Beta blockers in heart failure with preserved ejection fraction and reactive airway disease

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Introduction

In the United States alone, Heart Failure with Preserved Ejection Fraction (HFpEF) accounts for nearly five-hundred thousand admissions annually [1]. Despite medical therapy, patients with HFpEF have an estimated survival at one, three, and five years of 82%, 48%, and 33% respectively [2]. As such, reducing morbidity and mortality in these patients has become increasingly important [3,4]. Guideline recommendations suggest pharmacological strategies used in heart failure with a reduced ejection fraction (HFrEF) may benefit those with a preserved ejection fraction [4]. However, most recommendations rely heavily on expert opinion as limited data exists to direct management of HFpEF [4].

Beta blockers are a main stay in the treatment of HFrEF due to an abundance of evidence supporting reduced hospitalizations and mortality [5-7]. However, use of beta blockers in patients with HFpEF have not been proven in clinical evaluations. Rather, large trials supporting beta blocker usage may have major limitations restricting their application to practice [8,9]. Less robust data from observational and retrospective studies have demonstrated conflicting results further clouding the role of beta blockers in the preserved ejection fraction population [10-12]. Despite a lack of strong clinical data, guideline recommendations support beta blocker usage in patients with HFpEF and no contraindications for use [4].

The clinical decision to use beta blockers must weigh the benefits against the risks of adverse effects such as hypotension, atrioventricular block, and respiratory complications. In patients with no underlying respiratory disease, beta blockers rarely exhibit clinical relevant respiratory effects [13]. However, in patients with pulmonary conditions the risks of beta-induced respiratory dysfunction is higher due to abnormal pathology and predisposition for complications [14]. Therefore, in patients with respiratory disease the risks for respiratory decompensation must be weighed against the potential benefit in HFpEF. The following clinical case and review of the literature describes a patient with concomitant HFpEF and reactive airway disease.

Case

A 35 year old African American male presented with hypercapnic hypoxemic respiratory failure and bilateral lower extremity edema resulting in admission to internal medicine services. The patient’s past medical history was significant for HEpEF, hypertension, hyperlipidemia, type 2 diabetes mellitus and reactive airway disease. Approximately 3 months prior to current hospital admission the patient had an echocardiogram showing an ejection fraction of 55% and grade I diastolic dysfunction. Home medications included aspirin 81 mg daily, atenolol 25 mg daily, fosinopril 10 mg daily, amlodipine 5 mg daily, furosemide 40 mg daily, and pravastatin 20 mg daily. All home medications were continued as an inpatient except atenolol (changed to metoprolol succinate 25 mg daily) and furosemide (dose increased to 60 mg IV twice daily).

Physical exam at presentation revealed expiratory wheezes and 4+ pitting edema bilaterally in the lower extremities but was otherwise within normal limits. On admission, the patient’s vital signs were as follows: blood pressure 163/70 mmHg, heart rate 84 beats per minute, and respiratory rate 23 breaths per minute. His serum chemistry showed pO2 42 mmHg, HCO3 43 mEq/L. A chest x-ray in the emergency department showed cardiomegaly and early changes indicative of pulmonary edema. During the patient’s hospital course, amlodipine was discontinued due to its potential role in the peripheral edema and the fosinopril was up-titrated for blood pressure control. Intravenous furosemide 60 mg was used twice daily for 2 days with an appropriate diuretic response. Upon improvement in peripheral edema to 1+ bilaterally (patient’s baseline) furosemide was changed to 40 mg by mouth daily. A repeat echocardiogram showed no changes from the previous study completed three months prior except for the presence of a trivial pericardial effusion.

Pulmonary services were consulted and recommended discontinuing metoprolol due to worsening respiratory symptoms and scheduling nebulizer treatments with albuterol and ipratropium every 4 hours. The patient’s symptoms and ABG showed marked improvement over the next 24 hours and the patient was restarted on metoprolol for his heart failure. His breathing continued to improve over the next

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2 days resulting in discharge on nebulized albuterol solution with scheduled follow up with pulmonary and cardiology services.

Discussion

Although the patient case described is not an incredibly rare incident, it does describe a clinical dilemma for the management of patients with HFPpEF and reactive airway disease. The risks of respiratory decompensation must be weighed against the perceived benefit of beta blockade in this subset of heart failure patients. Additional considerations such as beta blocker selectivity, choice of respiratory therapy, and severity of cardiopulmonary disease can help guide clinical decision making.

The use of beta blockers are endorsed by current guidelines for use in HFPpEF patients despite limited data from randomized, controlled trials [4]. The recommendations are however, based highly on expert opinion and have a low level of evidence. It must be also be noted that while recommendations support use of beta blockers, its role is as an antihypertensive agent as opposed to their potential role in reducing morbidity and mortality [15]. In patients with a preserved ejection fraction and hypertrophic cardiomyopathy, a subset of HFPpEF, guideline recommendations more strongly support beta blocker use [15]. However, the evidence for use in hypertrophic cardiomyopathy focuses on symptomatic improvement, especially with obstructive pathophysiology, rather than a mortality benefit [15].

No large, randomized, controlled, clinical trials have set out to evaluate the benefit of beta blockers in HFPpEF. However, a pre-specified subgroup analysis of the SENIORS trial assessed the benefit of nebivolol in HFPpEF [8]. No difference was observed between nebivolol and placebo for the primary outcome of all-cause mortality or hospitalization for a cardiovascular reason (HR 0.81, 95%CI:0.63-1.04) [8]. While no benefit was seen, the SENIORS study is the largest trial that has evaluated beta blockers in HFPpEF. The limited difference in adverse effects and non-statistically significant reduction in cardiovascular outcomes compared with placebo suggest beta blockade may be a reasonable therapeutic option in heart failure patients with a preserved ejection fraction [8].

In the absence of other large clinical trials evaluating beta blocker therapy in HFPpEF, observational data has been analyzed from a large Medicare database of patients hospitalized for heart failure [9]. Out of 24,689 total heart failure patients, 4,153 patients had a preserved ejection fraction. Beta blocker therapy at discharge was associated with improved survival at 1 year (HR 0.65, 95%CI:0.57-0.73). However, after adjustment for baseline characteristics there was no significant difference in mortality or rehospitalization for heart failure. Analyses from smaller cohort data have failed to confirm these findings. Rather, studies described by Nevzorov et al and El-Reai et al suggest there may be reduced hospitalizations and all-cause mortality associated with beta blocker use irrespective of ejection fraction [11,12]. Nevzorov et al also concluded that there was an association of reduced death (p=0.001), hospitalization (p=0.016), or a combination of both (p=0.009), in patients with HFPpEF. Interestingly, a significant association was found in patients receiving traditional beta blockers for heart failure (metoprolol, carvediolol, bisoprolol) (p=0.014) as well as those receiving therapy with any beta blocker (p=0.009). This beneficial association from the smaller cohort evaluations favor the use of beta blockers in HFPpEF. However, these findings were not consistent in all studies and the possible benefits must be weighed against the potential risks of using beta blockers.

An important risk to consider is the potential for respiratory compromise with blocking beta receptors in the pulmonary system. Beta blockers are generally considered to have minimal respiratory side effects in patients with no underlying pulmonary disease [13]. However, in patients such as the one described in the patient case, reactive airway disease may predispose patients to respiratory complications [14]. Cardiovascular selectivity of the beta-blockers used in this population is an incredible important consideration. Indeed, the distribution of beta receptors fluctuate by location in the pulmonary tree. The alveoli, containing 90% of the pulmonary beta receptors, are primarily beta-2 whereas the larger airways are mostly beta-1 [14]. As such, beta-1 selective medications such as metoprolol and bisoprolol have lower risk of respiratory effects [14].

A recent meta-analysis including 32 randomized trials evaluated the risk for respiratory exacerbation with beta blocker use in reactive airway disease [14]. A profound reduction in respiratory function was observed with nonselective beta blockers [14]. Beta-1 selective drugs were also found to have a statistically significant risk of respiratory effects, though it was much less clinically relevant than the risk with nonselective beta blockers [14]. In addition, the presence of beta blockers attenuated patient’s response to beta-2 bronchodilators with a two-fold higher effect with nonselective beta blockers than with beta-1 selective ones [14]. The risks described in the meta-analysis suggest that beta 1-selective agents should be used with caution in patients with reactive airway disease.

Conclusion

Evaluations of beta-blockers in HFPpEF have produced conflicting results making the role in therapy unclear. Nevertheless, guidelines endorse the use of beta blockers due to potential benefit especially in patients with low risk of adverse effects. Respiratory depression, a concerning adverse effect, is not commonly experienced unless the patient has underlying reactive airway disease. The respiratory risks in patients with reactive airway disease are more profound with nonselective beta blockers but may still be clinically relevant with beta-1 selective drugs. Practitioners should weight the risks and benefits of beta blocker use to make individualized clinical decisions for patients with HFPpEF and reactive airway disease.

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