A REVIEW OF THE HAEMODYNAMIC EFFECTS OF LABETALOL IN MAN

J.N. COHN, J. MEHTA & G.S. FRANCIS
Cardiovascular Division, Department of Medicine, University of Minnesota, Medical School, Minneapolis, Minnesota, USA

1 Labetalol at a dose of 800 to 1600 mg daily inhibited isoprenaline-induced tachycardia and phenylephrine-induced elevation in arterial pressure in hypertensive subjects. The β-adrenoreceptor effect was four times more potent than the α-adrenoreceptor effect.

2 Isoprenaline-induced tachycardia was more effectively blocked than isoprenaline-induced inotropism, thereby raising the possibility of a subselective effect on cardiac β-adrenoceptors.

3 Labetalol reduced blood pressure in hypertensive subjects with no change in cardiac output in the supine or upright position and with marked inhibition of the heart rate and blood pressure response to treadmill exercise.

4 Labetalol administered in single doses to patients with stable, treated congestive heart failure impaired blood pressure support during exercise.

5 The unique adrenoceptor and haemodynamic effects of labetalol make it a potentially attractive drug for management of hypertension and other cardiovascular disorders.

Introduction

Blockade of β-adrenoceptors results in slowing of the heart rate and reduction in cardiac output at rest (Sowton *et al.*, 1966). During exercise the increase in heart rate and cardiac output is attenuated and a reduction in exercise tolerance results (Epstein *et al.*, 1965). Renal release of renin is also inhibited (Johnson *et al.*, 1976), but especially when a non-selective β-blocker is used there seems to be an increase in α-receptor vasoconstrictor activity in the periphery (Simon *et al.*, 1979). Thus, although β-adrenoceptor blockade might reduce arterial pressure by virtue of a number of haemodynamic effects, the increased α-adrenoceptor activity would be expected to counteract the anti-hypertensive property of the drug.

α-adrenoceptor blockade produces a quite opposite constellation of effects. Tachycardia and an increase in cardiac output generally result (Richards *et al.*, 1978), but inhibition of α-receptor stimulation during orthostasis leads to orthostatic hypotension (Graham *et al.*, 1976). Renin release is increased after α-adrenoceptor blockade, probably by virtue of reflex sympathetic stimulation which results in increased β-adrenoceptor activity (McDonald *et al.*, 1977). The combination of α- and β-adrenoceptor blockade would be expected to markedly enhance the anti-hypertensive effect of these two separate pharmacological effects but also might be expected to aggravate orthostatic hypotension and perhaps result in exercise hypotension (Khatri & Cohn, 1970).

We describe here the results of haemodynamic studies carried out before and during administration of labetalol, a drug which has combined β- and α-blocking properties. The responses to this drug indicate a unique circulatory effect that may make it a particularly attractive agent for therapy of hypertension and perhaps other cardiovascular disorders.

Methods

All studies were carried out in hospitalized subjects. Protocols were approved by the institutional human studies committee, and patients gave written, informed consent to participate.

Hypertensive subjects were hospitalized in a clinical research unit. All previous anti-hypertensive therapy had been withdrawn at least 2 weeks before the study. Cuff blood pressure was measured at three hour intervals throughout the day and the values meaned to provide a daily average. Single blind placebo was administered on days 1-3. On the fourth hospital day labetalol was administered in a dose of 50 mg four times daily (200 mg daily). The dose was increased progressively to 400 mg on day 5, 800 mg on days 6 and 7, 1200 mg on day 8 and 1600 mg on days 9 and 10. On days 11 and 12, placebo

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was again administered.

Haemodynamic studies were carried out in the placebo period (study 1) and on day 7 (low dose, 800 mg daily; study 2) and day 10 (high dose, 1600 mg daily; study 3). The brachial artery was cannulated and a central venous catheter positioned. Pressures were measured directly using Statham transducers and cardiac output was measured using the indocyanine green dye dilution technique. Measurements were made during rest in the supine position, during quiet upright standing, during incremental intravenous infusion of isoprenaline and phenylephrine, and during progressive treadmill exercise.

The acute haemodynamic response to labetalol and its effect on exercise tolerance was also studied in four subjects with stable congestive heart failure receiving maintenance therapy with digitalis and diuretics. These subjects were hospitalized free of oedema and were clinically stable. All suffered from chronic heart failure due either to previous myocardial infarction or to non-ischaemic cardiomyopathy and manifested by dyspnoea and/or fatigue on exertion. They were in functional class II or III based on New York Heart Association criteria. The brachial artery was cannulated and the pulmonary artery catheterized with a ballon-tipped floatation catheter. Cardiac output was measured by thermodilution.

Results and Discussion

Adrenoceptor-blocking effect

As previously reported (Mehta & Cohn, 1977), oral administration of labetalol produced inhibition of the response to both isoprenaline and phenylephrine. With low dose labetalol (800 mg daily) the dose of isoprenaline required to increase heart rate was increased eight-fold; after high dose (1600 mg daily) the required dose was increased by approximately 15-fold (Figure 1). The dose of phenylephrine required to increase diastolic arterial pressure was also increased by labetalol in these subjects. At a dose of 800 mg, the phenylephrine dose requirement was increased by approximately 2.5-fold and after 1600 mg by approximately three to four-fold (Figure 2). Thus in hypertensive human subjects it seems that labetalol is approximately four times more potent in producing inhibition of β-adrenoceptors than of α-adrenoceptors.

Anti-hypertensive effect

The anti-hypertensive effect of labetalol could be clearly demonstrated during a 7 d titration of the drug in hypertensive subjects (Figure 3). A marked decrease in arterial pressure appeared after the first day of therapy. At doses up to 800 mg daily the effect seemed to be largely non-orthostatic but when the dose was increased further an orthostatic hypotensive effect began to emerge. Heart rate decreased only slightly as the dose of labetalol was

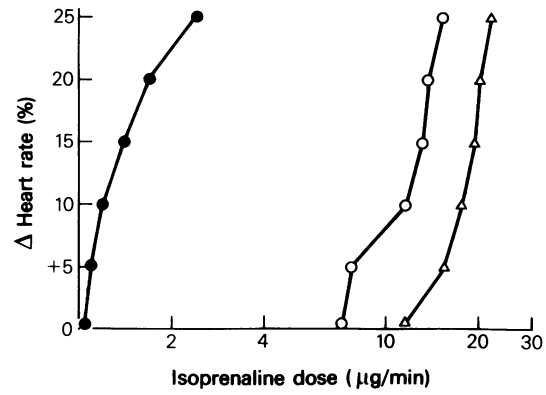

Figure 1 Effect of labetalol low dose (○, 800 mg daily), and high dose (△, 1600 mg daily) on heart rate response to isoproterenol. The dose of isoproterenol required to increase heart rate is markedly increased in the presence of labetalol. ●, Placebo. (Reprinted from *Circulation*, **55**, 370–375, 1977.)

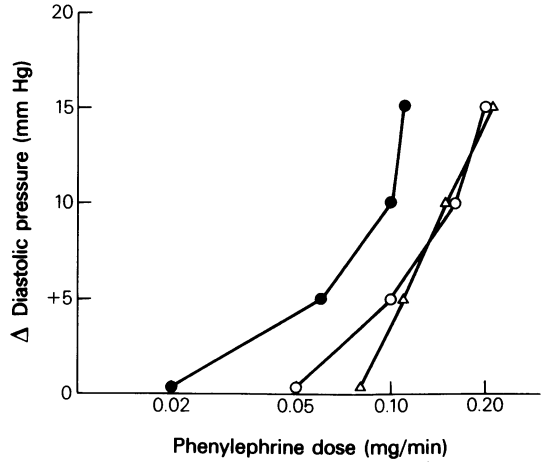

Figure 2 Effect of labetalol at low dose (○, 800 mg daily) and high dose (△, 1600 mg daily) on diastolic arterial pressure response to phenylephrine. The dose of phenylephrine required is increased 2.5-fold at the low dose and three to four fold at high dose. ●, Placebo. (Reprinted from *Circulation*, **55**, 370–375, 1977.)

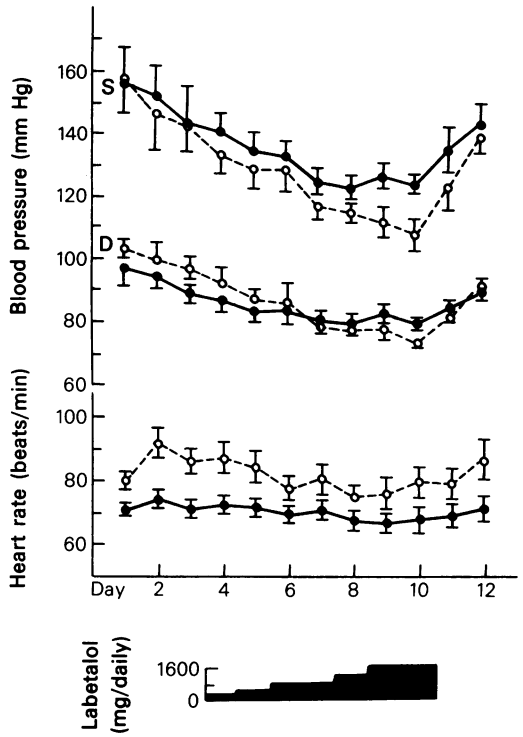

Figure 3 Blood pressure and heart rate responses to labetalol administration. ●, Supine; ○, standing. Both systolic and diastolic arterial pressures decreased with initiation of therapy, and the anti-hypertensive effect increased as the labetalol dose was increased. At the higher doses a mild orthostatic hypotensive effect was noted. (Reprinted from *Circulation*, **55**, 370–375, 1977.)

increased, and tachycardia in response to the standing position seemed to be largely unaffected. These data suggest that a significant α-adrenoceptor-blocking effect of the drug, sufficient to interfere with homeostatic mechanisms, may emerge only at higher doses. The absence of bradycardia at any dose of the drug despite its anti-hypertensive properties even at low doses, suggests that the normal bradycardia effect of β-blockade is being counteracted. Furthermore, haemodynamic studies carried out at both the low and high doses of labetalol showed that the decrease in arterial pressure was accompanied by an unchanged cardiac output and therefore by a striking reduction in systemic vascular resistance. This haemodynamic pattern of response (Figure 4) is quite atypical for β-blockade alone and indicates that at both low and high doses of labetalol, another pharmacological action is evident.

The response to exercise further distinguishes this drug: at both doses (800 and 1600 mg daily) marked attenuation of both the arterial pressure and heart response to exercise occurred (Figure 5). Although the heart rate attenuation is quite typical for β-blockers the magnitude of the blood pressure attenuation seemed to be considerably more striking than has been observed after both non-selective and selective β-adrenoceptor-blocking therapy.

Effects in stable chronic heart failure

β-blockers have recently been advocated by Swedberg *et al.* (1980) for the management of congestive heart failure complicating cardiomyopathy. Vasodilators, including α-adrenoceptor blockers, have been widely used in recent years for the treatment of congestive heart failure (Cohn & Franciosa, 1977).

In order to assess the effect on this patient population a study was undertaken in four stable patients with chronic congestive heart failure being treated with digoxin and diuretics. The haemodynamic effect of a single 100 mg oral dose was assessed at rest and during upright exercise on a bicycle ergometer. Little change in arterial pressure, pulmonary arterial pressure or cardiac output was observed in the supine position. Similarly, standing pressures were not altered. However, during and after exercise, the arterial pressure tended to decrease. In one patient hypotensive syncope occurred during exercise (Figure 6).

The findings, particularly in this one patient within the setting of left ventricular dysfunction, emphasize the importance of compensatory adrenergic mechanisms in supporting blood pressure during exercise. A possible explanation for this exercise hypotension is that the α-constrictor tone in non-exercising vascular beds is important in redistributing blood flow during exercise (Blair *et al.*, 1961). In the absence of α-adrenoceptor function and especially when β-adrenoceptor reflex cardiac activation also is inhibited, a decreasing peripheral resistance during exercise cannot be matched by an increased cardiac output when cardiac function is impaired. This response seems to be quite different from the post-exercise hypotension observed after treatment of hypertensive subjects with peripheral sympathetic blockers such as guanethidine. This latter phenomenon seems to be due in a large part to pooling of blood in the lower extremities immediately after exercise (Khatri & Cohn, 1970). It is of course possible that this adverse response was a first-dose effect (Graham *et al.*, 1976) and that the patients would become tolerant to the hypotensive effect of the drug.

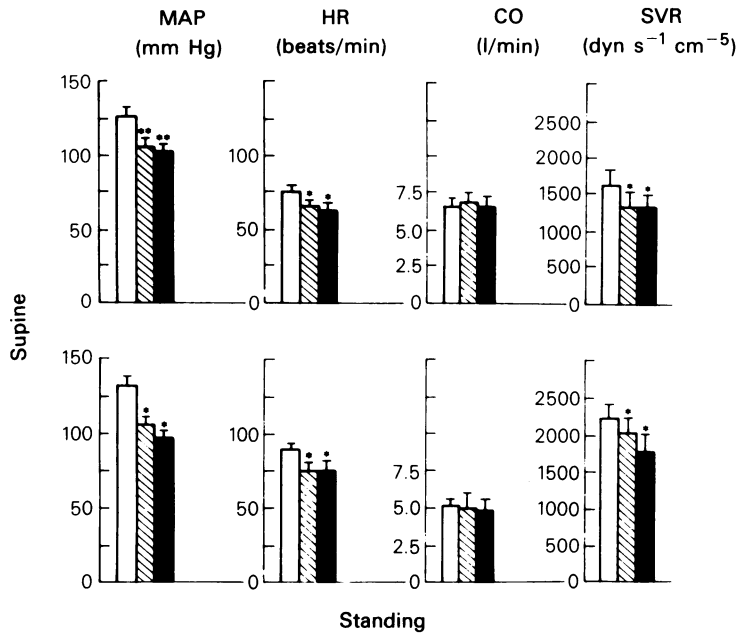

Figure 4 Hemodynamic response to labetalol administration in supine and standing positions. Decrease in mean arterial pressure (MAP), heart rate (HR), systemic vascular resistance (SVR) and unaltered cardiac output (CO) can be noted during labetalol administration. Open columns, Placebo; hatched columns, labetalol 800 mg daily; solid columns, 1600 mg daily. *P<0.01; *P<0.05. (Reprinted from *Circulation*, **55**, 370–375, 1977.)

Inotropic compared with chronotropic effects

Another observation made during studies with labetalol in the hypertensive subjects suggests that the drug may more effectively inhibit β-adrenoceptors involved in chronotropic effects rather than β-adrenoceptors involved with inotropic effects. Isoprenaline infusion during the placebo period (study 1) produced an increase in heart rate at the first dose tested (1.0 μg/min) (Table 1). A 25% increase in heart rate was achieved with 2.4 ± 0.3 μg/min. This heart rate response was associated with a decrease in diastolic pressure of 8 mmHg. Cardiac output was not measured during isoprenaline infusion in the placebo period. During treatment with low dose labetalol (study 2), the highest dose of isoprenaline which did not accelerate heart rate (threshold dose) had increased to 7.3 ± 1.7 μg/min. A 25% increase in heart rate (peak) required 15.0 ± 1.7 μg/min isoprenaline infusion. The diastolic pressure increased by an average of 5 and 7 mmHg at threshold and peak heart rate levels, respectively. During high dose labetalol therapy (study 3) the threshold and peak doses were 10.9 ± 2.0 and 21.0 ± 3.8 μg/min isoprenaline infusion, respectively. Diastolic arterial pressure increased by 7 and 10 mmHg at the time of threshold and peak doses (Table 1). The isoprenaline dose required to increase heart rate during studies 2 and 3 was significantly different than in the placebo phase ($P<0.001$).

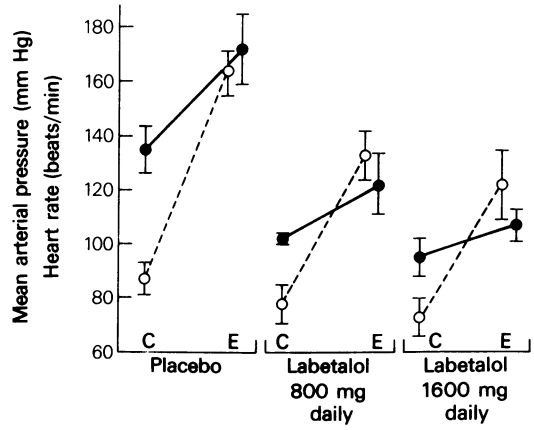

Figure 5 Exercise response to labetalol administration. Note the marked attenuation of the increase in mean arterial pressure (—) and in heart rate (----). C, Control; E, exercise.

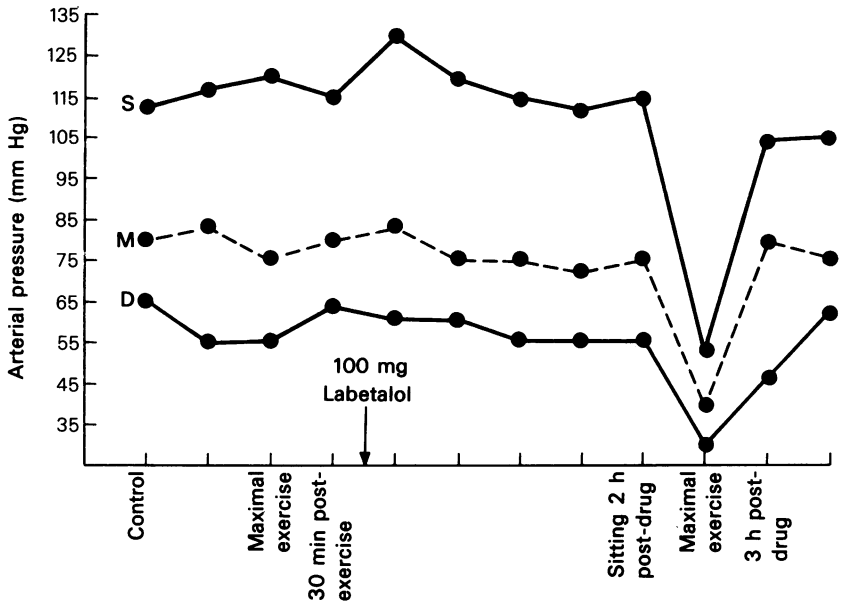

Figure 6 Effect of labetalol on arterial pressure response to exercise in a patient with heart failure. After labetalol, systolic (S), diastolic (D) and mean (M) arterial pressures decreased precipitously during submaximal exercise resulting in severe exercise hypotension.

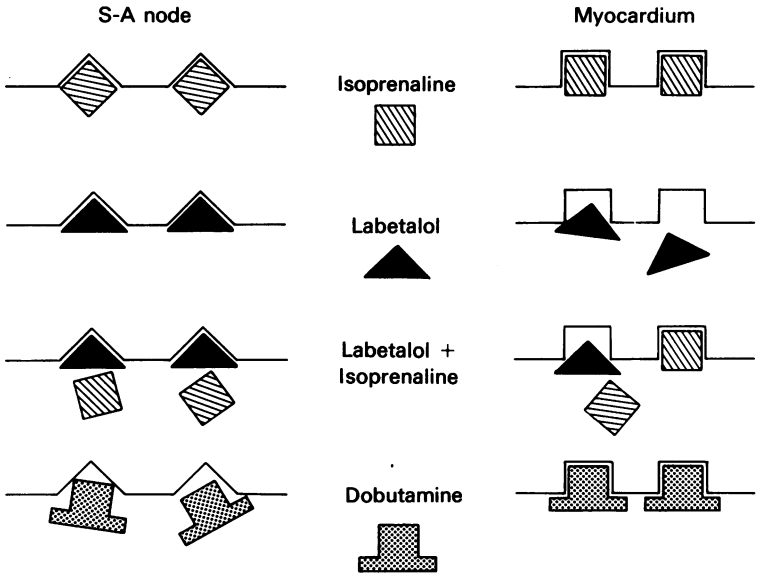

Figure 7 Theoretical schema for receptor configuration to account for the effects of isoprenaline, labetalol and dobutamine, a relatively selective inotropic β agonist.

Table 1 Diastolic pressure and stroke volume responses to isoproterenol infusion in labetalol-treated subjects

Subject	Control state		Labetalol 800 mg daily			Labetalol 1600 mg daily		
	Isoproterenol dose (μg/min)	*ΔDP (mmHg)*	*Isoproterenol dose (μg/min)*	*ΔDP (mmHg)*	*ΔSV (o/o)*	*Isoproterenol dose (μg/min)*	*ΔDP (mmHg)*	*ΔSV (o/o)*
1	T 1.0*	−6	10.0	+7	-	13.0	+10	-
	P 2.0	−9	18.0	+20	-	20.0	+2	-
2	T 1.0	−8	5.0	+5	+ 4.2	7.0	+10	+15.3
	P 1.5	+2	9.0	+5	+14.4	15.0	+15	− 1.0
3	T 1.0	0	1.5	+5	+14.4	8.0	+15	+6.7
	P 3.5	−4	14.0	+10	+ 2	17.0	+20	+20.2
4	T 1.0	−18	10.0	+5	+39.4	20.0	+ 7	+15.3
	P 2.5	−4	17.5	+5	+60.6	40.0	+12	+9.0
5	T 1.0	−1	10.0	+7	+37.6	10.0	+0	+28.0
	P 2.5	−14	20.0	+2	+17.6	20.0	+ 9	+25.6
6	T 1.0	−3	5.0	0	+15.3	7.5	+ 1	+27.9
	P 2.5	−20	12.5	+1	+21.4	16.0	+ 1	+11.8
Mean ± s.e.mean	T 1.0	−6±2.7	7.3±1.7	+5±1.0	+22.2±7.0	10.9±2.0	+7.2±2.0	+18.6±4.0
	P 2.4±0.3	−8±3.2	15±1.7	+7±3.0	+23.0±10.0	21±3.8	+10±3.0	+13.1±4.6

T, Threshold dose of isoproterenol producing no increase in heart rate. *First dose of isoproterenol (1:0 g/min) produced an increase in heart rate of 6.5 beats/min during the control period. P, Peak dose of isoproterenol resulting in 25% increase in heart rate. ΔDP, Change in diastolic pressure. ΔSV, Change in stroke volume.

During study 2, stroke volume increased from 109 ± 13 to 132 ± 15 ml ($P < 0.001$) without an increase in heart rate at threshold isoprenaline dose and to 132 ± 14 ml ($P < 0.001$) at peak dose. During study 3, stroke volume increased from 101 ± 12 to 118 ± 10 ml ($P < 0.001$) and 115 ± 15 ml ($P < 0.001$) at threshold and peak isoprenaline doses, respectively.

After labetalol treatment, therefore, a marked disparity occurred between the dose of isoprenaline required to increase stroke volume and the dose required to increase heart rate in hypertensive patients. At doses from 2-10 μg/min stroke volume was increased, the patients said they were aware of more forceful cardiac contraction but no increase in heart rate occurred nor decrease (actually a slight increase) in diastolic arterial pressure (Table 1). From this it seems unlikely that the increased stroke volume can be attributed to reflex cardiac stimulation or to a decreased impedance to left ventricular ejection.

Overall, our data suggest that infusion of isoprenaline after labetalol results in a haemodynamic state with increased contractility, an increase in cardiac output and no change in heart rate. This haemodynamic pattern is similar to the haemodynamic response to a drug such as dobutamine, which is used as a relatively pure β-adrenoceptor agonist with very limited chronotropic effects (Akhtar *et al.*, 1975). A possible explanation for this labetalol-induced effect may be that receptors mediating inotropism differ from those mediating chronotropism and that labetalol has preferential effects on the chronotropic receptor (Bonelli, 1978).

Regardless of mechanism, however, this pharmacological effect of combined isoprenaline and labetalol so closely mimics the effects of dobutamine that it leads one to conclude that structural alterations of drug molecules may be able to produce distinctive pharmacological effects (Figure 7).

Conclusions

These acute or short-term studies indicate that labetalol is a particularly potent agent that seems to have striking effects on both the cardiac function and the peripheral vascular bed. The haemodynamic profile of this drug suggests that it may be very effective in the management of hypertension, as its α-adrenoceptor-blocking effect seems to counteract the increase in systemic vascular resistance that usually accompanies β-adrenoceptor blockade. Furthermore, the potent inhibition of the exercise-induced increase in arterial pressure produces a striking reduction in the rate-pressure product during exercise. This should have a salutary effect on myocardial oxygen consumption that could be of use in the management of hypertensive subjects with angina pectoris. From our results in patients with compromised cardiac function, however, we cannot recommend its use in this type of patient.

Finally, the apparent effect of labetalol to dissociate the inotropic from chronotropic effects of isoprenaline should stimulate similar studies with other β-adrenoceptor blockers to determine if this is a unique or more generalized response to these drugs. Nonetheless, if this dissociation were to pertain to responses to endogenous adrenergic stimulation, it should provide for a safety factor in the use of this drug particularly in the setting of left ventricular dysfunction.

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