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Beneficial Effects of Chronic Bunazosin (α_1-blocker) Therapy on the Infarcted Left Ventricle of the Rats

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Abstract To determine whether long-term hemodynamic improvement could be occurred, bunazosin was administered intravenously for 28 days to rats with different sized chronic myocardial infarction. Left ventricular and aortic pressures and aortic blood flow were measured in bunazosin-treated and untreated rats. Infarct size was determined histologically. In untreated rats, cardiac index decreased and total vascular resistance and left ventricular end-diastolic pressure incresed progressively as a funcion of infarct size. Whereas, in bunazosin-treated rats, cardiac index and total vascular resistance were maintained in rats both with and without infarcts, and left ventricular end-diastolic pressure remained within normal limits in all except those with large infarct size. Thus, long-term therapy of bunazusin attenuated the impairment of left ventricular performance that were observed in rats with chronic myocardial infarction.

Key words : α_1-blocker, Myocardial infarction, Bunazosin

Introduction

In the treatment of patients with congestive heart failure, vasodilating agents have been introduced for over ten years[1]. Short-term studies showed that, regardless of the vasodilator used, the arteriolar and venous dilatation produced invariably improvement in hemodynamic status of patients. This short-term hemodynamic response, however, is not a reliable guide to favorable long-term clinical improvement. Rouleau et al.[2] reported that prazosin, α_1-blocker, caused clinical improvement and Arnold et al.[3] observed that rapid development of tolerance to prazosin occurred despite initial impressive response.

The model of myocardial infarction resulted form coronary artery ligation in the rat showed a wide spectrum of left ventricular impairment ranging from minimum to severe heart failure[4], as is observed in man.

The present study was undertaken to determine whether new α_1-blocker bunazosin, of which the structual formula is shown in Fig. 1 and α_1-blocking effect is more selective than that of prazosin[5], could have favorable and sustained effects on hemodynamics in

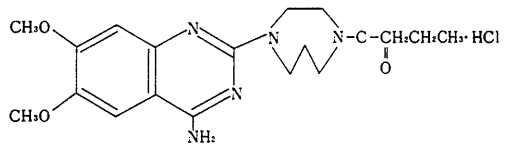

Fig. 1 Structure of bunazosin.

chronic infarcted rats.

Methods

Experimental Preparation

Ligation of the coronary artery was performed in female Wistar rat weighing 200-300g by a technique described elsewhere[6]. In brief, the rats were anesthetized with ether, weighed, intubated, and ventilated by a Harvard rodent ventilator (Model 683) with the minute volume adjusted according to body weight[7]. After a left-sided thoracotomy, the left atrium was retracted to facilitate ligation of the left coronary artery between the pulmonary outflow tract and left atrium, and then the thorax immediately closed. There are 30% and 43% mortality rate within the first 24 hours and 28 days following this procedure, respectively. Surviving rats were housed under identical conditions and maintained on standard rat chow and water ad libitum.

From the 28th day after coronary artery ligation, either bunazosin at a dose of 200mg/day or physiological saline solution was administered for 28 days from femoral vein by mini-osmotic pump(Alzet, Model 2002), via polyethylen tube (PE50).

Hemodynamics

On the 56th day after coronary artery ligation, the rats were again weighed and intubated under ether anesthesia, and ventilation and anesthesia were maintained by a positive pressure respirator connected in series with an ether-drip apparatus. Via right carotid artery, a Millar's micromanometer (Model PR-249) was placed in ascending aorta and left ventricle. A thoracotomy provided exposure of the ascending aorta for placement of an electromagnetic flow probe (Narco Corp.) with an internal diameter of 2.0mm[8]. Under light anesthesia and spontaneous respiration, measurements were made of heart rate, phasic and mean aortic pressures, left ventricular systolic and end-diastolic pressures, maximum rate of rise of left ventricular systolic pressure (+dP/dt), and cardiac output, neglecting the coronary blood flow. Cardiac index and stroke index were determined by dividing cardiac output and stroke volume by body weight, respectively. Total vascular resistance was calculated by dividing mean aortic pressure by cardiac output.

Pathology and Plasma Bunazosin Concentration

After hemodynamic study, blood was sampled from the aorta, and plasma bunazosin concentration was determined using a high-performance liquid-chromatographic method.

The rats were sacrificed and the heart was dissected, and the atria and great vessels were trimmed. The ventricle was fixed in 20 % formalin solution for histologic processing. Serial sections with each thickness of 6-μm were obtained every 1 mm separation from apex to base and were stained with Azan-Mallory stain for connective tissue. From 9 to 12 sections were obtained from each heart. Using an image analyzer (Luzex 500), the lengths of scar and of noninfarcted muscle for the endocardial surface of each histological section were determined and summed numerically for all histological sections. The ratio of the sums of the lengths of scar and of surface circumference defined the infarct size, expressed as percent[9].

For analysis, the rats were classified into groups according to infarct size. Results were expressed as mean$\pm$1.SEM. Analysis of variance was performed to determine the presence of significant differences between the various groups. A probability of less than 0.05 was regarded as significant.

Results

According to infarct size, the rats were classified as small ($<$15%), moderate (15%$\leqq$, $<$30%), and large (30%$\leqq$). This distribution produced groups with comparable infarct sizes for between-treatment comparisons (Table 1). Rats that underwent coronary artery ligation without sustaining myocardial infarction were designated as the noninfarcted group. Body weight gain after the coronary artery ligation was the smallest in untreated rats with large infarct size. There was a slight increase, not significant statistically, in plasma bunazosin concentration in treated rats with small and large infarct size.

Hemodynamic data are summerized in Table 2. There was no significant difference of heart rate among groups. Both left ventricular systolic pressure and mean aortic pressure of treated rats were reduced compared with untreated rats with comparable infarct size. In untreated rats, left ventricular end-diastolic pressure progressively rose with increasing infarct size, being significantly higher in rats with moderate

Table 1 Distribution of Myocardial Infarct Size and Plasma Bunazosin Concentration

Infarct-size	Non-Infarcted Rat	Infarcted Rat		
	0%	Small (<15%)	Moderate (15%≦, <30%)	Large (≧30%)
Number of the rats				
Untreated rat	9	8	4	5
Treated rat	5	5	7	4
ΔBW (g)				
Untreated rat	32±8	20±1	23±7	5±7
Treated rat	34±13	27±7	28±4	30±17
Plasuma Bunazosin Concentration (ng/ml)				
Treated rat	8.7±1.8	12.4±4.1	7.3±1.1	13.6±2.8

Each value represents the average ±SEM. ΔBW=body weight gain during the experiment. Difference compared with "non-Infarcted Rat" group in either treated or untreated rats ($P<0.05$).

Table 2 Effects of Bunazosin on Hemodynamics in Rats with Myocardial Infarction

Infarct-size	Non-Infarcted Rat	Infarcted Rat		
	0%	Small (<15%)	Moderate (15%≦, <30%)	Large (≧30%)
Heart Rate (beats/min)				
Untreated rat	345±15	331±15	320±21	307±25
Treated rat	348±24	333±17	334±16	333±14
Left Ventricular Systolic Pressure (mmHg)				
Untreated rat	112±6	111±5	105±4[a]	112±4
Treated rat	91±6[b]	92±2[b]	92±4	89±6[b]
Left Ventricular End-diastolic Pressure (mmHg)				
Untreated rat	4±1	5±1	12±3[a]	17±3[a]
Treated rat	5±1	6±2	6±2	16±4[a]
+dP/dt (mmHg/sec)				
Untreated rat	5797±356	4930±445	3687±216[a]	3693±234[a]
Treated rat	4630±690	4922±510	4258±570	3187±526
Mean Aortic Pressure (mmHg)				
Untreated rat	96±5	86±4	88±3	96±4
Treated rat	76±2[b]	77±4	75±4	81±4[b]
Stroke Index (μl/beats・kg)				
Untreated rat	712±67	616±69	532±76	552±119
Treated rat	659±112	807±65	762±31	666±53
Cardiac Index (ml/min・kg)				
Untreated rat	239±23	207±22	166±14	152±29
Treated rat	230±39	281±23[b]	262±10[b]	229±29
Total Vascular Resistance (kdyne・sec・cm^{-5})				
Untreated rat	94±12	130±16[a]	151±11[a]	160±24[a]
Treated rat	102±13	80±12[b]	78±4[b]	101±9[b]

Each value represents the average ±SEM. [a]Difference compared with "non-Infarcted Rat" group in either treated or untreated rats ($P<0.05$). [b]Difference between untreated and treated rats in comparable infarct size ($P<0.05$).

(12±3mmHg) and large infarct size (17±3mmHg) than in noninfarcted rats (4±1mmHg). In contrast, left ventricular end-diastolic pressure remained within normal range in treated rats except rats with large infarct size (16±4mmHg). The maximum

rate of rise of left ventricular systolic pressure, +dP/dt, decreased significantly in untreated rats with moderate (3687±216mmHg/sec) and large (3693±234mmHg/sec) infarct size compared with the noninfarcted rats (5797±356mmHg/sec). There was no significant difference of +dP/dt among groups in treated rats. In untreated rats, there was a progressive decline of cardiac index with increasing infarct size, such that this index was significantly decreased in rats with large infarct size (152±29ml/min kg), compared with noninfarcted rats (239±29ml/min kg). In contrast, in treated rats cardiac index was not reduced in any of the infarct groups. In untreated rats, total vascular resistance progressively increased with increasing infarct size, whereas in treated rats there was no increment of total vascular resistance in any of the infarct groups.

Discussion

The development of varying degree of left ventricular dysfunction, which has been shown to exert an adverse effect on prognosis, is observed in patients with myocardial infarction in acute phase and following recovery[10]. The failure of most studies in dogs with experimental myocardial infarction to which showed severe impairment of cardiac performance may be related to the relatively small size of infarcts[11]. In contrast, the rat model of myocardial infarction displayed a broad spectrum of cardiac dysfunction, from minimal impairment to overt heart failure in relation to infarct size[4]. We observed, in this study, that left ventricular end-diastolic pressure and total vascular resistance rose and cardiac index declined progressively with increasing infarct size in untreated rats. In addition, histological evolution of infarction after coronary artery ligation in rats closely resembled that in man and scar formation was completed usually by 21 days after coronary artery ligation[12]. For these reasons, we used rat model of chronic myocardial infarction produced by coronary artery ligation in this study.

As the pump function of left ventricle deteriorates and cardiac output decreases, a number of neurohumoral mechanisms, including the sympathetic nervous system and renin-angiotensin system, are activated in order to maintain circulatory stability. Arteriolar vasoconstriction results in an increased systemic vascular resistance, and venoconstriction causes an increase in ventricular filling pressure. Appreciation of the important role played by peripheral vasoconstriction in the pathophysiology of heart failure has led to the widespread use of vasodilators as treatment[13]. Vasodilators reduce systemic vascular resistance by arteriolar vasodilatation or decrease ventricular filling pressure by venodilatation or both. One of the reason for a higher incidence of tolerance with long-term administration of previously available α-blockers, such as phentolamine and phenoxybenzamine, appears to be related to a lower selectivity to α_1-adrenoceptor[13]. The action of α_1-blocker, such as prazosin[14] and bunazosin[5], is limited to postsynaptic α_1-adrenoceptor with little effect on presynaptic α_2-adrenoceptor, which may result in a greater vasodilation and absence of concomitant tachycardia and renin release through the negative feed-back mechanism mediated by intact α_2-adrenoceptor[15]. In the present study, the long-term administration of bunazosin to rats with chronic myocardial infarction yielded sustained favorable hemodynamic results: total vascular resistance, left ventricular systolic pressure, and mean aortic pressure were reduced, and cardiac index was preserved or augmented comparing with untreated rats with infarcts of comparable size, and heart rate did not change, and left ventricular end-diastolic pressure remained within normal limits except in rats with large infarct size.

Several recent reports indicated the development of tolerance to long-term administration of prazosin[16]. However, the action to α_1-adrenoceptor of bunazosin is more selective than that of prazosin[5]. In this study, favorable and long-term efficacy of bunazosin on hemodynamics was demonstrated. In the treatment of congestive heart failure, the present study suggests that chronic administration of bunazosin could produce sustained improvement of hemodynamic sta-

tus in patients with chronic myocardial infarction and possibly in patients with the other various heart diseases.

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