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Short Communications

Effects of Theophylline on Exercise Indices in a Patient with Chronotropic Incompetence

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Summary: Several investigators have documented the successful use of oral sustained-release theophylline in treating symptomatic bradycardia and sick sinus syndrome. This paper reports a case of chronotropic incompetence in which specific exercise indices, including the chronotropic response index, were used to measure the therapeutic efficacy of theophylline.

Key words: chronotropic incompetence, sick sinus syndrome, theophylline

Introduction

The term chronotropic incompetence (CI) was originally coined by Ellestad and Wan in 1975,[1] and refers to an inappropriately slow heart rate response to exertion. Using the maximum age-predicted heart rate (MPHR) as the reference, they defined CI as a peak exercise heart rate 1 (mild) or 2 (more severe) standard deviations below the mean. In 1989, Wilkoff *et al.*[2] introduced the concept of metabolic chronotropic relation, which refers to the mathematical relationship between heart rate reserve and metabolic reserve during exercise. Using 532 normal adults, they showed that the ratio of % heart rate reserve to % metabolic reserve achieved with exercise should equal 1 (95% confidence interval 0.8 to 1.3), regardless of the exercise protocol used, the age of the patient, or the state of physical conditioning (Fig. 1). In a majority of patients, CI is felt to be a manifestation of sick sinus syndrome, and as such conveys an increased mortality risk.[4] In a retrospective analysis of 1,575 men in the Framingham Offspring Study,[5] Lauer *et al.*[6] demonstrated that a low heart rate to metabolic reserve ratio (referred to as the chronotropic response index) is predictive of increased total and coronary heart disease mortality. Ellestad and Wan[1] reported similar findings in a review of 2,700 patients who underwent maximal exercise stress testing.

Currently, symptomatic sick sinus syndrome is a Class I indication for permanent pacing.[7] Alternatively, oral sustained-release theophylline has been used successfully in the treatment of symptomatic bradycardia and sick sinus syndrome.[8–11] The therapeutic efficacy of theophylline has generally been measured as subjective symptomatic improvement, an increase in resting and/or peak heart rate on Holter monitoring, or improvement in sinus node function during electrophysiologic testing. To date, the effects of theophylline on specific exercise parameters, such as the chronotropic response index and total exercise time, have not been described.

Case Report

The present case involves a 49-year-old man who presented with 3 months of progressive exertional fatigue. He could previously perform several hours of manual labor without difficulty, but recently was exhausted after working an hour. He denied anginal chest pain or dyspnea. Risk factors for coronary artery disease included hyperlipidemia and tobacco use. His only medication was pravastatin, 20 mg daily, which was recently started. Resting heart rate was 60 beats/min, and blood pressure was 125/80 mmHg. The remainder of the physical examination was within normal limits. A resting electrocardiogram showed sinus bradycardia at a rate of 56 beats/min, with no evidence of conduction abnormalities, ischemia, or previous myocardial infarction. Routine laboratory studies, including complete blood count and thyroid function studies, were within normal limits. Transthoracic echocardiogram revealed normal cardiac dimensions and mild mitral regurgitation, with no evidence of structural or ischemic heart disease. The results of a maximal exercise stress test are given in Table I. Coronary arteriography was performed, demonstrating normal coronary artery anatomy without atherosclerosis. The pa-

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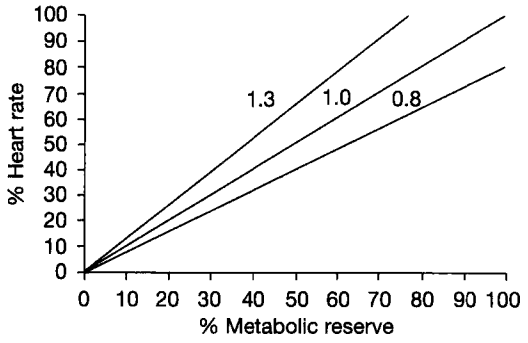

FIG. 1 Relationship between heart rate reserve and metabolic reserve during exercise. The percent heart rate reserve at any given stage of exercise = (heart rate at that stage-resting heart rate)/(maximum predicted heart rate-resting heart rate) × 100. The percent metabolic reserve for any given stage of exercise = (METS achieved at that stage-METS at rest)/(METS at peak exercise-METS at rest) × 100. The normal slope is 1.0 with a 95% confidence interval of 0.8–1.3. Adapted from Ref. No. 3.

TABLE I Results of maximal exercise stress testing before and after treatment with theophylline [a]

	Before treatment	Theophylline 300 mg twice daily
Resting heart rate (beats/min)	62	72
Resting blood pressure (mmHg)	120/80	110/70
Exercise time	7 min, 30 s	10 min, 6 s
Stage at termination	3	4
Maximum heart rate (beats/min)	115 (67% of MPHR)	155 (91% of MPHR)
Maximum blood pressure (mmHg)	120/80	170/80
Workload (METS)	9	11
Chronotropic response index	0.59	1.22
Electrocardiogram	No ischemic changes	No ischemic changes

[a] The patient was exercised using the Bruce[12] protocol.
Abbreviation: MPHR = maximum predicted heart rate.

tient was started on oral sustained-release theophylline, 300 mg twice daily, and exercise stress testing was repeated 2 weeks later (Table I). At 1 year of follow-up, the patient reports marked improvement in his exercise tolerance, with no appreciable side effects of therapy.

Discussion

Clinically, the most common cause of CI is the use of negative chronotropic drugs, such as beta blockers, nondihydropyridine calcium-channel antagonists, digoxin, and antiarrhythmics. In the majority of patients not treated with these agents, CI is felt to be secondary to sick sinus syndrome. This may manifest as resting bradycardia, sinus pauses, sinoatrial node exit block, or bradycardia inappropriate for physiologic circumstances. In a subgroup of patients, CI is thought to be secondary to ischemic heart disease. Ellestad reported a patient with CI, which resolved following coronary arterial bypass grafting.[13] Evaluation of a patient with CI should include a comprehensive history and physical examination, routine laboratory studies, including thyroid function tests, and transthoracic echocardiogram. In patients with CI and risk factors for coronary artery disease, who show no evidence of ischemia during exercise stress testing, additional testing with nuclear perfusion imaging or echocardiography should be performed. Evaluation of sinus node function with electrophysiologic testing is not indicated in patients with electrocardiographically documented symptomatic CI.

Over the last 20 years, there is mounting evidence that supports the role of adenosine in the pathophysiology of sick sinus syndrome.[14,15] Adenosine is known to depress sinus node activity, and attenuates the cardiac response to catecholamines.[16] While permanent pacing is currently considered to be the treatment of choice for sick sinus syndrome, several investigators have reported beneficial effects of theophylline, an adenosine antagonist, in the treatment of bradyarrhythmias.[8–11] Alboni *et al.* directly compared the effects of dual chamber rate-responsive pacing with oral theophylline administration versus untreated controls in 107 patients with sick sinus syndrome.[17] Theophylline was as effective as permanent pacing in improving symptoms of fatigue after 3 months of therapy, although many patients in the control group also had improvement in symptoms, suggesting spontaneous recovery of sinus node function in some cases. While CI was not evaluated as a clinical endpoint in this study, improvement in fatigue scores among theophylline-treated patients may have been due not only to increases in heart rate, but also to improvement in exercise indices such as the chronotropic response index. In the present case, administration of sustained-release theophylline improved subjective exercise tolerance. There was also objective improvement in exercise tolerance, as evidenced by a return of the chronotropic response index to the normal range, an increase in the peak exercise heart rate from 67 to 91% of maximum predicted heart rate, a 34% increase in total exercise time, and an increase in peak workload achieved. Spontaneous recovery of sinus node function prior to the second exercise test is unlikely in this patient, who continues to experience profound exercise intolerance if consecutive doses of theophylline are missed.

Conclusions

Further study is needed to determine which patients with sick sinus syndrome might benefit from medical therapy versus permanent pacing. For those patients with CI, therapeutic efficacy trials should include objective measures of exercise

capacity, including the chronotropic response index, total exercise time, peak heart rate, and level of metabolic work achieved. For younger patients, in whom permanent pacing may negatively affect quality of life, or in older patients, in whom age or comorbidities might prohibit placement of a permanent pacemaker, a trial of oral theophylline is a reasonable therapeutic alternative.

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