Original Article

Strategy for Identifying an Efficient Dosage of Beta-Blocker for Elderly Patients with Myocardial Ischemia and Preserved Left Ventricular Function

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Objective

To assess the strategy of titration for prescribing an efficient dosage of propranolol to reduce myocardial ischemia in the elderly.

Methods

The study comprised 14 elderly men (73.6 ± 5.3 years) with stable coronary heart disease documented on coronary cineangiography, ischemic response to exercise testing, and preserved left ventricular function. Titration was performed to identify the dosage of propranolol that would cause a 15% reduction in heart rate at the end of a 50 W load (corresponding to normal daily activities in the elderly) in weekly exercise tests. Synchronous scintigraphic study of the cardiac chambers was performed at rest and during exercise prior to and after propranolol use.

Results

The reductions in heart rate with the 50 W load and at rest were similar (21% vs 20%; P=0.5100). Propranolol improved the duration of exercise (12.2 ± 2.0 min vs 13.1 ± 1.8 min; P=0.0313) and abolished the changes in the ST segment induced by exercise in 8 (57%) patients. At rest, the ejection fraction was not modified by the beta-blocker. During maximum exercise, propranolol reduced the end-systolic volume index and increased ejection fraction.

Conclusion

The strategy of using beta-blockers to reduce heart rate by 15% with a 50 W load is safe and beneficial in the elderly patient with myocardial ischemia and preserved ventricular function. The dose of beta-blocker used reduced myocardial ischemia and improved tolerance to exercise without hampering ventricular performance during maximum exercise.

Key words

beta-blocker, elderly, myocardial ischemia

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The beta-adrenergic blockers frequently used for the treatment of coronary heart disease and heart failure[1,2] are believed to reduce the risk of mortality due to acute myocardial infarction and reinfarction[3]. Despite the recognized benefits, its use in the elderly, the age group most frequently affected by coronary heart disease, is less common than in younger individuals, due to the fear of occurrence of adverse effects, including the development of heart failure[4].

In fact, in young individuals at rest and during exercise, a significant reduction in heart rate and an increase in the end-diastolic, systolic, and end-systolic volumes have been well established due to the effect of the beta-adrenergic blocker[5]. On the other hand, both aging per se and myocardial ischemia have been associated with a reduction in the capacity of increasing left ventricular ejection fraction during exercise[6].

The metabolism and elimination of drugs are usually altered in the elderly due to reductions in the liver and renal functions. These alterations associated with the heterogeneity of the pharmacological responses account for a wide range of interindividual variability in the serum levels of beta-blockers. In addition, elderly patients are more susceptible to the adverse effects of the drug, and knowledge of the ideal dosage is required, although important studies on beta-blockers after myocardial infarction did not include adjustments in dosage[7-10]. Therefore, the ideal dosage of beta-blockers in the elderly remains unknown. One study showed that higher dosages of beta-blockers may be associated with a greater risk of developing heart failure in the elderly[11]. Therefore, the definition of a strategy to prescribe beta-blockers for elderly patients has a significant clinical value. This study aimed at assessing a strategy of titration for prescribing the efficient dosage of propranolol to reduce myocardial ischemia in the elderly with coronary heart disease and preserved left ventricular function.

Methods

The study comprised 14 men older than 65 (mean age = 73.6 ± 5.3) years with coronary heart disease documented on coronary cineangiography. These patients had symptoms of stable angina pectoris and ischemic response to exercise testing (tab. I). The committees on ethics of the Instituto do Coração and of the Hospital das Clínicas of the FMUSP approved the study. The

Table I - Characteristics of the patients studied

Patient	Age (years)	Coronary heart disease*	Propranolol dose (mg)	Maximum load (W)		Exercise duration (min)		Load at the beginning of ST depression (W)	
				pre	post	pre	post	pre	post
1	80	3	40	75	75	11.5	12.0	50	50
2	83	3	40	100	100	14.5	14.5	50	50
3	72	single	80	75	100	12.0	15.0	50	50
4	74	2	80	100	100	16.0	16.0	75	100
5	71	single	80	75	100	11.5	14.0	25	50
6	76	3	80	75	75	12.0	12.0	25	25
7	80	single	80	50	75	8.0	11.0	50	ni
8	67	single	80	75	75	11.5	11.5	75	ni
9	69	single	80	75	75	12.0	12.0	75	ni
10	68	single	120	75	100	11.5	15.0	75	ni
11	72	2	80	75	75	12.0	12.0	75	ni
12	78	2	30	75	75	10.5	11.5	75	ni
13	66	2	40	75	75	12.0	12.0	75	ni
14	74	single	120	100	100	15.5	15.5	100	ni
Mean and standard deviation	73.6 ± 5.3		73.6 ± 27.6			12.2 ± 2.0	13.1 ± 1.8		

*: single, 2-, or 3-vessel disease; ni: exercise test with nonischemic response

exclusion criteria were as follows: previous use of beta-blockers; impossibility of suspending nitrates and calcium antagonists; previous myocardial infarction; diastolic blood pressure ≥ 120 mmHg; valvular heart disease with hemodynamic repercussion; chronic atrial fibrillation; left ventricular ejection fraction < 50%; heart rate at rest < 55 bpm; second- or third-degree atrioventricular blockade; chronic obstructive pulmonary disease.

During 2 weeks, the selected patients received the following antianginal medication: isosorbide dinitrate, 40 mg twice a day orally, or isosorbide dinitrate, 5 mg sublingually, or both. After this period, a first exercise test was performed until the end of the stage corresponding to the 50 W load, followed, after 48 hours, by a scintigraphic study of the cardiac chambers at rest and during exercise. Based on these tests, oral propranolol was prescribed to each patient at an initial daily dose of 30 to 40 mg. The control of the dose administered was based on the heart rate at the end of the 50 W load, in weekly exercise tests. A 15% reduction in heart rate in regard to that obtained in the first test was considered the efficient effect of the beta-adrenergic blocker. When the expected effect was not observed, the dose of propranolol was increased to 80 mg per day in the second week, and to 120 mg per day in the third week. The expected effect was obtained in the first week in 4 cases, in the second week in 8 cases, and in the third week in 2 cases. When the desired reduction in heart rate was obtained, the patients underwent a new scintigraphic study of the cardiac chambers at rest and during exercise. All tests were performed after suspension of the nitrate for at least 48 hours.

In the tests to control the propranolol dose, an MFE ergometric bicycle, 400L model, was used. The test comprised 2 exercise stages (25 and 50 W) with a duration of 4 minutes each, and a constant velocity of 70 rotations/minute was maintained. An ischemic response during effort consisted of the following: depression of the ST segment, with horizontal or descending morphology, ≥ 1 mm, 80 ms apart from the J point.

In the scintigraphic studies, a Nuclear associates/Collins electromagnetic cycloergometer, 17571 model, with an approximate inclination of 45º was used.

Scintigraphic images in left anterior oblique projection (approximately 40º) were obtained at rest and at each exercise stage with the patient in a sitting position. Labeling of red blood cells was performed through the venous administration of 12.0 mg of stannous pyrophosphate and 3.4 mg of stannous chloride diluted in 2 mL of saline solution, followed, after 20 to 30 minutes, by the administration of 1,111 MBq of sodium pertechnate. A Siemens scintigraphic camera, LEM + model, with a crystal of sodium iodide activated with thallium was used, with a useful field of 25.9 cm in diameter and collimator with parallel orifices and high sensitivity. The images were stored in a magnetic disk and later underwent processing, always with the same observer.

The end-diastolic and end-systolic left ventricular volumes were determined based on the conversion of the countings of the respective ventricle into volume units, using one blood sample collected with the patient resting. The blood sample underwent counting with the same camera-collimator system[12], and the counting was corrected for the time elapsed between blood collection and the beginning of the counting. Correction regarding the attenuation of the countings was performed individually with the use of a static image obtained in the anteroposterior projection. This image was also used to measure the distance between the center of the left ventricle and one technetium source placed on the chest of the patient at the level of the region corresponding to the center of the ventricle in the left anterior oblique projection.

Heart rate, blood pressure, end-diastolic volume index (EDVI), end-systolic volume index (ESVI), cardiac index (CI), contractility index (CTRI) - obtained with the quotient between the systolic blood pressure value and the ESVI value – and ejection fraction were analyzed by calculating the means and standard deviations. These data were compared by analyzing the variance for repeated measures with multiple comparisons at rest and during maximum exercise. The nonparametric test was used to assess the duration of the exercise, and the Wilcoxon test was used to compare the reduction in heart rate at rest and with the 50 W load. The significance level adopted for the tests was 5%. The calculations were performed with the Statistical Analysis System.

Results

After titration of the propranolol dosage, mean = 73.6 ± 27.6 mg per day, heart rate decreased similarly at rest and with a 50 W load (21% versus 24%, respectively; P=0.272). During scintigraphy, the reduction in heart rate was also similar at rest and with a 50 W load (21% versus 20%, respectively; P=0.510). Propranolol was observed to cause a significant reduction in mean blood pressure during maximum exercise (140.4 ± 18.5 mmHg versus 130.0 ± 14.3 mmHg; P=0.0100). In the postpropranolol phase, 8 (57%) patients showed no alterations compatible with myocardial ischemia on exercise electrocardiography; on the other hand, that kind of alteration was observed in the 6 remaining patients, and, in 2 (14%) of them, the alteration appeared only in loads greater than that in the prepropranolol phase. Seventy-one percent of the patients showed an improvement in myocardial ischemia after the use of propranolol. A significant (P=0.0313) increase in exercise duration was observed between the pre- (12.2 ± 2.0 min) and postpropranolol (13.1 ± 1.8 min) phases.

The use of propranolol caused a significant increase in ventricular volumes. The EDVI increased from 67.5 ± 12.9 mL/m^2 to 76.2 ± 11.6 mL/m^2 (P=0.0088) and the ESVI from 29.1 ± 8.2 mL/m^2 to 33.8 ± 9.7 mL/m^2 (P=0.0440). Reductions in the CI from 2.9 ± 0.4 L/min/m^2 to 2.6 ± 0.3 L/min/m^2 (P=0.0172) and in the CTRI from 5.7 ± 1.6 mm Hg/mL/m^2 to 4.9 ± 1.8 mm Hg/mL/m^2 (P=0.0044) were observed. The ejection fraction did not change: 57.8 ± 6.4% versus 58.4 ± 7.3% (P=0.4395) (tab. II).

During maximum exercise, the use of propranolol reduced the ESVI from 37.6 ± 10.6 mL/m^2 to 34.5 ± 8.9 mL/m^2 (P=0.0224), increased the EF from 56.2 ± 6.5% to 60.2 ± 7.2% (P=0.0033), and did not change the EDVI (84.8 ± 21.0 mL/m^2 versus 86.5 ± 20.6 mL/m^2; P=0.5990), the CI (6.0 ± 1.4 L/min/m^2 versus 5.5 ± 1.5 L/min/m^2; P=0.0866), and the CTRI (6.0 ± 2.0 mm Hg/mL/m^2 versus 6.3 ± 2.8 mm Hg/mL/m^2; P=0.3779) (tab. III).

Table II - Means, standard deviations, and P values at rest

	prepropranolol	postpropranolol	P
HR (beats/min)	74.9 ±14.7	57.9 ± 8.3	0.0001
MBP (mm Hg)	113.7 ±16.5	106.6 ± 13.2	0.1142
EDVI (mL/m^2)	67.5 ±12.9	76.2 ± 11.6	0.0088
ESVI (mL/m^2)	29.1 ± 8.2	33.8 ± 9.7	0.0440
CI (L/min/m^2)	2.9 ± 0.4	2.6 ± 0.3	0.0172
CTRI (mm Hg/mL/m^2)	5.7 ± 1.6	4.9 ± 1.8	0.0044
EF (%)	57.8 ± 6.4	58.4 ± 7.3	0.4395

HR - heart rate; MBP - mean blood pressure; EDVI - end-diastolic volume index; ESVI - end-systolic volume index; CI - cardiac index; CTRI - contractility index; EF - ejection fraction

Table III - Means, standard deviations, and P values during maximum exercise

	prepropranolol	postpropranolol	P
HR (bpm)	128.1 ± 13.7	105.3 ± 14.1	0.0001
MBP (mm Hg)	140.4 ± 18.5	130.0 ± 14.3	0.0100
EDVI (mL/m^2)	84.8 ± 21.0	86.5 ± 20.6	0.5990
ESVI (mL/m^2)	37.6 ± 10.6	34.5 ± 8.9	0.0224
CI (l/min/m^2)	6.0 ± 1.4	5.5 ± 1.5	0.0866
CTRI (mm Hg/mL/m^2)	6.0 ± 2.0	6.3 ± 2.8	0.3779
EF (%)	56.2 ± 6.5	60.2 ± 7.2	0.0033

HR - heart rate; MBP - mean blood pressure; EDVI - end-diastolic volume index; ESVI- end-systolic volume index; CI - cardiac index; CTRI - contractility index; EF- ejection fraction

Discussion

Despite the recognized benefit of the use of beta-blockers in patients with myocardial ischemia, even in the presence of heart failure [1-3], this class of drugs is underused in the elderly patients[4], due to the fear of depression of left ventricular function. In addition, the precise dosage for elderly patients has not been well established. It is common practice to empirically prescribe lower doses of medications to elderly patients due to the increase in bioavailability and the reductions in the liver and renal clearances. However, the efficacy of lower doses has not been confirmed. Our study suggests a practical and simple strategy for prescribing beta-blockers at an efficient and safe dosage to elderly patients with myocardial ischemia and preserved left ventricular function. A protocol of titration was designed to determine the dosage of propranolol that would cause a 15% reduction in heart rate with an exercise load, which corresponds to the normal daily life activities of the elderly (50 W). The beta-blockade did not impair left ventricular performance at rest; however, it improved tolerance to exercise, reduced myocardial ischemia during exercise, and improved left ventricular ejection fraction during maximum exercise.

Our results confirm the expected hemodynamic effects of propranolol in the elderly with myocardial ischemia. At rest, the use of propranolol caused left ventricular dilation as a form of adaptation to maintain cardiac output due to its negative chronotropic and inotropic effect[13]. Left ventricular ejection fraction was maintained by an increase in the preload. During maximum exercise, propranolol improved left ventricular performance, increasing left ventricular ejection fraction and reducing the end-systolic volume index. This behavior reflected the antiischemic effect of propranolol, which was clinically confirmed by the abolition of changes in the ST segment induced by exercise in 8 patients, by the appearance of changes in the ST segment induced by exercise with greater loads in 2 patients, and by an increase in exercise duration.

The antiischemic action of beta-blockers results mainly from the reduction in the consumption of myocardial oxygen. This effect is clinically assessed by the reductions in heart rate and blood pressure. Frequently, heart rate at rest is used as a parameter to perform titration of the dosage of these drugs. However, the behavior of heart rate at rest and during exercise is heterogeneous among the elderly[14]. In addition, the effective minimum dosage of beta-blockers in the elderly has not yet been established. Despite the increasing evidence that beta-blockers should be used in patients with myocardial ischemia and heart failure, one study showed that the use of high doses in elderly patients was associated with a higher risk of hospitalization due to heart failure[11].

The 15% reduction in heart rate at the 50 W load reduced ischemia and improved tolerance to exercise and left ventricular performance. Despite the great heterogeneity, the objective to obtain this reduction at 50 W corresponded to the same degree of reduction in heart rate at rest. This reduction was obtained with the safe and well-tolerated dosage of propranolol usually

used. The correlation between the response of heart rate at rest and that obtained with a 50 W load shows that, in daily clinical practice, titration of the dose during exercise is not required.

Because only the elderly with stable angina and preserved left ventricular function were included in this study, the results cannot be applied to other populations of patients. The absence of placebo is another limitation. Therefore, the improvement in the response to exercise may be due more to the conditioning effect than to the beta-blocking effect. Although the population studied was very homogeneous, supporting the results, one cannot ignore that the case series was small.

In conclusion, the strategy to use beta-blockers at a dosage sufficient to reduce heart rate by 15% at the 50 W load is safe and beneficial in the group of elderly patients with myocardial ischemia and preserved left ventricular function. That dose reduced myocardial ischemia and improved tolerance to exercise, without hindering left ventricular performance during maximum exercise. The reduction in heart rate with a 50 W load corresponded to the reduction in heart rate at rest. This correlation between the behavior at 50 W load and at rest suggests that a 15% reduction in heart rate is a good strategy for elderly patients with myocardial ischemia and preserved left ventricular function.

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