Hemodynamic-inotropic response to β-blocker with intrinsic sympathomimetic activity in patients with congestive cardiomyopathy

PHILIP F. BINKLEY, M.D., ROBERT F. LEWE, JOHN J. LIMA, PHARM.D., ABDULKADER AL-AWWA, M.D., DONALD V. UNVERFERTH, M.D., AND CARL V. LEIER, M.D.

ABSTRACT The rest and exercise hemodynamic-inotropic response to administration of the β-blocker pindolol was evaluated in 10 patients with congestive cardiomyopathy to determine whether the intrinsic sympathomimetic activity (ISA) of this agent may preserve ventricular function in the setting of β-blockade. A significant (p < .05) rise in systemic and pulmonary vascular resistance and a decline in stroke volume and cardiac index was observed after a single 10 mg dose. The change in cardiac index was negatively correlated with free drug concentration (r = −.59, p < .01); the change in pulmonary and systemic vascular resistance showed a positive correlation with plasma concentration (r = .67, r = .57, respectively; all p < .05). The response to exercise reflected a predominant β-blocking effect, with a significant decrease in peak heart rate and cardiac index and an increase in pulmonary vascular resistance. There were no significant changes in variables of right or left ventricular inotropy after administration of the drug. The mean baseline plasma norepinephrine concentration for the population was 609 ± 172 pg/ml (normal = 196 ± 7 pg/ml) and was markedly elevated in two patients (931 and 2053 pg/ml) who developed severe pindolol-induced hypotension. Renin increased markedly in these two patients, but decreased in each of the remaining eight patients. These data indicate that although inotropy is not adversely affected by pindolol, increased afterload, which appears to be mediated by peripheral β-blockade, results in a reduction in ventricular performance. ISA may not protect against possible adverse effects of β-blockade in patients with congestive cardiomyopathy; the baseline norepinephrine concentration and renin response to drug administration may define patients at highest risk for hemodynamic compromise after administration of this β-blocker.

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β-BLOCKERS with intrinsic sympathomimetic activity (ISA) manifest β-agonist as well as β-blocking effects in animal preparations and human subjects.1-6 It has been postulated that ISA accounts for the difference in hemodynamic and inotropic effects of these agents as compared with pure β-blockers. Unlike the latter, β-blockers with ISA do not alter baseline cardiac index or systemic and pulmonary vascular resistances over the short term in normal subjects.2 A similar hemodynamic profile has been noted after long-term administration of these agents in patients with essential hypertension.3 Examination of noninvasive indexes of resting ventricular function has demonstrated that ISA β-blockers do not reduce ventricular contractility to the same degree as do pure β-blockers and may in some populations improve resting ventricular function.4-6

These observations suggest that, in the setting of normal ventricular function, the myocardial depressant effects of ISA β-blockers are less than those of pure β-blockers, perhaps as a result of their sympathomimetic influence. Because the hemodynamic and inotropic effects mediated by these agents in the setting of normal ventricular function would be desirable in those with reduced ventricular contractility, it has been proposed that ISA β-blockers would be preferable to pure β-blockers for use in a population with congestive heart failure.7 This, however, has not yet been verified.

The current study tests the hypothesis that the beneficial effects of ISA β-blockers noted in patients with normal ventricular function will also be expressed in a
population with reduced ventricular contractility. The rest and exercise hemodynamic-inotropic reactivity to administration of the potent ISA β-blocker pindolol is described in a population with idiopathic congestive cardiomyopathy. The observed changes in these variables are correlated with neurohumoral factors and free drug concentrations to provide insight into the mechanism of action of this complex class of β-blockers.

**Methods**

**Patient population (table 1).** Ten patients with idiopathic congestive cardiomyopathy (ages 28 to 57 years) comprised the study population. Each had a reduced ejection fraction (all <30%) as determined by contrast or radionuclide angiography. Criteria for exclusion included evidence of pulmonary, renal, or hepatic dysfunction and high-grade sinus node or atrioventricular conduction abnormalities. All vasodilator drugs were discontinued at least 48 hr before entry into the protocol. Informed consent was obtained before the study from all patients in accordance with the Human Rights Review Committee of the Ohio State University, which reviewed and approved this investigation.

**Hemodynamic monitoring and drug administration.** All patients were admitted to the cardiovascular monitoring section of the Clinical Research Center of the Ohio State University Hospitals. Shortly after admission a balloon-tipped flow-directed catheter was inserted via the subclavian or internal jugular vein (Seldinger technique) and advanced until the distal tip was positioned in the pulmonary artery.

On the morning after catheter placement, baseline standard hemodynamic measurements were made. Calculated variables derived from these measurements included cardiac index (liters/min/m²) = cardiac output/body surface area; stroke volume index (ml/beat/m²) = cardiac index x 1000/heartrate; mean systemic blood pressure (mm Hg) = (systolic − diastolic pressure)/3 + diastolic pressure; total systemic vascular resistance (dyne·sec·cm⁻⁵) = (mean systemic blood pressure x 80)/cardiac output; total pulmonary vascular resistance (dyne·sec·cm⁻⁵) = (mean pulmonary arterial pressure x 80)/cardiac output. Cardiac outputs were determined by the thermodilution technique and were taken as the mean of at least three measurements (six measurements if variation was >10%). Systemic blood pressures were measured by cuff auscultation.

After duplicate baseline measurements were obtained, a 5 mg oral dose of pindolol was administered and hemodynamic variables were measured at 15 and 30 min and 1, 2, 4, 6, and 8 hr after dosing. In the absence of an adverse response to the drug, a 10 mg oral dose of pindolol was given 24 hr after the first dose and hemodynamic variables were measured at intervals corresponding to those after the 5 mg dose. A second, third, and fourth 10 mg dose were given at eight hr intervals after the first 10 mg dose. Hemodynamic variables were measured through the 8 hr after the fourth dose.

**Inotropic indexes.** Indexes of the inotropic state of the right and left ventricles were obtained in subjects in the supine posture. These measurements were acquired immediately before and 2 hr after the 5 mg dose, the first 10 mg dose, and the fourth 10 mg dose. The inotropic indexes were derived from the M mode echocardiogram, carotid pulse tracing, phonocardiogram, apaxcidiagram, right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, and electocardiogram. Left ventricular inotropic variables consisted of (1) percent fractional shortening = (EDD − ESD)/EDD x 100%, where EDD and ESD are the end-diastolic and end-systolic minor-axis dimensions of the left ventricle, respectively, (2) systolic time intervals, consisting of total electromechanical systole (QS2), preejection period (PEP), left ventricular ejection time (LVET), and the ratio PEP/LVET, (3) mean velocity of circumferential fiber shortening defined as (EDD − ESD)/ (EDD x LVET), (4) (and) (isovolumic) developed pressure/ (isovolumic contraction time (ΔP/ΔT) = (systemic diastolic pressure-pulmonary capillary wedge pressure)/(PEP − EMCP), where EMCP is the electrical-mechanical coupling interval defined as the interval from the onset of the Q wave of the electrocardiogram to the onset of the rapid upstroke of the apexcardiogram. (5) Right ventricular inotropic indexes were (1) systolic time intervals, including right ventricular electromechanical systole (Qp₂), right ventricular PEP (RV-PEP), and right ventricular ejection time (RVET) derived from the pulmonary arterial pulse tracing, and (2) ΔP/ΔT of the right ventricle (RV-ΔP/ΔT) = (pulmonary arterial diastolic pressure − right atrial pressure)/RV-PEP. All determinations represent the mean of measurements obtained from 10 consecutive cardiac cycles.

**Exercise evaluation.** A baseline, upright, bicycle exercise study using a Quinton model 845 Uniprof ergometer was performed on all patients on the day before administration of the first dose of pindolol at least 2 hr after insertion of the pulmonary arterial catheter. The exercise protocol consisted of 3 min stages at an initial workload of 100 kilopond-meters per minute (kpm) with increments of 100 kpm per stage to maximal exercise. Maximal bicycle ergometry was repeated 2 hr after the last dose of pindolol. Values for hemodynamic variables were obtained at baseline, during the last 30 sec of each 3 min stage, and at maximal exercise.

**Neurohumoral variables.** Blood for the determination of plasma norepinephrine and renin concentration was obtained after 12 hr of bed rest preceding administration of the 5 mg dose and the first 10 mg dose. Blood samples for determination of these variables were again obtained 2 hr after the 5 mg dose and the first 10 mg dose. The neurohumoral determinations, performed by radioimmunassay in the core laboratory of the Clinical Research Center of the Ohio State University, have the following coefficients of variation: norepinephrine, 4.2% (Cat-A-KIT Upjohn Diagnostics); renin, 5.2% (Rianen Assay System, New England Nuclear).

**Determination of plasma concentrations of pindolol.** Blood samples for determination of total (unbound plus bound) plasma concentrations of pindolol were obtained before dosing.
and at 15 min, 30 min, and hourly intervals for 12 hr after the 5 mg dose. Samples were obtained before dosing and at 1, 2, 4, and 8 hr after each 10 mg dose. Analysis for pindolol concentration was performed by reversed-phase liquid chromatography with ultraviolet detection at a wavelength of 220 nm. The plasma protein binding of pindolol was determined by equilibrium dialysis with use of [14C]-pindolol. Quenching was controlled for by internal standardization with [14C]-toluene. The unbound fraction of pindolol in plasma was determined by calculation of the ratio of the concentration of disintegrations per minute in buffer to disintegrations per minute in plasma after equilibrium. Unbound concentrations of pindolol were determined by calculating the product of the unbound fraction and total plasma concentrations of pindolol. Details on the method used and the plasma protein binding and pharmacokinetics of pindolol have been published.

Statistical analysis. Data were analyzed by the CLINFO Data Management and Analysis system of the Ohio State University (GCRC RR-34). Analysis of variance for repeated measures was used to test significant differences between hemodynamic-inotropic variables and neurohumoral factors at baseline and after administration of drug. Correlations between free drug concentrations and hemodynamic and inotropic indexes were sought by linear regression analysis with Pearson’s correlation coefficient.

Results

Adverse responses. Three patients did not complete the protocol due to adverse responses to the drug. In patient 9, systolic and diastolic blood pressure fell from a baseline of 104/88 mm Hg to 80/0 mm Hg 2 hr after the 5 mg dose. In patient 6, systolic and diastolic blood pressure declined from a baseline of 92/60 mm Hg to 70/0 mm Hg 6 hr after the first 10 mg dose; only a mild decline in blood pressure was observed after the 5 mg dose in this patient. In both patients, administration of a vasopressor (dopamine) was required for 12 to 18 hr. Patient 7 developed frequent (20/min) premature ventricular contractions, one to three ventricular couplets per hour, and salvos of ventricular tachycardia (occurring one to three times per hour) starting 15 min after the first 10 mg dose and persisting for 10 hr after the administration of the drug. Further details on this adverse response have been reported.

Hemodynamic responses. Significant changes in cardiac index, stroke volume index, systemic vascular resistance, and pulmonary vascular resistance (PVR) were noted after the first 10 mg dose of pindolol (figure 1). A significant decrease in cardiac index (p < .05) was observed 30 min after this dose (2.50 ± 0.56 to 2.27 ± 0.45 liters/min/m²) and remained significantly depressed throughout the 2 hr after dosing. Similarly, a significant (p < .05) decline in stroke volume index was observed 30 min after the first 10 mg dose (34.2 ± 7.9 to 31.2 ± 6.5 ml/beat/m²). Systemic and pulmonary vascular resistance both increased significantly (p < .05) over those at baseline during this period. Systemic vascular resistance returned to baseline within 2 hr after dosing, but pulmonary vascular resistance tended to remain elevated through the 8 hr after dosing. No significant changes in any of these variables were noted after the 5 or the last 10 mg dose. There were no significant differences in these measures during the baseline periods preceding each dosing interval.

Significant decreases in heart rate were noted after the 5 mg dose and the first and last 10 mg doses (all p < .05).

FIGURE 1. From top to bottom: heart rate, cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) at predose baseline and after the first 10 mg dose of pindolol. A significant (p < .05) decline in heart rate, CI, and SI was noted coincident with significant increases in SVR and PVR.
The decline in heart rate was observed within 2 hr after dosing and returned to baseline 4 to 6 hr after dosing. A significant (p < .05) decline in mean blood pressure was observed within 1 hr after the 5 mg dose (96 ± 18 to 89 ± 20 mm Hg) and persisted for 8 hr. No significant changes in mean systemic pressure were noted after the first or fourth 10 mg dose. There was no significant deviation in pulmonary capillary wedge pressure from the mean baseline value of 19 ± 11 mm Hg after any of the drug doses.

**Exercise hemodynamics.** The mean baseline exercise duration of 11.4 ± 3.4 min tended to decline (to 10.1 ± 3.0 min) after pindolol, but this change was not statistically significant. Changes in hemodynamic variables at peak exercise before drug and 2 hr after the last 10 mg dose are illustrated in figure 2. Peak heart rate fell from 127 ± 61 to 93 ± 11 beats/min (p < .0001). Peak cardiac index fell from 4.46 ± 0.67 to 3.44 ± 0.96 liters/min/m² (p < .05), but stroke volume index did not change. Peak mean blood pressure declined significantly from 123 ± 13 to 107 ± 16 mm Hg (p < .005); peak exercise systemic vascular resistance was unchanged before and after dosing. A significant (p < .05) increase in peak pulmonary vascular resistance was noted (375 ± 211 to 500 ± 287 dynes-sec-cm⁻²). Pulmonary capillary wedge pressure at peak exercise was not changed after administration of pindolol.

**Inotropic indexes (Table 2).** QS2I shortened slightly, but significantly (p < .005), from 565 ± 50 to 560 ± 52 msec after the first 10 mg dose of pindolol. Significant changes in QS2I were not observed after the 5 or the last 10 mg dose. There were no significant changes compared with the predose baseline values for any of the remaining left ventricular inotropic indexes. A significant trend toward an increase in mean right ventricular ΔP/ΔT was noted after the 5 mg dose (p = .08) and a decrease in mean RV-ΔP/ΔT that did not attain statistical significance was observed after the final 10 mg dose.

**Neurohumoral response.** Mean baseline plasma norepinephrine was 609 ± 171 pg/ml (normal in our laboratory = 196 ± 7 pg/ml). Norepinephrine level at baseline in patients 6 and 9 (the two patients developing hypotension after receiving the drug) was 2053 pg/ml and 931 pg/ml, respectively, and exceeded the range of 247 to 475 pg/ml in the remaining patients. Significant changes in norepinephrine levels were not seen after the 5 mg dose, but a trend toward an increase was seen after the first 10 mg dose (p < .1).

Plasma renin increased in patients 6 and 9 after the 5 mg dose (figure 3). In the remaining eight patients, mean renin level decreased significantly (p < .05) and individual renin concentrations decreased in each subject after dosing. No significant change in mean renin level was noted after the 10 mg dose.

**Relationship of drug concentration to hemodynamic and inotropic responses.** Mean free plasma concentrations of pindolol after the 5 mg and the first and fourth 10 mg doses are shown in figure 4. Peak drug concentration was noted from 1.5 to 2 hr after administration of drug.

With respect to the hemodynamic variables measured, the mean cardiac index declined from baseline with increasing drug concentration (r = −.59, r² =
.35, p < .01). There was no correlation between the change in heart rate and drug concentration. A positive correlation between free pindolol concentration and mean change from baseline in pulmonary (r = .67, r² = .45, p < .005) and systemic (r = .57, r² = .32, p < .05) vascular resistances was observed, as demonstrated in figure 5, A.

A positive correlation (figure 5, B) between free drug concentration and mean change in percent fractional shortening was demonstrated (r = .82, r² = .67, p < .05). The change in QS2I was negatively correlated with free drug plasma concentration (r = -.79, r² = .63, p < .05). There was a significant trend toward a positive correlation between pindolol concentration and mean change in circumferential fiber shortening (r = .70, r² = .49, p = .1).

Discussion

This study demonstrates that, in patients with congestive cardiomyopathy, the hemodynamic response to the ISA β-blocker pindolol differs from that observed in subjects with normal ventricular function.

FIGURE 3. Plasma renin concentrations at baseline and 2 hr after the 5 mg dose of pindolol. A marked increase in renin concentration was noted after pindolol in the two patients having the highest baseline plasma concentrations of norepinephrine and who did not tolerate the drug due to drug-induced hypotension (open circles). In the remaining patients, baseline plasma renin concentration declined after dosing (closed circles). An increase in mean plasma renin, which did not attain statistical significance, was noted for the entire population (open triangles). Excluding the two patients who became hypotensive, a modest, but significant, decrease in mean plasma renin (X) was observed.

TABLE 2

Values for inotropic indexes at baseline and 2 hr after pindolol

<table>
<thead>
<tr>
<th></th>
<th>5 mg pindolol</th>
<th></th>
<th></th>
<th>10 mg pindolol</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 10)</td>
<td>After dose (n = 10)</td>
<td>Baseline (n = 9)</td>
<td>After dose (n = 9)</td>
<td>Baseline (n = 7)</td>
<td>After dose (n = 7)</td>
</tr>
<tr>
<td>ΔD%</td>
<td>16.1 ± 1.5</td>
<td>16.4 ± 1.7</td>
<td>16.8 ± 1.4</td>
<td>18.6 ± 1.8</td>
<td>17.8 ± 1.8</td>
<td>18.2 ± 2.4</td>
</tr>
<tr>
<td>Vcf (msec)</td>
<td>0.70 ± 0.07</td>
<td>0.70 ± 0.07</td>
<td>0.69 ± 0.07</td>
<td>0.76 ± 0.07</td>
<td>0.70 ± 0.07</td>
<td>0.71 ± 0.09</td>
</tr>
<tr>
<td>ΔP/ΔT (mm Hg/sec)</td>
<td>776 ± 124</td>
<td>707 ± 128</td>
<td>927 ± 209</td>
<td>862 ± 184</td>
<td>817 ± 148</td>
<td>921 ± 161</td>
</tr>
<tr>
<td>QS2I (msec)</td>
<td>567 ± 15</td>
<td>564 ± 17</td>
<td>565 ± 17</td>
<td>560 ± 0.5</td>
<td>566 ± 19</td>
<td>568 ± 20</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.62 ± 0.04</td>
<td>0.63 ± 0.06</td>
<td>0.57 ± 0.05</td>
<td>0.60 ± 0.06</td>
<td>0.57 ± 0.04</td>
<td>0.56 ± 0.07</td>
</tr>
<tr>
<td>RV-ΔP/ΔT</td>
<td>72.1 ± 27.3</td>
<td>104.1 ± 39.3</td>
<td>68.1 ± 18.8</td>
<td>75.9 ± 17.8</td>
<td>83.1 ± 27.1</td>
<td>60.3 ± 24.6</td>
</tr>
<tr>
<td>RV-PEP/RVET</td>
<td>0.67 ± 0.10</td>
<td>0.65 ± 0.08</td>
<td>0.73 ± 0.16</td>
<td>0.57 ± 0.07</td>
<td>0.65 ± 0.14</td>
<td>0.68 ± 0.12</td>
</tr>
</tbody>
</table>

Data are the mean ± SEM. ΔD% = percent fractional shortening; Vcf = velocity of circumferential shortening; other abbreviations are as under "inotropic indexes" in the Methods section.

*p < .05 change from predose baseline; *p < .1 change from predose baseline.
Unlike previous reports in subjects with normal or mildly reduced ventricular contractility, a significant decline in cardiac index and stroke volume index associated with an increase in systemic and pulmonary vascular resistance was noted after administration of drug in this study. Moreover, pulmonary and systemic vascular resistance increased and cardiac index decreased with increasing drug concentration.

Neurohumoral profile of the study population. The differences from the response in normal subjects that we noted may in part be attributable to the markedly abnormal neurohumoral profiles characteristic of patients with congestive cardiomyopathy. Elevated plasma norepinephrine levels were noted in the study population. Remarkable was the greatly increased baseline plasma norepinephrine in the two patients who developed severe hypotension after the administration of pindolol. Evidence suggests that there is an inverse correlation between the plasma level of norepinephrine and the degree of hemodynamic compensation in the patient with heart failure. These two patients, having the highest levels of norepinephrine, may represent a subset of patients with minimal hemodynamic reserve and a greater dependence on endogenous catecholamines for the central inotropic and/or chronotropic stimulation necessary for maintenance of cardiac output.

That peripheral and pulmonary vascular resistance increased after pindolol suggests that the β-agonist effects of pindolol, which are known to mediate vasodilation in normal and hypertensive subjects, are not expressed in a heart failure population. This may indicate that (1) the intrinsic sympathomimetic activity of pindolol contributes little above the near maximal stimulation of receptors by elevated endogenous catecholamines, or (2) responsiveness of peripheral β-receptors to agonist stimulation is reduced due to mechanisms such as receptor downregulation. In either case, the β-blocking rather than β-agonist properties of pindolol would predominate, leading to an “unmasking” of α-receptor-mediated effects and subsequent elevation of systemic and pulmonary vascular resistance.

The renin profile of the study population is a second neurohumoral characteristic that appears to distinguish patients most sensitive to β-blockade (figure 3). The two patients who did not tolerate pindolol hemodynamically had the highest baseline renin levels. Also, in these two patients, renin concentration increased after the 5 mg dose of pindolol, whereas renin decreased in each of the remaining eight patients (figure 3). Similar to the case for norepinephrine, baseline renin levels appear to be inversely related to the degree of hemodynamic compensation in the patients with congestive heart failure. Second, in normal subjects, β-blockade decreases resting renin concentration and attenuates the rise in renin associated with hemodynamic stress such as upright tilt. In patients 6 and 7...
9, this attenuation was not observed, perhaps reflecting deterioration of marginal hemodynamic compensation and a reduction in renal perfusion pressure of a magnitude sufficient to override the influence of β-blockade.24

Response to exercise. Previous reports in hypertensive subjects have noted an increase in peak exercise stroke volume after administration of an ISA β-blocker.25 It has been proposed that ISA may account for this improvement through a beneficial inotropic effect on the myocardium. Such an increase in exercise stroke volume was not seen in the current study, suggesting that an effect of ISA is not present during exercise in a population with congestive cardiomyopathy. The significant reduction in peak cardiac index and peak heart rate as well as the increase in pulmonary vascular resistance at peak exercise would further imply that the sympathomimetic properties of pindolol are not expressed to an observable degree under these conditions. Reduction of peak heart rate has been previously noted after pindolol in patients with ischemic heart disease and normal ventricular function.4,26 In the study reported by Frishman et al.4 the reduction in maximal heart rate after pindolol was equivalent to that observed after propranolol, even though there was no reduction in resting heart rate with pindolol. It was hypothesized that the marked increase in endogenous catecholamines known to occur during exercise outweighed the intrinsic sympathomimetic activity of the drug, thus eliminating effects of ISA with exercise.4 It is known that catecholamine levels increase markedly during exercise in patients with congestive heart failure,27 and thus, as in the resting state, ISA appears to be masked in the environment of increased catecholamines encountered during exercise in a heart failure population.

Inotropic response to drug administration. There were no significant changes in right or left ventricular ino-
tropic variables after dosing other than a modest improvement in QS2I, and correlation of changes in these variables with drug level did not reveal an adverse inotropic effect. The observed correlation between drug level and change in circumferential fiber shortening, percent fractional shortening, and QS2I are in fact consistent with an improvement rather than a decline in left ventricular contractility.9, 28, 29

Thus, the negative influence of pindolol on overall ventricular performance would appear to result predominantly from a disadvantageous elevation in right and left ventricular afterload mediated through peripheral β-blockade, rather than a primary alteration in ventricular inotropy. Whether the intrinsic sympathomimetic activity of pindolol is responsible for preservation of contractility, as has been suggested by studies in normal subjects, remains speculative.5

In conclusion, in the setting of greatly elevated levels of catecholamines characteristic of congestive heart failure and exercise, the potent intrinsic sympathomimetic activity of a drug such as pindolol may not be expressed in the peripheral vasculature due to the already marked stimulation of β-receptors by endogenous norepinephrine. The result is a profile that resembles that after administration of pure β-blockers to subjects with normal ventricular function.30 However, there does not appear to be a significant decline in left or right ventricular inotropic state after pindolol. The net response in this population appears to be determined by the effects of systemic and pulmonary vascular β-blockade and the consequent rise in ventricular afterload. Thus, the intrinsic sympathomimetic activity of agents such as pindolol may not protect against the potential adverse effects of β-blockade in patients with congestive heart failure. Markedly elevated baseline levels of plasma norepinephrine and increases in renin levels after the administration of drug appear to identify patients at increased risk for a potential adverse hemodynamic response to this ISA β-blocker. The response to long-term administration of ISA β-blockers in patients with congestive heart failure may differ from the hemodynamic-inotropic profile after short-term use, as suggested by findings after repeated drug dosing, and requires further study.

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1397


P F Binkley, R F Lewe, J J Lima, A Al-Awwa, D V Unverferth and C V Leier

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