that no patients in this study had an FEV₁ of less than 30% of predicted values. Therefore severe obstructive airways disease patients were not represented. Physicians should nevertheless acknowledge that many treatments in cardiovascular medicine carry a potential adverse risk to the patient. This usually tends to be the case in high risk situations, to name but a few: thrombolysis in acute myocardial infarction (risk of intracerebral hemorrhage); inotrope support during cardiogenic shock (risk of ventricular arrhythmias); cardiac resynchronization therapy for severe heart failure (risk of cardiac tamponade, coronary sinus perforation). It might still prove to be the case that widespread use of β -blockers in CHF and reversible airways disease could result in occasional adverse respiratory events. However, one would expect from available data that this problem is likely to occur in a minority. Therefore we would still advocate, with the current evidence, that β -blockers should at least be offered to these patients, after a full explanation of benefits vs potential risks.

Finally we should comment that despite their statement on asthma, the current 2008 ESC guidelines do in fact support β -blocker use in those with a diagnosis of COPD.

Perhaps future guidance may extend to a specific mention of those with reversible airways disease.

Limitations

This was a retrospective case analysis and therefore there are limitations connected with this methodology. Clearly, it would be advantageous to demonstrate the safety of β -blockers in this setting through the careful planning of a placebo controlled randomized control trial. However, given that a large group of patients would have β -blockers withheld in such a study, this would raise several concerns. The determination of safety therefore has relied exclusively on the documentation within a patient's hospital notes. In addition, information was missing for several patients on parameters such as days of exposure to treatment. However, we believe that collectively these limitations do not detract from the value of the article to the literature for which there is very little data available to current date. Our primary aim was to reflect on our real life experience of challenging the longstanding resistance to β -blocker treatment in this frequently encountered situation.

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