Blockade of AT_1 receptors enhances baroreflex control of heart rate in conscious rabbits with heart failure

HIROSHI MURAKAMI, JUN-LI LIU, AND IRVING H. ZUCKER
Department of Physiology and Biophysics, University of Nebraska College of Medicine, Omaha, Nebraska 68198–4575

Murakami, Hiroshi, Jun-Li Liu, and Irving H. Zucker. Blockade of AT_1 receptors enhances baroreflex control of heart rate in conscious rabbits with heart failure. *Am. J. Physiol.* 271 (*Regulatory Integrative Comp. Physiol.* 40): R303–R309, 1996.—Because the renin-angiotensin system is activated in heart failure, we hypothesized that angiotensin II (ANG II) plays a role in altering baroreflex sensitivity in the setting of heart failure. Accordingly, we evaluated the baroreflex control of heart rate (HR) in conscious, chronically instrumented rabbits in the normal state and after the establishment of heart failure. Heart failure was induced by rapid ventricular pacing at a rate of 360–380 beats/min for an average of 14.5 ± 1.4 days. The data were compared with normal rabbits instrumented in a similar fashion. Baroreflex curves were generated by inflation of implanted hydraulic occluders on the vena cava and aortic arch or by administration of phenylephrine and sodium nitroprusside. Experiments were carried out before and after intravenous administration of the AT_1 antagonist L-158,809. Rabbits with heart failure exhibited significantly lower arterial pressure (81 ± 3 vs. 69 ± 4 mmHg, $P < 0.05$), elevated resting HR (230 ± 5 vs. 260 ± 10 beats/min, $P < 0.05$), and elevated left atrial pressure (3.6 ± 0.7 vs. 13.1 ± 0.7 mmHg, $P < 0.05$). ANG II blockade had little effect on resting or baroreflex parameters in normal rabbits. However, in rabbits with heart failure, L-158,809 enhanced baroreflex sensitivity (2.7 ± 0.5 vs. 4.7 ± 0.8 beats·min^{-1}·mmHg^{-1}; $P < 0.05$), primarily by increasing the minimum HR evoked during baroreceptor activation. β_1-Blockade had no effect on any baroreflex parameter after L-158,809 in rabbits with heart failure. However, L-158,809 significantly reduced the minimum HR after pretreatment with atropine in rabbits with heart failure. These data suggest that ANG II plays a role in modulation of cardiac sympathetic tone in this model of heart failure and may be responsible for the depressed baroreflex sensitivity observed in heart failure.

sympathetic nerve activity; arterial pressure

IT IS WELL KNOWN THAT there are potent interactions between the renin-angiotensin system and the autonomic nervous system (27). Exogenous angiotensin II (ANG II) resets the baroreflex control of heart rate (HR) without changing its sensitivity (3, 13). ANG II also has been shown to attenuate the sensitivity of the baroreflex control of HR (15, 19). Although ANG II may participate in both phenomena, some of the differences in these results may be attributed to experimental design, including the dose of ANG II used (27).

The renin-angiotensin system is activated in human (25) and experimental heart failure (28). Sympathetic outflow is increased in heart failure, as suggested by an increase in plasma catecholamine levels as well as directly recorded muscle sympathetic nerve activity (10, 24). In experimental heart failure, the baroreflex control of HR is significantly impaired (6). These observations raise the hypothesis that both the renin-angiotensin system and the arterial baroreflex may be involved in the enhancement of sympathetic outflow in heart failure. Furthermore, it is conceivable that the blunted baroreflex is the result of augmented ANG II levels, either in the peripheral circulation or centrally.

The aim of the present study was to clarify the role of endogenous ANG II on baroreflex control of HR both in normal, conscious rabbits and in conscious rabbits with pacing-induced heart failure. Because ANG II has been implicated in the control of sympathetic outflow and norepinephrine release (27), we also determined the autonomic components of HR control before and after blockade of AT_1 receptors in normal rabbits and in rabbits with pacing-induced heart failure. These data suggest a role for ANG II in regulating cardiac sympathetic outflow in heart failure.

MATERIALS AND METHODS

Male New Zealand White rabbits, weighing 2.5–4.0 kg, were used in the present study. The rabbits were divided into two groups: a normal (sham) group and a heart failure group. All rabbits were fed and housed according to institutional guidelines at the University of Nebraska Medical Center. These studies were approved by the University of Nebraska Medical Center Institutional Animal Care and Use Committee and conform to the guidelines for the care and use of laboratory animals of the National Institutes of Health and the American Physiological Society.

Surgical Procedures

Rabbits were anesthetized with a formula consisting of ketamine hydrochloride (58.8 mg/kg; Ketaset, Fort Dodge), acepromazine maleate (1.2 mg/kg, Fermenta), and xylazine (5.9 mg/kg; Rompun, Miles) in lactated Ringer solution given by intramuscular injection (1 ml/kg). Supplemental anesthesia was provided by pentobarbital sodium (0.3–0.35 mg/kg, Anpro Pharmaceutical) injected intravenously via a marginal ear vein.

After the rabbit was intubated and placed on positive-pressure ventilation, a left thoracotomy was performed through the fifth intercostal space. Balloon occluders were placed around the descending thoracic aorta and the inferior vena cava to generate arterial pressure changes. A Micro-Renathane (Braintree Scientific) catheter was placed in the left atrium for the recording of left atrial pressure. Finally, a pacing electrode was secured to the apex of the left ventricle. The lead was brought out of the chest and connected to a pacemaker (Medtronic, 8529), which was implanted subcutaneously in the back. The chest was closed in layers and evacuated. The left atrial catheter and the two Tygon catheters connected to the occluders were exteriorized and tunneled subcutaneously to exit at the back of the neck. The normal rabbits were subjected to the same procedures as the

heart failure group, except for implantation of the pacemaker. Postoperatively, the rabbits were placed on an antibiotic regimen for 3–5 days (2.5 mg/kg im; Baytril, Miles).

At least 1 wk after this surgery, the rabbit was anesthetized as described above and Micro-Renathane catheters were inserted into the left common carotid artery and jugular vein. The catheters were flushed daily with heparin sodium (1,000 U/ml, Elkins-Sinn). During the recovery period, the rabbits were brought to the laboratory and trained to stand quietly in a plastic box of our own design.

Heart Failure Model

Heart failure was induced using the model of ventricular pacing originally described for the dog by Coleman et al. (7) and subsequently used in this laboratory (6). After control measurements were taken, the pacemaker was programmed to 360–380 beats/min and the rabbits were paced continuously for an average duration of 14.5 ± 1.4 days. At periodic intervals, the pacemaker was programmed to a rate of 30 beats/min to monitor resting hemodynamics.

Experimental Protocol

Normal group (n = 7). After full recovery from the surgeries, three types of baroreflex experiments were performed on different days and in random order. At least 48 h were allowed for recovery between experiments. On the day of the experiment, the rabbit was placed in a plastic box. The catheters were connected to pressure transducers (Gould) to measure arterial and left atrial or central venous pressures. HR was measured by a cardiotachometer (Gould biotach), triggered by the arterial pressure pulse. The signals were led to a MacLab data acquisition system (model 8s, Apple Computer) and sampled at 100 Hz/channel.

To investigate the role of endogenous ANG II on baroreflex control of HR, baroreflex curves were compared before and after intravenous injection of L-158,809 (a selective nonpeptide AT_1-receptor antagonist, 0.33 mg/kg; provided by Merck) (30). ANG II blockade was demonstrated by the complete inhibition of the pressor response to 0.1 μg of ANG II administered intravenously. This dose of ANG II increased mean arterial pressure (MAP) by 35 ± 3 mmHg before blockade and 3 ± 1 mmHg after blockade ($P < 0.01$). Ten to fifteen minutes were allowed to elapse before the postblockade curve was constructed. Baroreflex curves were generated by measuring the HR response to increases and decreases in arterial pressure by inflation of the aortic and vena caval occluders. Aortic and vena caval occlusions were carried out randomly. MAP was altered at a rate of 1–2 mmHg/s. In three rabbits, blood pressure was changed with either phenylephrine or sodium nitroprusside. This was done if a given occluder failed to function. The change in arterial pressure was similar whether occluders or vasoactive drugs were used.

To examine the parasympathetic components of the interaction between ANG II and autonomic innervation of the sinoatrial (SA) node, metoprolol bitartrate (a selective β_1-antagonist, 2 mg/kg) was injected intravenously and a baroreflex curve was generated before and after L-158,809 administration. Supplemental doses of metoprolol (0.2 mg/kg) were injected every 30 min.

To examine the sympathetic components of the interaction between ANG II and the autonomic innervation of the SA node, atropine methyl bromide (0.2 mg/kg) was injected intravenously and a baroreflex curve was generated before and after L-158,809 administration. Supplemental doses of atropine (0.02 mg/kg) were injected every 30 min.

Heart failure group (n = 12). After recovery from surgery, control hemodynamic measurements were made. Baroreflex curves were generated as described for the normal group. The pacemaker was then programmed to 360–380 beats/min. Hemodynamic measurements were made at periodic intervals after pacing.

When the left atrial pressure or central venous pressure was above 12 or 6.5 mmHg, respectively, the rabbits were placed into the experimental box and the pacemaker was turned off. The pacemaker was off for ~30 min before the first baroreflex curve was generated. Baroreflex curves were generated under three conditions, as described for normal rabbits. Namely, a control curve was followed by a curve after L-158,809; on a separate day, a control curve was followed by a curve after either atropine or metoprolol; and, finally, a curve was constructed after the autonomic blocker plus L-158,809.

Data Analysis

The HR and MAP data were taken every 2 s from the threshold to the saturation point, and a sigmoid logistic function was fit to the data using a nonlinear regression program (Sigma Plot ver. 4.16, Jandel) run on a Macintosh computer. Four parameters were derived from the following equation

$$HR = A/[1 + \exp[B(MAP - C)]] + D \quad (1)$$

where A is HR range, B is the slope coefficient, C is the pressure at the midpoint of the HR range (BP_{50}), and D is minimum HR. The peak slope (or maximum gain) was determined by taking the first derivative of the baroreflex curve described by *Eq. 1*. The first derivative was described by *Eq. 2*

$$Slope = [A \times B \times \exp[B(MAP - C)]]/([1 + \exp[B(MAP - C)]]^2) \quad (2)$$

All values are expressed as means ± SE.

Data were analyzed using a one-way analysis of variance for repeated measures when more than two sets of mean data were compared. When the F ratio exceeded the critical value, Fishers protected least-significant difference test was applied to test the significance of the differences among the values of each group. To evaluate the baseline parameters before and after L-158,809 alone, a paired t-test was used. A P value <0.05 was considered statistically significant.

RESULTS

Effects of L-158,809 on the Baroreflex Control of HR in Normal Rabbits

Table 1 shows the effects of L-158,809 on baseline hemodynamics and on curve parameters in the control state and after atropine or metoprolol. There was no significant effect of L-158,809 on arterial pressure for any treatment. Composite baroreflex curves generated during control and after L-158,809 are shown in Fig. 1*A*. L-158,809 caused a leftward shift in the curve, producing a significant reduction in BP_{50} from 85 ± 3 to 76 ± 4 mmHg ($P < 0.05$). In the control state, the HR range was 152 ± 9 beats/min. After L-158,809, the range was 149 ± 9 beats/min (not significant). The maximum gain was 5.6 ± 1.0 beats·min^{-1}·mmHg^{-1} in the control state and 6.9 ± 1.7 beats·min^{-1}·mmHg^{-1} after L-158,809 (not significant). There were no significant differences in any other parameter before and after administration of L-158,809. These results indicate that blockade of endogenous ANG II shifts the

Table 1. *Effect of L-158,809 on baseline MAP, HR, and logistic curve parameters in normal rabbits*

	MAP, mmHg	HR, beats/min	Range, beats/min	Average Slope, beats·min^{-1}·mmHg^{-1}	BP_{50}, mmHg	Min HR, BPM	Max Gain, beats·min^{-1}·mmHg^{-1}
Control	76 ± 1	221 ± 7	152 ± 9	0.15 ± 0.02	85 ± 3	158 ± 8	5.6 ± 1.0
L-158	71 ± 4	236 ± 7	149 ± 9	0.18 ± 0.03	76 ± 4*	158 ± 6	6.9 ± 1.7
Control	72 ± 3	197 ± 8	149 ± 8	0.17 ± 0.03	75 ± 3	145 ± 8	6.6 ± 1.7
Atropine	78 ± 3	248 ± 6*	49 ± 4*	0.26 ± 0.03	79 ± 2	238 ± 6*	3.2 ± 0.5*
Atr + L-158	72 ± 3	252 ± 7*	74 ± 7*†	0.17 ± 0.04	81 ± 4	219 ± 9*	2.7 ± 0.4*
Control	75 ± 3	214 ± 9	166 ± 9	0.15 ± 0.05	86 ± 4	145 ± 10	6.4 ± 2.3
Metoprolol	73 ± 4	206 ± 6	103 ± 5*	0.17 ± 0.05	78 ± 5	149 ± 6	4.6 ± 1.7
Met + L-158	68 ± 2	205 ± 6	108 ± 11*	0.13 ± 0.03	76 ± 3	145 ± 6	3.4 ± 1.1

Values are means ± SE; n = 7 rabbits. MAP, mean arterial pressure; HR, heart rate; BP_{50}, pressure at midpoint of HR range; Min, minimum; Max, maximum; L-158, L-158,809; Atr, atropine; Met, metoprolol. *Significantly different from control for each treatment; †significantly different from autonomic blockade value, $P < 0.05$.

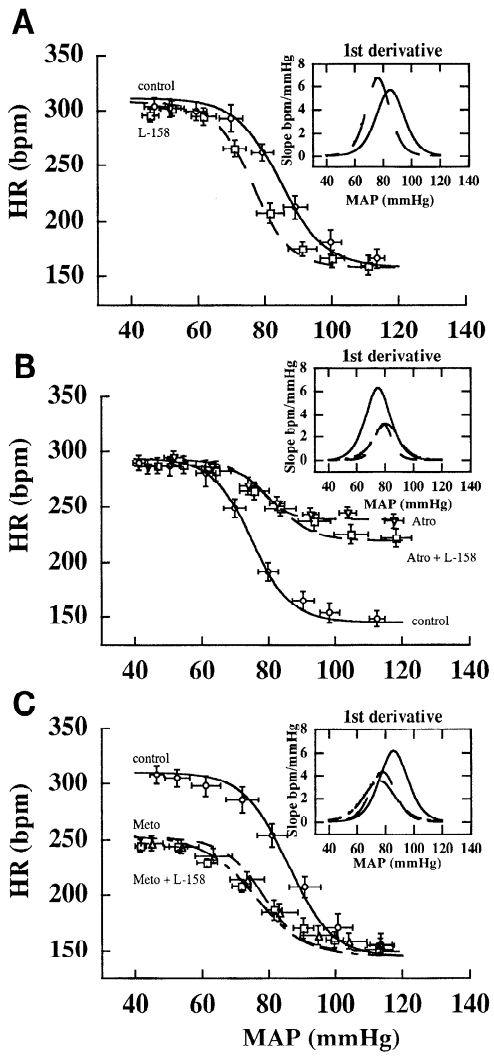

Fig. 1. *A*: composite baroreflex curves generated in control state and after administration of the ANG II antagonist L-158,809 (L-158) in normal rabbits (n = 7). *B*: baroreflex curves generated in control state, after pretreatment with atropine (Atro), and after L-158,809 plus atropine in normal rabbits (n = 7). *C*: baroreflex curves generated in control state, after pretreatment with metoprolol (Meto), and after metoprolol plus L-158,809 in normal rabbits (n = 7). Curves in *insets* depict gain at any given arterial pressure. HR, heart rate; bpm, beats/min; MAP, mean arterial pressure.

mean baroreflex curve to a lower pressure without changing its sensitivity. Given the nonsignificant change in baseline arterial pressure, the percent resetting was substantial, ~200%.

Effects of L-158,809 on the Baroreflex Control of HR in Normal Rabbits After Autonomic Blockade

Pretreatment with atropine. As can be seen from Table 1, atropine had no effect on arterial pressure but significantly increased HR. The addition of L-158,809 did not further affect resting HR. Composite baroreflex curves generated during control, after pretreatment with atropine, and after L-158,809 are shown in Fig. 1*B*. Although BP_{50} was not altered, the HR range was reduced from 149 ± 9 to 49 ± 4 beats/min ($P < 0.05$) by atropine alone. The addition of L-158,809 slightly but significantly increased the range to 74 ± 7 beats/min ($P < 0.05$). This range enhancement was due, in part, to a decrease in the minimum HR that occurred during increases in arterial pressure, even though the change in minimum HR (238 ± 6 beats/min after atropine vs. 219 ± 9 beats/min after L-158,809) was not significant.

Pretreatment with metoprolol. Table 1 shows the effects of metoprolol and metoprolol plus L-158,809 on resting MAP, HR, and curve parameters in normal rabbits. There were no significant effects on MAP or HR after treatment with the β_1-blocker or in combination with the AT_1 antagonist. Although metoprolol alone reduced the HR range from 166 ± 9 to 103 ± 5 beats/min ($P < 0.05$), the addition of L-158,809 had no additional effect.

Effects of Chronic Pacing on Hemodynamics and Baroreflex Control of HR

In the rabbits subjected to chronic pacing, the resting MAP, HR, mean left atrial pressure (LAP), and mean central venous pressure (CVP) before and after pacing are shown in Table 2. Pacing induced a significant reduction in MAP and a significant increase in HR, LAP, and CVP. The heart weights were significantly greater in the rabbits with heart failure compared with the normal rabbits (11.4 ± 0.5 vs. 7.9 ± 0.3 g, respectively; $P < 0.05$). In addition, the heart weight-to-body weight ratios were significantly increased when this group of paced rabbits was compared with the ratios for

Table 2. *Effects of pacing on resting MAP, HR, LAP, CVP, and logistic curve parameters*

	MAP, mmHg	HR, beats/min	LAP, mmHg	CVP, mmHg	Range, beats/min	Average Slope, beats·min^{-1}·mmHg^{-1}	BP_{50}, mmHg	Min HR, beats/min	Max Gain, beats·min^{-1}·mmHg^{-1}
Prepace	81 ± 3	230 ± 5	3.6 ± 0.7	0.6 ± 0.2	192 ± 7	0.13 ± 0.02	77 ± 3	143 ± 8	6.2 ± 0.6
Postpace	69 ± 4*	260 ± 10*	13.1 ± 0.7*	7.1 ± 0.5*	105 ± 9*	0.09 ± 0.01*	67 ± 4	212 ± 8*	2.3 ± 0.4*

Values are means ± SE; n = 12 rabbits. LAP, mean left atrial pressure; CVP, mean central venous pressure. *Significantly different from prepaced data.

the normal rabbits (3.8 ± 0.2 vs. 2.6 ± 0.1 g/kg; $P < 0.05$).

Composite baroreflex curves generated before and after pacing-induced heart failure are shown in Fig. 2. Heart failure induced several changes in the curves that can be described by the logistic parameters shown in Table 2. The HR range was decreased from 192 ± 7 to 105 ± 9 beats/min ($P < 0.05$), the minimum HR was increased from 143 ± 9 to 212 ± 8 beats/min ($P < 0.05$), and the maximum gain was decreased from 6.2 ± 0.6 to 2.3 ± 0.4 beats·min^{-1}·mmHg^{-1} ($P < 0.05$). There was no significant change in BP_{50} or maximum HR.

Effects of L-158,809 on Baroreflex Control of HR in Conscious Rabbits With Pacing-Induced Heart Failure

Table 3 shows baseline MAP, HR, and logistic curve parameters of paced rabbits before and after L-158,809 and after autonomic blockade. There were no significant differences in resting MAP or HR before and after administration of L-158,809. The higher apparent resting HR in the control state was due to one rabbit whose resting HR was in excess of 400 beats/min. Composite baroreflex curves generated during control and after L-158,809 are shown in Fig. 3*A*. In contrast to the normal rabbits, the maximum gain was significantly altered by administration of L-158,809. The maximum gain was changed from 2.7 ± 0.5 to 4.7 ± 0.8 beats·min^{-1}·mmHg^{-1} ($P < 0.05$) after administration of L-158,809. The average minimum HR for these seven rabbits tended to be reduced by L-158,809, but did not reach statistical significance. This was due to two rabbits in which the minimum HR was not reduced even though the maximum gain was dramatically enhanced.

Effects of L-158,809 on the Baroreflex Control of HR After Autonomic Blockade in Conscious Rabbits With Pacing-Induced Heart Failure.

Pretreatment with atropine. Atropine and atropine plus L-158,809 had no effect on MAP (Table 3). Atropine increased resting HR by 11% to 273 ± 7 beats/min (not significant). The addition of L-158,809 did not change HR from the level after atropine alone. The composite baroreflex curves generated during control, after atropine alone, and after atropine plus L-158,809 are shown in Fig. 3*B*. Although L-158,809 did not affect the maximum gain after atropine (2.0 ± 0.5 vs. 2.0 ± 0.3 beats·min^{-1}·mmHg^{-1}), it did significantly reduce the minimum HR from 251 ± 9 to 213 ± 2 beats/min ($P < 0.05$).

Pretreatment with metoprolol. Metoprolol had no effect on resting MAP or CVP (Table 3). However, it reduced resting HR from 264 ± 10 to 221 ± 10 beats/min ($P < 0.05$). The addition of L-158,809 had no further effect on resting HR. Composite baroreflex

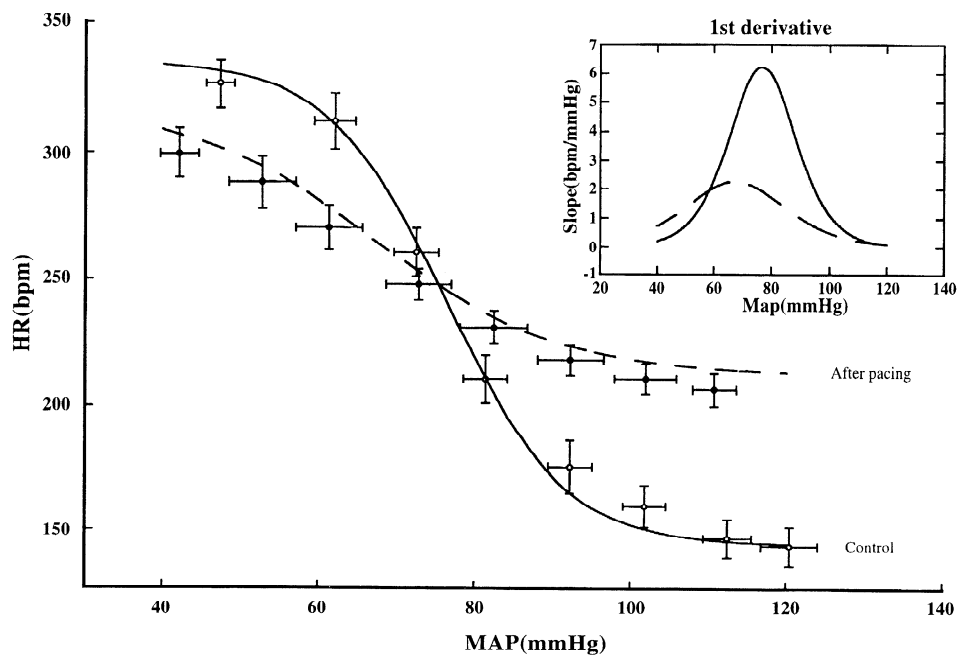

Fig. 2. Composite baroreflex curves generated before (control) and after pacing-induced heart failure (n = 12).

Table 3. *Effect of L-158,809 on baseline MAP, HR, and logistic curve parameters in rabbits with heart failure*

	MAP, mmHg	HR, beats/min	Range, beats/min	Average Slope, beats·min^{-1}·mmHg^{-1}	BP_{50}, mmHg	Min HR, beats/min	Max Gain, beats·min^{-1}·mmHg^{-1}
Control	68 ± 4	258 ± 9	138 ± 11	0.08 ± 0.02	67 ± 4	200 ± 7	2.7 ± 0.5
L-158	65 ± 3	265 ± 14	150 ± 12	0.13 ± 0.02*	71 ± 3	182 ± 11	4.7 ± 0.8*
Control	71 ± 8	245 ± 8	104 ± 17	0.07 ± 0.01	73 ± 7	193 ± 11	1.8 ± 0.3
Atropine	73 ± 7	273 ± 7	56 ± 10	0.14 ± 0.03	72 ± 7	251 ± 9*	2.0 ± 0.5
Atr + L-158	67 ± 7	271 ± 9	87 ± 13	0.10 ± 0.02	72 ± 7	213 ± 11†	2.0 ± 0.3
Control	73 ± 6	264 ± 10	80 ± 16	0.12 ± 0.03	71 ± 8	224 ± 6	2.8 ± 0.9
Metoprolol	69 ± 6	220 ± 10*	60 ± 16	0.10 ± 0.04	70 ± 8	194 ± 8*	1.6 ± 0.5
Met + L-158	64 ± 6	219 ± 10*	68 ± 14	0.11 ± 0.04	66 ± 7	189 ± 9*	1.9 ± 0.8

Values are means ± SE; n = 7 for control and atropine data. n = 6 for metoprolol data. *Significantly different from control for a given treatment; †significantly different from pretreatment value.

curves generated during control, after pretreatment with metoprolol, and after L-158,809 are shown in Fig. 3*C*. L-158,809 given after metoprolol had no significant effects on any of the curve parameters.

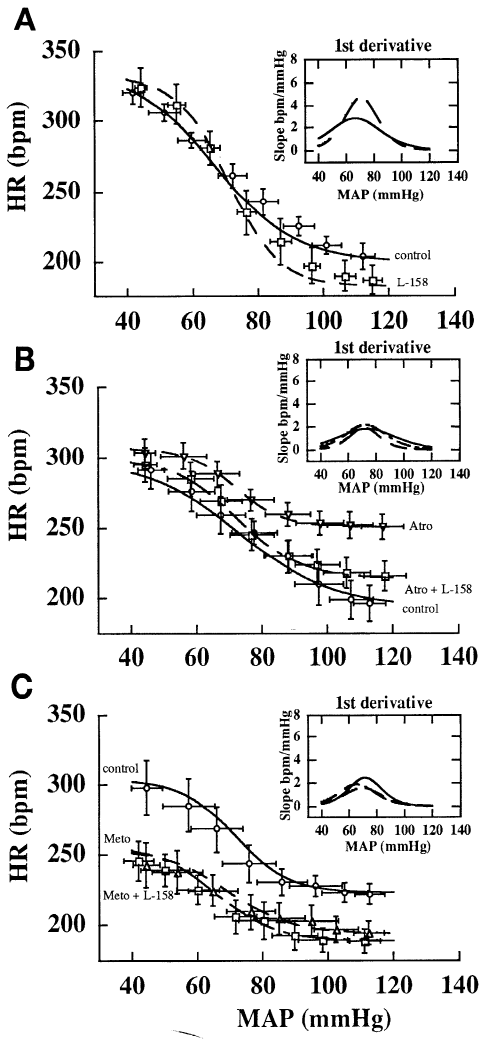

Fig. 3. *A*: composite baroreflex curves generated during control and after L-158,809 in rabbits with pacing-induced heart failure (n = 7). *B*: composite baroreflex curves generated in control state, after pretreatment with atropine, and after atropine plus L-158,809 in rabbits with pacing-induced heart failure (n = 7). *C*: composite baroreflex curves generated in control state, after pretreatment with metoprolol, and after metoprolol plus L-158,809 in rabbits with pacing-induced heart failure (n = 6).

DISCUSSION

The major findings of the present study are that *1*) the impaired baroreflex control of HR in conscious rabbits with pacing-induced heart failure is partially restored by blockade of endogenous ANG II using the selective AT_1-receptor antagonist L-158,809, *2*) the major effect on resting HR and on the baroreflex after AT_1-receptor blockade in rabbits with heart failure appears to be due to inhibition of cardiac sympathetic outflow, and *3*) blockade of endogenous ANG II in the conscious, normal rabbit resets the baroreflex to a lower pressure without changing its sensitivity.

The model of heart failure used in these studies was that of rapid ventricular pacing. This model has been used extensively in a variety of species, including dogs (7), sheep (26), and rabbits (22). In the dog, the model is characterized by an increase in left atrial and left ventricular end diastolic pressure and an increase in resting HR, whereas resting arterial pressure, cardiac output, and maximal rate of fall of left ventricular pressure are reduced. Indeed, after 15 days of pacing, the rabbits in this study exhibited significantly lower arterial pressure and elevated resting HR, LAP, and CVP, all of which characterize the state of congestive heart failure. The rabbits in the present study are similar to those described by Masaki et al. (22), using the same model.

The depressed baroreflex control of HR in experimental heart failure has been reported by several investigators (5, 31), and this depression appears to be mediated by both the sympathetic and parasympathetic components of the baroreflex control of HR (5). In the present study, we determined which arm of the efferent pathway of baroreflex control of HR was primarily affected after blockade of AT_1 receptors in rabbits with heart failure. Rabbits with heart failure exhibited a decrease in the maximum gain and range of the baroreflex control of HR. The maximum gain was restored by AT_1-receptor blockade. AT_1-receptor blockade had little effect, however, in normal rabbits, except for a shift in the baroreflex curve to a slightly lower pressure.

Although the mechanisms of this restoration of baroreflex sensitivity are unclear, it is well known that ANG II modulates sympathetic function at many loci in the central and peripheral nervous systems. For in-

stance, ANG II has been shown to augment sympathetic outflow in various portions of the hypothalamus and medulla (29). In addition, ANG II facilitates ganglionic transmission (9) and enhances norepinephrine release from nerve terminals (11). In fact, a facilitation of norepinephrine release has been demonstrated in the heart failure state (23). ANG II has major effects in the nucleus of the solitary tract and plays a prominent role in a central hypertensive process (1). All of these actions may contribute to the sympathoexcitation of heart failure and to impairment of baroreflex control of HR. ANG II receptor antagonists have been administered to patients with congestive heart failure. These data also suggest a role for sympathoinhibition. For instance, Gottlieb et al. (14) administered several doses of losartan to 66 patients with ejection fractions of <40%. They found a significant reduction in cardiac filling pressures and a decrease in plasma norepinephrine from 650 ± 156 to 361 ± 60 pg/ml. Angiotensin-converting enzyme inhibitors have also been shown to augment baroreflex function in animals when given intracerebroventricularly (4).

Recent data from this laboratory in a canine rapid pacing model indicate that the arterial baroreflex per se is not solely responsible for the sympathoexcitation of heart failure (32). In a study by Levett et al. (20), it was shown that cardiac denervation did not alter sympathetic function in dogs with pacing-induced heart failure. These two studies suggest that another mechanism is responsible for augmenting sympathetic outflow in heart failure. Because the renin-angiotensin system is activated in severe heart failure, it is tempting to speculate that ANG II plays a key role in stimulating sympathetic outflow by either a central or peripheral mechanism. Because, after administration of L-158,809, there were no significant changes in resting arterial pressure and HR, it is likely that L-158,809 acted by a specific neuronal mechanism to restore baroreflex gain. It is unlikely that this mechanism operates at the afferent level because ANG II does not have direct effects on baroreceptor afferents (1).

Pretreatment with atropine in the heart failure group resulted in a significant decrease in the minimum HR achieved during baroreflex activation. The change was restored by subsequent treatment with L-158,809. This would suggest that this decrease in minimum HR is due to enhanced withdrawal of sympathetic outflow in the heart failure state (21), which is, in part, dependent on ANG II. In support of this notion, pretreatment with metoprolol exhibited no effect on the baroreflex control of HR before or after L-158,809.

The failure to observe an increase in gain when L-158,809 was administered after either autonomic blockade is curious because there was clearly an effect in the intact state. Baroreflex gain is determined by a complex interaction between the sympathetic and parasympathetic innervation of the SA node (12, 16), so that blockade of one may not allow for a further increase in gain. However, the minimum HR achieved during baroreflex activation is a function of vagal activation and sympathetic withdrawal. This situation may be similar to the lack of correlation between resting HR and baroreflex peak gain (17). In the present study, blockade of AT_1 receptors after pretreatment with atropine further reduced minimum HR only in rabbits with heart failure. These data, along with the lack of effect of metoprolol, provide evidence for a role of ANG II in sympathetic activation targeted to the SA node.

Although ANG II modulates the baroreflex control of HR (18), it has been shown that ANG II evokes a sympathetically mediated hypertensive response that is independent of the baroreflex (8). As cited in a recent review by Brooks and Osborne (2), Pawloski and Fink have provided evidence that sympathetic activation in response to ANG II is greater after sinoaortic denervation in rats.

In summary, these data strongly suggest that ANG II plays an important role, via its AT_1 receptors, in altering the baroreflex control of HR in rabbits with pacing-induced heart failure. The primary effect of ANG II is to increase cardiac sympathetic tone, which, in turn, prevents the full development of baroreflex-mediated bradycardia. Therefore, the range of the reflex is reduced, which alters the ability to buffer changes in arterial pressure in the heart failure state. Further study will be necessary to determine the exact location of the effect of ANG II on baroreflex and sympathetic regulation in heart failure.

Perspectives

A characteristic of the chronic heart failure state is neurohumoral excitation. Many studies have documented increases in plasma norepinephrine, vasopressin, atrial natriuretic peptide, angiotensin, endothelin, cytokines, and many other substances. The literature is filled with references to the resumed mechanism of the sympathoexcitation that occurs in heart failure. It is thought that attenuated arterial baroreflexes or blunted cardiopulmonary reflexes are responsible for this phenomenon. Unfortunately, there are no data to prove a cause-and-effect relationship for these two phenomena. In fact, there are data that suggest that the arterial baroreflexes and the cardiopulmonary reflexes are not responsible for the sustained increase in plasma norepinephrine seen in heart failure. ANG II is an important hormonal regulator of vascular tone by virtue of its direct vascular effects and its effects on sympathetic outflow. The experiments reported here provide new information that suggests that ANG II may indeed contribute to the blunted baroreflex control of HR in a model of heart failure. This finding implies that blockade of ANG II receptors may be beneficial in breaking the vicious cycle of positive feedback that occurs in heart failure. These data provide an experimental basis for the rational use of ANG II antagonists in the treatment of patients with heart failure.

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Address for reprint requests: I. H. Zucker, Dept. of Physiology and Biophysics, Univ. of Nebraska College of Medicine, 600 S. 42nd St., Omaha, NE 68198–4575.

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