HEMODYNAMIC BENEFITS OF LONG-TERM BUNAZOSIN (α_1 -BLOCKER) THERAPY IN RATS WITH MYOCARDIAL INFARCTION AND HEART FAILURE

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To determine whether bunazosin (α_1 -adrenoceptor blocking agent) can alter the hemodynamic profile of chronic heart failure secondary to myocardial infarction, the drug was administered to Wistar rats 4 weeks after coronary ligation, and continued for 4 weeks. In rats without bunazosin treatment, the left ventricular end-diastolic pressure (LVEDP) and the total vascular resistance index (TVRI) increased as a function of infarct size, while the cardiac index (CI) decreased. But in infarcted rats with bunazosin treatment, the mean aortic pressure and TVRI were reduced, the LVEDP was modestly lessened, and the CI was maintained. The greatest increase in CI after the treatment occurred in rats with infarcts of small and moderate size. Thus, long-term therapy with bunazosin improved LV dysfunction, relative to the size of infarction. This study suggests the beneficial effects of bunazosin therapy in patients with chronic heart failure.

VASODILATOR therapy has been shown to be effective in the management of patients with heart failure.¹⁻⁵ Although the vasodilating action of α -adrenoceptor blocking agents (α -blockers) after acute administration has been well documented, evidence for their long-term efficacy has been controversial.¹ The hemodynamic effects of several α -blockers, including prazosin,² indramine⁶ and trimazosin,⁷ have been extensively studied. These agents have been advocated particularly for hypertension and heart failure. A tolerance to beneficial effects of prazosin has been reported after short-term clinical and hemodynamic improvement.²

Bunazosin, a quinazoline derivative, is a potent α -blocker.⁸⁻¹⁰ The major difference between bunazosin and other α -blockers is the selectivity of effect on vascular α_1 - and α_2 -receptors: the action of bunazosin is highly selective to α_1 -receptors.⁸ There are no reports of the effects of chronic treatment with bunazosin in heart failure.

Our study was carried out to evaluate the hemodynamic efficacy of bunazosin treatment in a rat model of myocardial infarction and heart failure,^{3,11} since this drug may be useful for chronic vasodilator therapy.

METHODS

Experimental animals: Myocardial infarction was produced in female Wistar rats weighing 200 to 300g each, by ligating the left coronary artery, using a technique described by Johns et al,¹² with

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some modifications. Briefly, under ether anesthesia, the heart was exteriorised, and the left coronary artery was ligated 1 to 2 mm from its origin, and the heart was repositioned in the chest, which was then closed. The operation mortality was 30%. The rat was allowed to recover and was maintained on standard rat chow and water ad libitum.

Treatment procedures: Four weeks after the ligation, by which time the necrotic myocardium was completely replaced by scar tissue,¹³ either

Fig.1. Histological section of the ventricle of a rat killed 8 weeks after ligation of the left coronary artery (HE stain, 1X). The border of the infarction is shown by dashed lines. LV = left ventricle; RV = right ventricle.

bunazosin at a dose of 200 μ g/day or physiological saline solution was injected via polyethylene tube (PE 50) into the femoral vein by mini-osmotic pump (Alzet, Model 2002).

Hemodynamic studies: After treatment for 4 weeks, each rat was lightly anesthetized with ether and hemodynamic measurements were made. The rat was intubated and maintained under anesthesia by an ether drip apparatus arranged in series with the respirator (Harvard Apparatus, Model 680).¹⁴ Via the right carotid artery, a 3F Millar's micromanometer (Model PR-249) was placed in the ascending aorta and was advanced into the left ventricle. A thoracotomy exposed the ascending aorta for placement of an electromagnetic flow probe (Narco Coop.) with an internal diameter of 2.0 mm.¹⁵ After stabilization, these signals were recorded by an Electronics for Medicine recorder (VR-12). With this preparation, the cardiac output was defined as the total ascending aortic flow and, as such, it excluded coronary blood flow. The CI was obtained by dividing the cardiac output by the body weight.

Plasma bunazosin concentration: After the hemodynamic study, blood was sampled from the aorta, and the plasma bunazosin concentration was determined using high-performance liquid-chromatography.

Determination of infarct size: After the physiological measurements were finished, the

TABLE I PLASMA BUNAZOSIN CONCENTRATION AND BODY WEIGHT GAIN

Infarct-size	Non-MI 0%	Infarcted Rat		
		Small (3–15%)	Moderate (16–30%)	Large (31–48%)
Number of rats				
Untreated rat	12	10	10	7
Treated rat	5	6	6	6
Infarct Size (%)				
Untreated rat	0	8 $\pm$ 1	21 $\pm$ 1	40 $\pm$ 4
Treated rat	0	11 $\pm$ 1	20 $\pm$ 2	42 $\pm$ 2
Plasma Bunazosin Concentration (ng/ml)				
Treated rat	8.7 $\pm$ 1.8	12.4 $\pm$ 4.1	7.3 $\pm$ 1.1	13.6 $\pm$ 2.8
Body weight gain (g)				
Untreated rat	29 $\pm$ 6	24 $\pm$ 2	28 $\pm$ 11	19 $\pm$ 10
Treated rat	34 $\pm$ 13	29 $\pm$ 6	28 $\pm$ 4	28 $\pm$ 11

Infarct sizes are expressed as the mean $\pm$ SD. Body weight gain and plasma bunazosin concentration are expressed as mean $\pm$ SEM.

Non-MI = non-infarcted rats; Treated = bunazosin treated.

TABLE II EFFECTS OF BUNAZOSIN ON HEMODYNAMICS

Infarct-size	Non-MI 0%	Infarcted Rat		
		Small (3–15%)	Moderate (16–30%)	Large (31–48%)
<i>Heart rate (beats/min)</i>				
Untreated rat	314 ± 18	319 ± 12	323 ± 10	300 ± 18
Treated rat	348 ± 24	323 ± 17	342 ± 16	314 ± 15
<i>LV systolic pressure (mmHg)</i>				
Untreated rat	116 ± 5	112 ± 4	107 ± 4	103 ± 7
Treated rat	91 ± 6*	91 ± 2*	92 ± 4*	89 ± 6*
<i>LV end-diastolic pressure (mmHg)</i>				
Untreated rat	4 ± 1	4 ± 1	9 ± 2	20 ± 4#
Treated rat	5 ± 1	7 ± 2	6 ± 2	17 ± 3#
<i>LV(+)dP/dt max (mmHg/sec)</i>				
Untreated rat	5386 ± 392	4651 ± 293	3891 ± 234#	3069 ± 467#
Treated rat	4630 ± 690	4568 ± 547	4258 ± 570	2662 ± 475#
<i>Mean aortic pressure (mmHg)</i>				
Untreated rat	93 ± 3	86 ± 3	90 ± 4	96 ± 3
Treated rat	76 ± 2*	77 ± 3	75 ± 4*	73 ± 6*
<i>Stroke index (μl/kg)</i>				
Untreated rat	816 ± 110	603 ± 63#	493 ± 44#	537 ± 97#
Treated rat	659 ± 112	861 ± 76*	763 ± 31*	635 ± 66
<i>Cardiac index (ml/min·kg)</i>				
Untreated rat	251 ± 23	189 ± 19#	157 ± 12#	149 ± 20#
Treated rat	230 ± 39	274 ± 19*	261 ± 13*	203 ± 27
<i>Total vascular resistance index (mmHg·min·kg/l)</i>				
Untreated rat	404 ± 3	496 ± 5	592 ± 32#	715 ± 9#
Treated rat	370 ± 4	289 ± 3*	291 ± 16*	376 ± 3*

Results are expressed as the mean ± SEM.

Non-MI = non-infarcted rats; Treated = bunazosin treated; LV = left ventricular.

#: Difference compared with "non-Infarcted Rats" group in either treated or untreated rats ($p < 0.05$).

*: Difference between untreated and treated rats in comparable infarct size ($p < 0.05$).

heart was excised, and the atria and great vessels were trimmed from the ventricle, which was fixed in 20% formalin for histological study. Transverse 6 μm sections were cut from the apex to the base of the left ventricle, and 1-mm segments of these sections were mounted and stained for connective tissue with Azan-Mallory stain. With a planimeter (Digital Image Analyzer, Luzex 500), the endocardial circumference of the infarcted and non-infarcted portions of the left ventricle were determined. The infarcted circumference of all (9 to 12) sections were summed and then expressed as ratio of the summed circumference of the left ventricle⁴.

Statistical analysis: The results of infarct size measurements are presented as means ± SD. Other data are presented as means ± SEM. The

infarcted rats were divided into three groups according to infarct size: small, 3–15%; moderate, 16–30%; large, 31–48%. Student's t-test was used for between-treatment comparisons. A one-way analysis of variance was used for within-treatment comparisons.

RESULTS

Eight weeks after coronary artery ligation, the hemodynamics of 62 rats were studied. Seventeen of these rats did not have histological evidence of a myocardial infarction and are termed non-infarcted rats. The 45 infarcted rats demonstrated well-healed areas of infarction ranging from 3% to 48% of the left ventricular (LV) endocardial circumference (Fig. 1). Infarcted rats

Fig. 2. The vasodilating effects of bunazosin in non-infarcted rats, and rats with small, moderate and large infarct. Open and closed circles denote bunazosin-untreated and treated rats, respectively. Non-MI = non-infarcted rats; Small = rats with small infarcts; Moderate = rats with moderate infarcts; Large = rats with large infarcts.

were not readily discernible by general appearance, since there were no clinical signs of heart failure. There were no differences in infarct size in between-treatment comparisons, and no differences of plasma bunazosin concentration in the treated rat groups (Table I). The body weight gain was the smallest in the untreated rats with large infarcts, of which two lost weight. There were no significant differences in the plasma bunazosin concentration in the treated groups.

Hemodynamic data are summarized in Table II. There were no significant differences in heart rate among the groups. In untreated rats, the left ventricular end-diastolic pressure (LVEDP) and total vascular resistance index (TVRI) progressively increased with increasing infarct size, and the (+)dP/dtmax (the maximum rate of rise of LV systolic pressure), stroke index and cardiac index (CI) decreased progressively. The LV systolic pressure in untreated rats tended to decline as infarct size increased. Mean aortic pressure in untreated rats was not changed with increasing infarct size.

In bunazosin-treated rats, the mean aortic and LV systolic pressures and TVRI were always lower than in untreated rats with comparable infarcts. The differences in these indexes were

Fig. 3. The effects of bunazosin-treatment on the total vascular resistance index and the cardiac index in non-infarcted rats and in rats with small, moderate and large infarcts.

Abbreviations are the same as in Fig. 2.

significant in rats with moderate and large infarcts. The LVEDP of the treated rats also increased with increasing infarct size. However, in rats with moderate and large infarcts, this variable was lower than that of the untreated rats with comparably sized infarcts, but not significantly so. With increasing infarct size, the (+)dP/dt of the treated rats also declined. Both cardiac and stroke indexes of the treated rats with small and moderate infarcts were significantly higher than those of untreated rats with infarcts of comparable size, but the increase in those indexes in the rats with large infarcts was not significant.

DISCUSSION

Left coronary artery ligation in rats provided LV free wall infarction, the size of which varied from 3% to 48% in this study. The relative size of infarction was quantitatively related to hemodynamic impairments: the LVEDP and TVRI progressively increased and CI was decreased, as a function of infarct size, as reported by Pfeffer et al.¹¹ Thus, the hemodynamic profile of this model is similar to that of patients with chronic myocardial infarction.¹⁶ The rats with large infarcts are comparable to patients with severe heart failure, with low CI, elevated LVEDP, increased peripheral resistance and modestly low

aortic pressure. Weight gain in the untreated rats with large infarcts was smallest, as may also be characteristic of severe heart failure with so-called cardiac cachexia.

Vasoconstriction has recently become recognized as an important pathophysiologic factor in the syndrome of congestive heart failure.^{1,5} An important consequence of the usual type of heart failure is low cardiac output. To maintain arterial pressure in such circumstances, the peripheral vascular resistance must rise; this adaptive change is achieved mainly by catecholamine stimulation of the α -receptors. The postsynaptic α_1 -receptor is the major mediator of sympathetic constriction of vascular smooth muscle. The presynaptic α_2 -receptor inhibits postsynaptic release of norepinephrine.¹⁷ Therefore, inhibition of vasoconstriction by interference with the α_1 -receptor has appeared to be a rational approach to therapy for heart failure.⁵

Bunazosin [4-amino-2- (4-butyrylhexahydro-1H-1, 4-diazepine-1-yl)- 6, 7-dimethoxyquinazoline hydrochloride] is one of a series of quinazolines with α_1 -receptor antagonist properties.⁸⁻¹⁰ This drug is more selective to α_1 -receptor than prazosin.⁸ In this study, bunazosin lowered the mean aortic pressure without significantly increasing the heart rate. This is in agreement with earlier studies of patients with hypertension,¹⁸ and spontaneously hypertensive rats.⁹ Apparently, the absence of tachycardia in response to bunazosin should be attributed to the maintenance of α_2 -receptor activity which inhibits further norepinephrine release and limits the tachycardia.¹⁷ Bunazosin markedly reduced TVRI (afterload) in rats with and without infarcts (Fig. 2). It modestly lowered LVEDP (preload) in rats with moderate and large infarcts, while the LVEDP of non-infarcted rats and rats with small infarcts remained within normal ranges. Because the LV afterload and preload mainly depend respectively on the peripheral resistance and the capacitance of the vascular bed, its dilating action appears to be exerted on resistance as well as capacitance vessels. Reduction of the TVRI, produced by bunazosin, increased the CI in infarcted rats, particularly in rats with moderate infarcts (Fig. 3).

The development of tolerance to the effects of vasodilators during maintenance therapy in patients with chronic heart failure has been the subject of several recent studies.¹ Packer et al reported that initial doses of orally administered prazosin produced improvement in patients with

heart failure, yet serial doses of the drug were accompanied by the development of tolerance.² In view of the results of our study, therapy of bunazosin for 8 weeks improved the LV function. This indicates that the beneficial effects of this drug are sustained without development of tolerance during prolonged administration.

Because of the ability of bunazosin to reduce LV preload and afterload, it appears to be potentially useful in patients with chronic heart failure.

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