Effects of Nebivolol Therapy on Angina, Health Related Quality of Life, and Cardiopulmonary Function in Women with Microvascular Angina

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Abstract

Background: Identifying therapeutic agents to reduce the morbidity and mortality and symptom burden of women with microvascular angina (MVA) remains a priority. The aim of this study was to investigate the effects of nebivolol, a cardioselective beta-blocker with nitric oxide mediated vasodilatory effects, on angina, health-related quality of life, and cardiopulmonary function of women with MVA.

Methods and Results: In this study, women with MVA underwent cardiopulmonary exercise testing and completed the Seattle Angina Questionnaire and Short-Form 36 version 2. Subjects were then started on nebivolol (5-10 mg daily) and repeat testing performed at 12 weeks. Anginal stability improved significantly (29.2 ± 18.8 vs. 83.3 ± 25.8, p<0.034). There was also a trend towards improvement in anginal frequency and quality of life. Despite expected lower peak heart rate (pHR) (145 ± 17 vs. 119 ± 11 beats/min, p<0.001, -18%) the peak O₂ pulse was significantly higher (11.0 ± 2.5 vs. 13.1 ± 2.3 mL/beat, p<0.01, +20%) and the peak oxygen consumption (peak VO₂) was unchanged (22.9 ± 6.3 vs. 22.0 ± 4.8 mL/kg/min, p=0.41).

Conclusions: Nebivolol improved anginal stability without impairment in peak VO₂. Further research is needed to identify the mechanism by which the nitric oxide mediated vasodilatory effects of nebivolol relate to enhanced peak O₂ pulse and whether this finding reflects improved stroke volume or peripheral oxygen extraction.

Keywords

Microvascular angina; Nebivolol; Cardiopulmonary exercise testing

Introduction

Although women have less obstructive coronary artery disease (CAD) then men, women continue to have a greater burden of symptoms, more ischemia and a higher rate of adverse outcomes compared to age-matched male counterparts [1]. This has led to the recognition of microvascular angina (MVA) as an alternative to the flow limiting atherosclerotic CAD mechanism [2]. Identifying effective therapeutic agents to improve the morbidity and mortality of women suffering from MVA remains a priority. Nebivolol has antioxidant and vasodilator properties via its effect on nitric oxide bioactivity. Its subsequent endothelial effects make it a potential therapeutic agent for women with MVA.

The aim of this study was to investigate the effects of nebivolol on angina, the health-related quality of life, and cardiopulmonary function of women with MVA.

Methods

This was a 12-week, open-label, interventional study conducted at the Massachusetts General Hospital. The Partners Human Research Committee approved this project and all participants provided written informed consent.

Women between the ages of 40-80 years with coronary microvascular dysfunction were included in the study. Men were excluded from this study, as primary coronary microvascular dysfunction primarily occurs in women, with more data in this population subset required. The diagnosis of coronary microvascular dysfunction was determined by the presence of (a) rest and/or exertional chest tightness, (b) a history of either an elevated troponin level, positive stress test (electrocardiogram criteria or imaging) or a diagnosis of microvascular angina by their primary cardiologist, and (c) non-obstructive CAD (<50% epicardial obstruction) by either diagnostic catheterization with coronary angiography or computed tomography angiography. Exclusion criteria for the study included intolerance to beta-blocker therapy, the inability to exercise, left ventricular systolic function <40%, Prinzmetal's angina, myocardial bridging, decompenesated heart failure,
severe hepatic impairment, significant renal disease or neurologic disease, and current malignancy. Women on hormone replacement therapy or of child-bearing age not on an adequate birth control method were also excluded from the study.

Enrolled subjects underwent a washout period during which beta-blockers, ranolazine, and long-acting nitrates were discontinued. A standardized regimen of amiodipine (2.5-10 mg daily) plus PRN sublingual nitrates was then initiated. After weeks on the standardized regimen, subjects underwent baseline testing which included cardiopulmonary exercise testing (CPET) as well as completion of the Seattle Angina Questionnaire (SAQ) and the Short-Form 36 Version 2 (SF-36v2) health survey. Subjects were then started on open label nebivolol (5-10 mg daily) which was uptitrated as tolerated. After weeks of treatment, repeat testing was performed on nebivolol. Patients were monitored for potential nebivolol adverse reactions including: bradycardia, presyncope and fatigue.

Continuous variables were reported as the mean ± standard deviation (SD) and categorical data presented as frequency and percentage of the sample. Comparisons between baseline and post-treatment SAQ scores, SF-36v2 scores, and CPET variables were performed using a paired t-test for normally distributed variables or a Wilcoxon signed-rank test for non-normally distributed variables. Normality was defined by the Shapiro-Wilk test. For categorical variables, data were compared using a chi-squared test. All statistical tests were two-sided and p-values <0.05 were considered significant.

Results

Twelve women were enrolled in the study. Seven patients completed both baseline and post-treatment CPET testing of which one patient did not complete post-treatment study questionnaires. The mean age was 61.6 ± 10.0 years and 85.7% were postmenopausal. The most common cardiovascular risk factors were postmenopausal state, hypertension, family history of premature CAD, followed by tobacco use, dyslipidemia, and obesity. Of the patients who completed the study, all underwent cardiac catheterization of which 5 patients had normal epicardial coronary arteries and 2 patients were found to have non-obstructive coronary artery disease. A total of 2 patients had undergone percutaneous coronary intervention but had patent epicardial coronary arteries at time of study inclusion. One patient had a history of a previous myocardial infarction with preserved ejection fraction. Reasons for which enrolled patients were withdrawn from the study included the inability to be weaned off baseline medications in preparation to start the standardized regimen (n=1), markedly abnormal baseline CPET testing warranting further care by primary cardiologist (n=1), the inability to complete CPET testing by the study close out date (n=1), and patient personal preference (n=2). There were no serious adverse events during the duration of the study.

SAQ results are presented in Table 1. After weeks of treatment, SAQ anginal stability scores were significantly higher (29.2 ± 18.8 vs. 83.3 ± 25.8, p=0.034). There was also a trend towards a higher (improved) anginal frequency score (7.0 ± 15.5 vs. 80.0 ± 20.0, p=0.076) as well as quality of life score (51.4 ± 23.2 vs. 83.3 ± 25.8, p=0.076) as well as post-treatment scores for all health related quality of life domains of the SF-36v2 survey.

Key CPET finding are presented in Table 2. After weeks of treatment with nebivolol, peak heart rate (pHR) was significantly lower (145 ± 17 vs. 119 ± 11 beats/min, p<0.01, -18%) as well as resting heart rate (83 ± 16 vs. 66 ± 9 beats/min, p<0.001, -20%). Peak O₂ pulse was significantly higher (11.0 ± 2.5 vs. 13.1 ± 2.3 mL/beat, p<0.01, +20%) and peak oxygen consumption (peak VO₂) was unchanged (22.9 ± 6.3 vs. 22.0 ± 4.8 mL/kg/min, p=0.41, -3.9%). The changes observed in all other CPET variables including exercise duration were not statistically significant.

Discussion

To the best of our knowledge, this is the first study to examine the effects of nebivolol therapy on angina, the health-related quality of life, and cardiopulmonary function in women with MVA. The findings from this study demonstrated that after treatment with nebivolol, angina stability was significantly improved in women with MVA. Furthermore, there was a trend towards improvement in anginal frequency and quality of life.

We also examined the impact of nebivolol on cardiopulmonary function in women with MVA by performing CPET testing at baseline followed by post-treatment testing. As the subjects, did not undergo any exercise training (endurance or strength) as part of the study protocol, any improvement in peak VO₂ was not expected. Nebivolol treatment did result in a significant reduction in pHR consistent with beta-1 adrenergic receptor blockade. However, surprisingly there was not an associated impairment in peak VO₂ as has been previously reported with other beta-blockers, primarily non-cardioselective beta-blockers [4]. The increase in peak O₂ pulse observed post-treatment as compared to baseline suggests that peak VO₂ was preserved either by improvement of cardiac stroke volume or enhancement of peripheral oxygen extraction.

Similarly, to many of the other published studies assessing the efficacy of therapeutic agents in MVA patients, the primary limitations of this study was the small sample size as well as the relatively short term follow-up period. The main recruitment difficulty encountered in this study was successfully enrolling eligible patients willing to undergo a washout period followed by a standardized medication regimen. Another barrier to recruitment includes the reduced awareness for this disorder by physicians in general, thereby reducing the pool of eligible patients. Lastly, patients themselves are often resistant to treatment as women are often too engrossed and occupied as the primary caregiver for their households to manage...
impulse, is either improvement or placebo-controlled. However, despite its limitations, to the best of our knowledge this study is the first to date to examine the effects of nebivolol therapy on angina, health-related quality of life, and cardiopulmonary function in women with MVA. Furthermore, given the current limited understanding of MVA and scariness of targeted, effective therapies this study provides valuable insight to inform future investigations.

The treatment of MVA remains largely empirical due to limited outcomes data regarding symptom alleviation as well as major adverse cardiac outcomes reduction. Women with MVA continue to report more frequent angina and worse quality of life. They frequently seek medical attention for the evaluation of cardiovascular symptoms including chest pain and shortness of breath. Consequently, these women incur greater healthcare costs, with more office visits, hospitalizations, and adverse cardiovascular events. In fact, more than one half of women without obstructive CAD continue to have ischemic symptoms that lead to further consumption of resources, most often because of diagnostic uncertainty [5-8].

In the absence of robust outcomes data to drive the care of women with MVA, various treatment strategies have been utilized by healthcare professionals. In addition to focusing on the management of traditional cardiovascular risk factors via lifestyle modifications and pharmacotherapy, some physicians treat women with MVA as they would treat patients with known obstructive CAD, while some, in the setting of angiographically normal appearing coronary arteries and persistent angina, simply opt for reassurance. Nevertheless, given that women with MVA continue to have higher morbidity and mortality, as well as increased resource consumption, there is a widely recognized need for effective therapeutic agents to alleviate symptoms, improve quality of life, decrease resource consumption, and ultimately reduce morbidity and mortality.

To date, there have not been any interventions that have demonstrated a reduction in adverse cardiac events in women with signs and symptoms of cardiac ischemia and non-obstructive CAD. However, there have been several studies that have demonstrated an improvement in symptomatology with the use of various different antianginal therapies, treatments that effect pain perception, and finally agents that directly target underlying microvascular dysfunction [9]. Although many conventional therapies have been tested, it remains to be determined which is the most effective agent in this patient population in terms of ischemic symptom burden, quality of life, healthcare related costs, and long-term cardiovascular outcomes.

Although several different pathogenic mechanisms have been described in MVA, vascular endothelial dysfunction and inflammation are believed to play major role. Endothelial dysfunction is believed to lead to a reduction in plasma NO levels in patients with MVA and ultimately a reduction in coronary vasodilation [10,11]. Given our current pathophysiologic understanding of MVA, the potential for nebivolol to serve as an effective therapy secondary to its NO-mediated vasodilatory effects has started to be preliminarily explored over the last several years. One previous study demonstrated that treatment with nebivolol resulted in an improvement in endothelial function and NO release [12]. Another study showed that nebivolol improved exercise parameters, as well as endothelial function, more effectively than beta blockade with metoprolol, among patients with persistent angina and non-obstructive CAD [13]. Based on the findings of these previous studies as well as of this present study, nebivolol has shown promise as a therapy for MVA, but further work is needed to further examine its effects in this unique patient population on a larger scale.

Conclusion

In conclusion, the results from this study suggest that nebivolol is a promising therapeutic agent for women with MVA and suffering from inadequately controlled symptoms. Nebivolol therapy improved angina stability without decreasing peak VO2. Impairment in peak exercise capacity has been demonstrated with other beta blocker therapies and is mediated by pharmacologically induced chronotropic incompetence. The proposed mechanism of action for preservation of peak VO2 with nebivolol therapy in this study, given the observed augmentation in peak O2 pulse, is either improvement of cardiac stroke volume or peripheral oxygen extraction. Further work is necessary to determine which of these two mechanisms is responsible, and whether the augmentation in peak O2 pulse is due to the unique NO-mediated vasodilatory effects of nebivolol. Future research efforts should also focus on further examining the effects of nebivolol treatment on the long-term clinical outcomes of women with MVA.

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Disclosures

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References


