*Brazilian J Med Biol Res (1989) 22: 825-831*

# IMPROVEMENT IN WALL MOTION AFTER PINDOLOL: A MECHANISM FOR THE PRESERVATION OF LEFT VENTRICULAR FUNCTION IN CORONARY ARTERY DISEASE

W.C. MANFROI, S.R. VIEIRA, V.F. KOPPE, J.R. GOLDIN, F.M. FREITAS, E.Z. FARACO and J.P. RIBEIRO

*Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, 90210 Porto Alegre, RS, Brasil*

1. In order to evaluate the mechanism by which beta blockers with intrinsic sympathomimetic activity preserve left ventricular systolic function at rest, 46 patients with coronary artery disease were studied by right and left heart catheterization and left ventriculography. Patients were studied using a double-blind, randomized protocol before and after a single intravenous dose of 3 mg propranolol (N = 22) or 0.5 mg pindolol (N = 24).

2. Mean right atrial pressure increased similarly after both drugs. Mean pulmonary artery pressure, left ventricular end-diastolic pressure, mean aortic pressure, and peripheral vascular resistance did not change significantly after either drug. Cardiac index (before: 3.0 ± 0.7 (mean ± SEM); after: 2.8 ± 0.2 l $min^{-1}$ $m^{-2}$) and heart rate (before: 78 ± 15; after: 72 ± 12 bpm) decreased only after propranolol administration.

3. Ejection fraction decreased only after propranolol (48 ± 16 to 41 ± 15%). Improvement in segmental wall motion abnormalities was noted (23 of 47 segments) only after pindolol. The total left ventricular wall motion score improved after pindolol and worsened after propranolol ($P < 0.05$). In patients with impaired left ventricular function, pindolol administration resulted in improved resting ejection fraction.

4. Thus, the acute hemodynamic consequences of pindolol administration differ from those of propranolol owing to the preservation of left ventricular systolic function which seems to be related to the intrinsic sympathomimetic effect of pindolol on areas of reversible wall motion abnormality.

**Key words:** beta blockers, intrinsic sympathomimetic activity, propranolol, pindolol, segmental wall motion.

## Introduction

Because of some unfavorable evidence for the role of beta blockers showing intrinsic sympathomimetic activity in secondary prevention after myocardial infarction, these agents have not been recommended for intravenous administration during the acute phase of myocardial infarction (Yusuf et al., 1985). However, pindolol, a beta blocker with partial intrinsic sympathomimetic activity (Frishman, 1983), may provide potential benefits compared to propranolol for intravenous use since it preserves left ventricular systolic

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J.P.R. is a CNPq investigator.

Correspondence: Dr. J. P. Ribeiro, Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, 90210 Porto Alegre, RS, Brasil.

function (Svendsen et al., 1981). However, the mechanism by which pindolol preserves systolic function while exerting a beta-blocking effect is not understood.

The present study was conducted to compare the effects of acute intravenous administration of propranolol and pindolol on the resting hemodynamic variables and segmental wall motion of patients with coronary artery disease. The data obtained identify the mechanism by which pindolol administration results in preservation of left ventricular systolic function.

## Material and Methods

*Patients*

The study population of 46 patients, referred for diagnostic cardiac catheterization to evaluate coronary artery disease, consisted of 38 men and 8 women aged 33 to 70 years. All patients exhibited significant coronary artery disease as defined by a 75% obstruction of at least one major coronary artery. The protocol employed was approved by the research committee of our institution, and informed consent to participate in the study was obtained from each patient.

*Cardiac catheterization*

All cardioactive medications except short-acting nitrates were withheld 48 to 72 h prior to the study. Patients were admitted to the hospital on the day before the study and cardiac catheterization was performed without premedication after an overnight fast. Catheters were inserted under local anesthesia by dissection of the right basilic vein and of the brachial artery. Right heart catheterization was performed with a 7 F pulmonary artery catheter. Cardiac output was measured by the thermodilution method. Left heart catheterization was performed with a 7 F Lehman catheter. The catheters were connected to Statham (P23DB) pressure transducers and recordings were made using a VR12 Electronics for Medicine system. Derived hemodynamic variables were calculated by standard formulas (Grossman, 1986).

Left ventriculography was performed by injecting Isopaque contrast with a Contract III injection pump at a rate of 15 ml/s. The ventriculogram was filmed with an Arritekno camera at 48 frames/s in the $30^{o}$ right anterior oblique view. The left ventricular ejection fraction was measured by planimetry following the method of Greene et al. (1967). Five left ventricular segments were identified: anterobasal, anterolateral, apical, diaphragmatic, and posterobasal. The systolic motion of these segments was scored according to Alderman et al. (1983), i.e., normal = 1, moderate hypokinesia = 2, severe hypokinesia = 3, akinesia = 4, and dyskinesia = 5. The sum of all segmental scores was considered to be the left ventricular whole motion score. Mean circumferential fiber shortening was measured by the method of Karliner et al. (1971). Selective coronary angiography was performed under multiple projections using the Sones technique (Sones and Shirey, 1962).





*Experimental Protocol*

Baseline hemodynamic values were established as the mean of two sets of measurements separated by at least 5 min, and left ventriculography was then performed. The patients remained at rest for 5 min and hemodynamic variables were measured again. After these had returned to baseline levels, a single dose of 0.5 mg pindolol or 3 mg propranolol was administered via the atrial port of the right heart catheter over a period of 5 min, following a double-blind, randomized protocol. Right and left heart pressures and thermodilution cardiac output were obtained 5 min after the end of drug infusion, and a further ventriculogram was obtained under the same conditions as the first. Finally, a Sones catheter was used for selective coronary angiography.

*Statistical analysis*

Descriptive data are reported as means ± SEM. A two-way analysis of variance for repeated measurements was used to compare the following variables under baseline conditions and after pindolol or propranolol administration: right atrial, pulmonary artery, left ventricular end diastolic and aortic pressures; heart rate; cardiac output; systemic vascular resistance; left ventricular ejection fraction and velocity of circumferential fiber shortening. Segmental wall motion was compared before and after drug administration by one of the investigators who had no information as to the drug given. Analysis of the results was performed by the chi-square test and the Wilcoxon signed rank test. Differences were considered to be statistically significant at $P \leq 0.05$.

## Results

Propranolol was administered to 22 patients and pindolol to 24 patients. The distribution of sex, age, body surface area, and coronary anatomy was similar in the two groups of patients after randomization (Table 1). Likewise, the hemodynamic variables were similar in the groups after randomization (Table 2). No complications occurred after the administration of either drug.

*Hemodynamic variables (Table 2)*

Mean right atrial pressure increased similarly after the administration of either drug. Mean pulmonary artery pressure increased after pindolol and remained unchanged after propranolol, although the response to the drugs was not significantly different when evaluated by analysis of variance. Left ventricular end diastolic pressure and mean aortic pressure were not significantly altered by the administration of either drug. Cardiac index decreased after the administration of propranolol but was unchanged after pindolol. Similarly, heart rate decreased after propranolol but was not changed after pindolol. Stroke volume and systemic vascular resistance remained unchanged after the administration of either drug.

*Angiographic variables (Table 2)*

The ejection fraction decreased after propranolol but was not significantly changed by pindolol. Similarly, the mean velocity of circumferential fiber shortening decreased only after propranolol. In 12 patients from each group with baseline left ventricular dysfunction, defined as an ejection fraction lower than 55%, pindolol administration resulted in improvement of ejection fraction (37.7 ± 3.0 to 42.1 ± 2.3%, $P<0.05$), while the administration of propranolol resulted in a nonsignificant reduction in ejection fraction (37.8 ± 3.1 to 34.0 ± 2.8%). The response of these patients was statistically different according to the analysis of variance. Likewise, propranolol resulted in a reduction in the velocity of circumferential fiber shortening (0.72 ± 0.06 to 0.62 ± 0.07 circ/s, $P<0.05$), while pindolol administration resulted in an increase in the velocity of circumferencial fiber shortening (0.58 ± 0.07 to 0.69 ± 0.06 circ/s, $P<0.05$) in the patients with left ventricular dysfunction.

Table 1 - *Clinical and angiographic characteristics of the patients after randomization into prospective groups.*

CAD, coronary artery disease. Results are reported as means ± SEM. Groups were compared using the Wilcoxon signed rank test and the chi-square test ($P=0.05$). There were no statistically significant differences between groups.

| | Propranolol group | Pindolol group |
|---|---|---|
| Number | 22 | 24 |
| Age (years) | 54 ± 6 | 55 ± 5 |
| Sex (% male) | 86 | 78 |
| Body surface area ($m^2$) | 1.8 ± 0.2 | 1.8 ± 0.2 |
| 1 vessel CAD (% of patients) | 27 | 25 |
| 2 vessel CAD (% of patients) | 41 | 40 |
| 3 vessel CAD (% of patients) | 32 | 35 |

Before propranolol administration, 44 left ventricular segments showed wall motion abnormalities. Of these abnormally contracting segments 10 showed worsening, while no segment showed improved wall motion by at least one score point after propranolol. Of the 47 segments showing abnormal wall motion before pindolol, 23 showed improvement and only 2 showed worsening by at least one score point after pindolol administration. The response of wall motion to pindolol was significantly different ($P<0.01$) from the response to propranolol. This difference was also reflected in the significant increase in total left ventricular wall motion score after propranolol, while the total left ventricular wall motion score decreased significantly after pindolol ($P<0.01$).

## Discussion

The acute hemodynamic responses to the intravenous administration of propranolol and pindolol observed in the present study are similar to those described by others (Parker et al., 1968; Frishman et al., 1979; Svendsen et al., 1981). Svendsen et al. (1981) studied the dose-response curve of these drugs along with other beta blockers. The doses utilized here are equivalent to the fourth in the series of doses used by Svendsen et al. (1981), who found a similar reduction in cardiac output with propranolol and no change with pindolol. During exercise, the dose used by those investigators resulted in a reduction in heart rate and blood pressure, demonstrating an appropriate beta blocking effect. At higher doses, Svendsen et al. (1981) found that propranolol administration also resulted in a decrease in stroke volume index and an increase in mean pulmonary artery pressure, systemic vascular resistance, and pulmonary vascular resistance. In our patients neither propranolol nor pindolol caused a significant change in these hemodynamic variables.

In the present study, indices of left ventricular systolic function were obtained by contrast cineangiography. Injection of the contrast medium itself may induce hemodynamic changes (Brown et al., 1965) which may have altered the post-beta blockade results. During the experimental procedures, care was taken to avoid these effects by waiting for the hemodynamic variables to return to baseline levels after the first ventriculography. Furthermore, even if the contrast agent did influence the acute response to each of the drugs, comparison between the effects of the two drugs is appropriate since the same methods were applied.

Beta blockers with intrinsic sympathomimetic activity are believed to have a less negative inotropic effect on the left ventricle than beta blockers without this property. Our



Table 2 - *Hemodynamic and angiographic responses after intravenous administration of 3 mg propranolol or 0.5 mg pindolol.*

Data are reported as means ± SEM. RAP, mean right atrial pressure; PAP, mean pulmonary artery pressure; LVEDP, left ventricular end diastolic pressure; AP, mean aortic pressure; CI, cardiac index; HR, heart rate; SVR, systemic vascular resistance; EF, ejection fraction; Vcfs, velocity of circumferential fiber shortening. ns, No significant difference between groups before drug administration ($P>0.05$); NS, response to propranolol not significantly different from the response to pindolol ($P>0.05$); *response to propranolol significantly different from the response to pindolol ($P<0.05$).

| | | Propranolol group | Pindolol group | ANOVA |
|---|---|---|---|---|
| RAP (mmHg) | Before | 4.3 ± 2.4 | 4.8 ± 1.9 | ns |
| | After | 5.6 ± 2.7 | 6.0 ± 2.4 | NS |
| PAP (mmHg) | Before | 17.2 ± 6.0 | 16.5 ± 3.5 | ns |
| | After | 17.6 ± 6.1 | 18.7 ± 5.4 | NS |
| LVEDP (mmHg) | Before | 16.8 ± 11.2 | 15.7 ± 8.9 | ns |
| | After | 16.9 ± 9.4 | 15.0 ± 7.6 | NS |
| AP (mmHg) | Before | 103 ± 19 | 97 ± 17 | ns |
| | After | 105 ± 17 | 100 ± 17 | NS |
| CI ($l\ min^{-1}\ m^{-2}$) | Before | 3.0 ± 0.7 | 2.8 ± 0.5 | ns |
| | After | 2.7 ± 0.2 | 2.9 ± 0.6 | * |
| HR (bpm) | Before | 78 ± 15 | 73 ± 12 | ns |
| | After | 72 ± 12 | 71 ± 8 | * |
| SVR ($dynes\ s^{-1}\ cm^{-5}$) | Before | 1560 ± 456 | 1560 ± 448 | ns |
| | After | 1632 ± 488 | 1536 ± 424 | NS |
| EF (%) | Before | 48 ± 16 | 48 ± 16 | ns |
| | After | 41 ± 15 | 51 ± 15 | * |
| Vcfs (circ/s) | Before | 0.94 ± 0.37 | 0.92 ± 0.47 | ns |
| | After | 0.73 ± 0.32 | 0.95 ± 0.45 | * |
| Wall motion score | Before | 9.3 ± 1.0 | 9.6 ± 0.7 | ns |
| | After | 10.0 ± 1.0 | 7.3 ± 0.6 | * |

results indicate that the preservation of the left ventricular systolic function after the administration of pindolol to patients with coronary artery disease is at least partially due to its positive inotropic effect on areas of wall motion abnormalities. Heikkila and Nieminem (1978) gave 0.2 mg pindolol intravenously to patients during the acute phase of myocardial infarction, and these patients responded with improvement in wall motion abnormalities of ischemic segments. Manyari et al. (1983) compared the effects of pindolol and propranolol in patients with angina pectoris and normal or near normal ventricular function but were unable to demonstrate any improvement in left ventricular function with pindolol. Among our patients, the improvement in systolic function was most marked in those who previously exhibited left ventricular dysfunction. Indeed, in the subgroup of patients with left ventricular dysfunction, the ejection fraction increased after pindolol. Thus, our data confirm previous findings that the effect of partial intrinsic sympathomimetic activity is more marked in patients with impaired left ventricular performance (Gebhardt and Wisenberg, 1985). Furthermore, our data indicate that the effect of pindolol is the result of the improvement of systolic function in areas with wall motion abnormalities.

The mechanism by which the administration of pindolol results in improvement of wall motion abnormalities in patients with coronary artery disease who have no clinical evidence of myocardial ischemia is not clear. It has been shown that some wall motion abnormalities may improve with the administration of nitrates (Helfant et al., 1974), in post-extrasystolic potentiation (Popio et al., 1977), by the infusion of epinephrine (Nesto et al., 1982), immediately after exercise (Rozanski et al., 1982), and after revascularization (Helfant et al., 1974; Popio et al., 1977; Nesto et al., 1982; Rozanski et al., 1982). Such inotropic contractile reserve is characteristic of ventricular segments which consist of viable, chronically ischemic myocardium (Bodenheimer et al., 1976). The administration of pindolol with its intrinsic sympathomimetic activity may stimulate these areas, resulting in improvement of left ventricular systolic function.

Taylor et al. (1982) favor beta blockers with intrinsic sympathomimetic activity for intravenous administration because they are more effective in maintaining cardiac function. The present study confirms that intravenous pindolol resulted in the preservation or even improvement of left ventricular systolic function in patients with coronary artery disease. However, several questions remain unanswered. It is possible that the improvement in left ventricular function with pindolol may produce an unfavorable effect on the balance between oxygen demand and supply by the myocardium. It is not clear whether these acute hemodynamic effects are maintained under chronic administration, although Gebhart and Wisenberg (1985) demonstrated that the chronic administration of pindolol to patients with coronary artery disease and left ventricular dysfunction results in improvement of resting left ventricular function, preserving its beta blocking effects during exercise. Finally, the net result of the acute intravenous administration of pindolol to patients with acute myocardial infarction and left ventricular dysfunction remains to be determined.

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*Received October 7, 1988*
*Accepted March 10, 1989*