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Ohta, Takafumi, Naoyuki Hasebe, Shiro Tsuji, Kazuma Izawa, Yin-Tie Jin, Shinsuke Kido, Syunsuke Natori, Motohiko Sato, and Kenjiro Kikuchi. Unequal effects of renin-angiotensin system inhibitors in acute cardiac dysfunction induced by isoproterenol. *Am J Physiol Heart Circ Physiol* 287: H2914–H2921, 2004. First published August 5, 2004; doi:10.1152/ajpheart.00221.2004.—Several clinical trials have demonstrated that angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II type 1 receptor blocker (ARB) are equally effective in the treatment of chronic heart failure. However, this has not been confirmed for acute cardiac dysfunction. We examined whether ACEI or ARB prevents isoproterenol-induced acute left ventricular (LV) dysfunction in dogs. LV dysfunction induced by a large dose of isoproterenol (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 3-h infusion) was compared in dogs treated with ACEI (temocaprilat) or ARB (olmesartan). Atrial pacing induced a constant heart rate and use of adjustable aortic banding provided a nearly constant afterload. LV systolic function (LV d*P*/d*t*, fractional shortening, and ejection fraction) and diastolic function (τ and LV end-diastolic pressure) were significantly deteriorated after isoproterenol infusion. The LV dysfunction was almost totally prevented by ARB but was only partially prevented by ACEI. The partial effect of ACEI was complemented by cotreatment with HOE-140, a bradykinin B_2 receptor antagonist. At baseline, the response to low doses of isoproterenol was significantly attenuated by ACEI but not by ARB, and the ACEI-induced attenuation was totally abolished by cotreatment with HOE-140. The response to isoproterenol was significantly attenuated after 3 h of excess isoproterenol loading, and it was almost completely preserved by ARB but not by ACEI. In conclusion, acute LV dysfunction and β-adrenergic desensitization induced by excess isoproterenol administration were almost totally prevented by ARB but only partially prevented by ACEI. These differences were attributable at least in part to bradykinin pathways activated by ACEI administration in acute LV dysfunction.

bradykinin; nitric oxide; catecholamine; oxidative stress

THE RENIN-ANGIOTENSIN SYSTEM (RAS) plays a crucial role in chronic congestive heart failure. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II (ANG II) type 1 (AT_1) receptor blocker (ARB) improve the derangement of hemodynamics and myocardial sympathetic activity (15, 31, 34, 35, 39) and prevent cardiovascular remodeling (24, 41) in heart failure.

Apart from inhibition of the RAS, ACEI administration enhances the bradykinin and nitric oxide (NO) pathways, whereas ARB treatment stimulates ANG II type 2 (AT_2) receptors. These additional effects of ACEI and ARB appear to make no essential differences in the consequences of treatment of chronic heart failure; several clinical trials have demonstrated that ACEI and ARB are equally effective in patients with chronic heart failure (31, 34, 35). However, it is unknown whether ACEI and ARB are equally effective in acute cardiac dysfunction.

Three major clinical trials have demonstrated that ACEI is effective in patients with acute myocardial infarction when it is started 3–16 days after the onset (16) of the infarction. A recent meta-analysis of four clinical trials showed that ACEI administration that is started 0–36 h from symptom onset is also beneficial for acute myocardial infarction (1). Importantly, however, two of the included trials, the Cooperative New Scandinavian Enalapril Survival Study II (40) and the third subanalysis of Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [Italian Group for the Study of Streptokinase in Myocardial Infarction (3)] queried the beneficial effect of ACEI in the very early phase of acute myocardial infarction.

Circulating catecholamine levels increase beyond a physiological level during heart failure (12). An excess amount of catecholamines exacerbates cardiac dysfunction (6, 13, 36). Consequently, the vicious circle of activation of the β-adrenergic system and the RAS plays a crucial role in exacerbation of heart failure (38).

We introduced an acute cardiac dysfunction model induced by infusion of a large amount of isoproterenol (Iso) in dogs. Excess stimulation of β-adrenergic receptors causes desensitization and downregulation of the β-adrenergic signal transduction system (9, 10, 28). We investigated whether ACEI and ARB equally prevent Iso-induced acute cardiac dysfunction and β-adrenergic desensitization in this model.

MATERIALS AND METHODS

Experimental Animals and Preparation

This investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH Pub. No. 85-23, revised 1996) and the guidelines of the Committee on Laboratory Animals of the Asahikawa Medical College.

Twenty-two adult mongrel dogs of either sex were anesthetized with pentobarbital sodium (30 mg/kg iv) and ventilated with oxygen-enriched air using a volume-limited ventilator (model 613; Harvard Apparatus; South Natick, MA). Arterial blood gas values were kept within a physiological range by adjusting the ventilator. An incision was made in the fifth left intercostal space. An aortic occluder made of polyethylene tubing was placed around the descending aorta. A

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bipolar pacing electrode was positioned on the left atrial appendage through a small pericardial incision and connected to a cardiac stimulator (SEC-2102; Nihon Kohden; Tokyo, Japan). A polyethylene catheter was inserted through the left carotid artery into the ascending aorta to withdraw blood samples and was connected to strain-gauge manometers (TP-101T; Nihon Kohden) to monitor arterial pressure. The catheters were inserted through the bilateral femoral veins to infuse drugs. LV pressure (LVP), LV end-diastolic pressure (LVEDP), rate of change of LVP (LV dP/dt), and the time constant of isovolumic relaxation of the left ventricle (τ) were measured by a catheter-tipped transducer (PC-350; Millar; Houston, TX) inserted from the right carotid artery into the left ventricle. A 5-MHz single-plane transducer for transesophageal echocardiography (SSD-830; Aloka; Tokyo) was placed just behind the LV to monitor the changes in LV dimension (Fig. 1).

Experimental Protocol

Dogs were randomly assigned to three groups. One group received only a 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Iso infusion (control group, $n = 5$ dogs). The second group received infusion of 0.05 mg/kg olmesartan (Sankyo; Tokyo, Japan) 15 min before Iso infusion was started (ARB group, $n = 6$ dogs). The third group received infusion of 0.05 mg/kg temocaprilat (Sankyo) 15 min before Iso infusion was started (ACEI group, $n = 6$ dogs). In the preliminary study, we tested the infusion of 0.01, 0.02, 0.05, 0.08, and 0.1 mg/kg temocaprilat and olmesartan in dogs. The pressor effects of 1.0 μg/kg angiotensin I (ANG I) and 0.5 μg/kg ANG II were dose dependently suppressed by temocaprilat and olmesartan, respectively. However, >0.08 mg/kg temocaprilat or olmesartan showed slight but significant depressor effects. Accordingly, we determined that for both agents, 0.05 mg/kg was the maximum dose that did not significantly affect systemic blood pressure but sufficiently suppressed the equivalent pressor effects of ANG I and ANG II by temocaprilat and olmesartan, respectively: the pressor effects of 1.0 μg/kg ANG I were significantly suppressed by 0.05 mg/kg temocaprilat (from 56.5 $\pm$ 3.3 to 11.5 $\pm$ 2.3 mmHg, $n = 4$ dogs; $P < 0.01$), and the pressor effects of 0.5 μg/kg ANG II were suppressed by 0.05 mg/kg olmesartan (from 57.0 $\pm$ 2.9 to 9.5 $\pm$ 0.6 mmHg, $n = 4$ dogs; $P < 0.01$). There were no significant differences in the antipressor effects of temocaprilat ($-79.9 \pm 3.4\%$) and olmesartan ($-83.1 \pm 1.9\%$). The changes in hemodynamics were compared under conditions of constantly maintained aortic pressure and heart rate to the baseline levels, which were finely and hourly readjusted using an aortic occluder and atrial pacing (Fig. 1). The responses to test applications of low doses of Iso (0.025, 0.05, 0.1, and 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were compared before and 3 h after the continuous infusion of the Iso loading with 15-min cessation of the loading infusion under conditions in which the pretest aortic pressure and heart rate were adjusted to baseline levels.

Additionally, the results from the ACEI group led us to test a fourth group, which received a 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ HOE-140 infusion in addition to ACEI (ACEI + HOE-140 group, $n = 5$ dogs). We determined the dose of HOE-140 that completely abolished the depressor effects of a 2.0 μg/kg bradykinin injection (which caused an approximately -50-mmHg reduction in systemic blood pressure) and did not affect systemic blood pressure itself.

Blood Sampling

Aortic blood samples were periodically collected from left carotid artery. Aortic blood gas values were checked with a blood gas analyzer (Bayer 850; Sudbury, UK). Plasma rennin activity (PRA) and serum aldosterone and ANG II levels were measured via radioimmunoassay, plasma atrial natriuretic peptide (ANP) values were obtained by immunoradiometric assay, and lipid peroxide (LPO) quantities were identified via a hemoglobin-methylene blue method.

Data Analysis and Statistics

All hemodynamic data were monitored on a direct-writing oscillograph (polygraph system RM 6200; Nihon Kohden) and were continuously digitized and recorded on a personal computer throughout the study using a physiological data-acquisition system (ADInstrument; Taustralia; NSW, Australia). We derived τ values from a digitized LV pressure wave against time. LV end-diastolic dimension (LVEDd) and LV end-systolic dimension (LVESd) were measured by M-mode transesophageal echocardiography. LV percent fractional shortening (%FS) was calculated as [(LVEDd $-$ LVESd)/LVEDd] $\times$ 100. LV

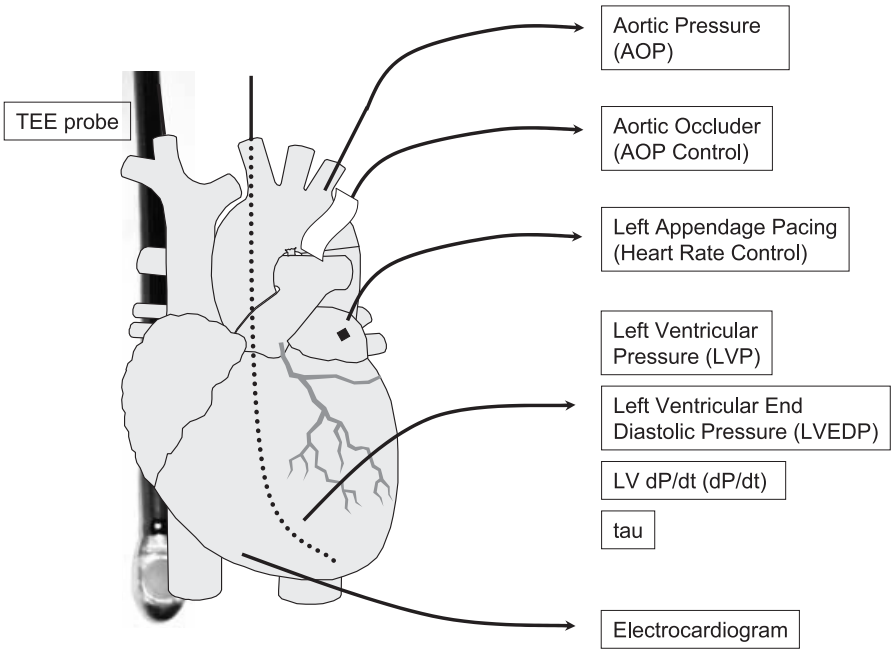

Fig. 1. Schematic illustration of instrumentation used in assessing hemodynamics and left ventricular (LV) function. A 5-MHz transducer for transesophageal echocardiography (TEE) was placed just behind the LV to monitor changes in LV dimension.

Table 1. *Hemodynamic parameters*

Parameter	Treatment Group: Control[a]	ARB[b]	ACEI[b]	ACEI + HOE − 140[a]
Heart rate, beats/min				
Pretreatment	140±7	142±7	147±8	140±6
Baseline	138±9	139±6	143±7	138±5
After 3 h	138±9	139±6	143±7	138±5
Mean aortic pressure, mmHg				
Pretreatment	119±13	121±6	122±9	121±11
Baseline	118±11	119±4	118±7	117±10
After 3 h	105±5	104±6	106±9	106±6
Maximum LV dP/d*t*, mmHg/s				
Pretreatment	2,424±93	2,427±73	2,417±93	2,424±79
Baseline	2,416±87	2,406±69	2,411±81	2,400±59
After 3 h	1,819±99[c]	2,128±154[d]	1,837±71[c]	1,949±60[e]
LV ejection fraction, %				
Pretreatment	67±3	67±4	66±3	67±2
Baseline	67±4	67±4	66±2	67±1
After 3 h	45±3[c]	61±2[f]	51±1[c]	59±1[c,f]
LV fractional shortening, %				
Pretreatment	31±2	31±3	30±2	31±2
Baseline	31±3	31±3	30±2	31±1
After 3 h	18±2[c]	27±1[f]	21±1[c]	26±1[e,f]
LV end-diastolic pressure, mmHg				
Pretreatment	3.4±0.6	3.3±0.6	3.2±0.7	3.4±0.6
Baseline	3.4±0.7	3.2±0.6	3.2±0.8	3.4±0.4
After 3 h	9.0±1.5[c]	4.5±0.8[f]	7.8±0.9[c]	6.6±1.2[e]
τ, ms				
Pretreatment	32±2	33±1	33±2	33±2
Baseline	33±1	33±1	32±2	33±3
After 3 h	41±3[e]	37±5	40±4	38±4

Values are means ± SE; [a]$n = 5$; [b]$n = 6$ dogs. Treatment infusions: control, 1 μg·kg^{-1}·min^{-1} isoproterenol (Iso); ARB (ANG II type I receptor blocker), Iso + 0.05 mg/kg olmesartan; ACEI (ANG II-converting enzyme inhibitor), Iso + 0.05 mg/kg temocaprilart; and ACEI + HOE-140, ACEI + 0.05 μg·kg^{-1}·min^{-1} HOE-140. Each group (except control) received treatment agent 15 min before Iso infusion. LV dP/d*t*, rate of change of LV (left ventricular) pressure; τ, diastolic function. [c]$P < 0.01$ vs. baseline; [d]$P < 0.05$ vs. control; [e]$P < 0.05$ vs. baseline; [f]$P < 0.01$ vs. control.

ejection fraction (LVEF) was calculated as [(LVEDd^3 − LVESd^3)/LVEDd^3] ×100 (19). The data were stored and analyzed using a personal computer. All values are expressed as means ± SE. Differences between baseline measurements and subsequent values were analyzed using repeated-measures ANOVA. When significant differences were detected, individual mean values were compared using Fisher's protected least-significant difference test. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Changes in LV Function by Iso Infusion in Each Group

There were no significant differences in baseline hemodynamic parameters among the four groups (Table 1). Heart rate and mean aortic pressure values were maintained almost constant by applying atrial pacing and aortic banding throughout the protocol. Consequently, there were no significant differences in heart rate and mean aortic pressure among the four groups after 3 h (Table 1). After 3 h of Iso infusion, the maximum LV dP/d*t* (LV dP/dt_{max}) was maintained and was still significantly higher in the ARB group than in the control and ACEI groups ($P < 0.05$; Table 1). The significant difference with ACEI tended to be diminished by cotreatment with HOE-140.

In the control group, there were significant decreases in LVEF (−22 ± 3%) and %FS (−13 ± 2%) values at 3 h after Iso infusion compared with the baseline values ($P < 0.01$; Fig. 2; Table 1). These changes in LV systolic function were diminished in the ARB group in LVEF (−6 ± 2%) and %FS (−4 ± 2%) compared with the control group ($P < 0.01$). The changes tended to diminish (but not significantly) in the ACEI group in LVEF (−15 ± 2%) and %FS (−9 ± 1%) compared with the control group. In contrast, these changes were significantly suppressed in the ACEI + HOE-140 group in LVEF (−8 ± 1%) and %FS (−6 ± 1%; $P < 0.01$ vs. control group; Fig. 2 and Table 1).

LVEDP values were elevated significantly in all groups except ARB at 3 h after Iso infusion (Fig. 3 and Table 1). The elevation of LVEDP was significantly lower in the ARB (1.3 ± 0.3 mmHg) compared with the control (5.6 ± 1.0 mmHg) and ACEI (4.7 ± 0.7 mmHg) groups ($P < 0.01$). It was relatively but significantly lower in the ACEI + HOE-140 group (3.2 ± 1.0 mmHg) compared with the control group ($P < 0.05$). The

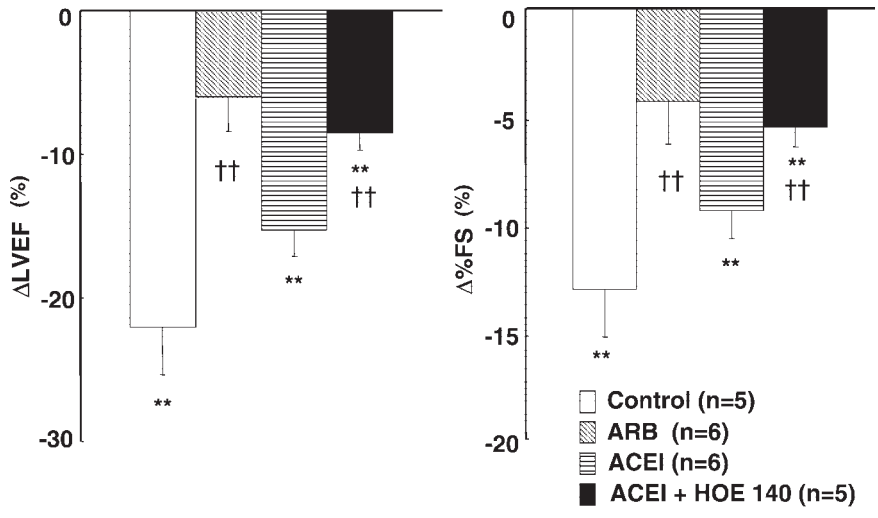

Fig. 2. Changes in LV ejection fraction (ΔLVEF, *left*) and LV fractional shortening (Δ%FS, *right*) 3 h after isoproterenol (Iso) infusion. Both indexes were significantly decreased in control animals. These changes were suppressed significantly by angiotensin II type 1 receptor blocker (ARB), partially by angiotensin-converting enzyme inhibitor (ACEI), and again significantly by ACEI with HOE-140. Data are means ± SE. **$P < 0.01$ vs. baseline; ††$P < 0.01$ vs. control.

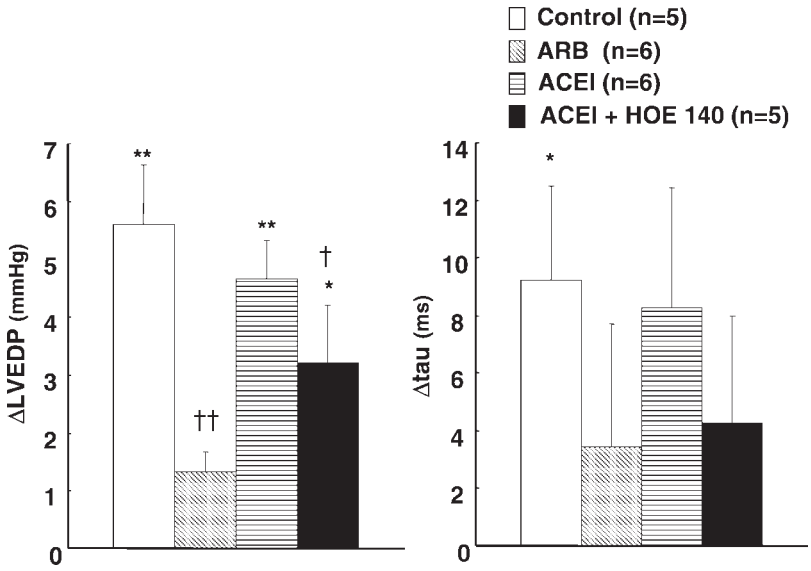

Fig. 3. Changes in LV end-diastolic pressure (ΔLVEDP, *left*) and time constant of isovolumic relaxation of the left ventricle (Δτ, *right*) 3 h after Iso infusion. ΔLVEDP values were significantly increased in control and ACEI groups. These changes were attenuated significantly in ACEI + HOE-140 group and more markedly in ARB group. In control group, Δτ was significantly prolonged 3 h after Iso infusion. $*P < 0.05$; $**P < 0.01$ vs. baseline; $\dagger P < 0.05$; $\dagger\dagger P < 0.01$ vs. control.

prolongation of τ was observed in the control group (9.2 ± 3.2 ms; $P < 0.05$); however, it was not evident in the ARB, ACEI, and ACEI + HOE-140 groups (Fig. 3 and Table 1).

Changes in Dose Responses to Test Applications of Iso

Baseline responses. LV dP/dt_{max} was dose dependently increased by test application of Iso in all groups. However, the response in the ACEI group was significantly attenuated compared with the control group ($P < 0.05$) and was totally restored by cotreatment with HOE-140. There were no significant differences between the control and ARB groups (Fig. 4).

Responses 3 h after Iso infusion. The responses of LV dP/dt_{max} to test applications of Iso, which were assessed after matching the heart rate and afterload to pretreatment levels in all groups, were significantly attenuated in the control and ACEI groups at 3 h after Iso infusion compared with the baseline responses. The attenuation in responses was not abolished in the ACEI + HOE-140 group but was almost completely abolished in the ARB group (Fig. 5).

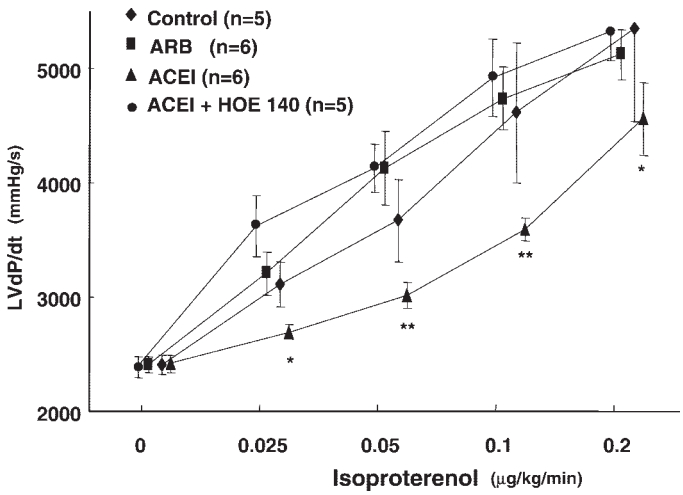

Fig. 4. Dose responses of LV dP/dt to test Iso application at baseline. LV dP/dt increased dose dependently in all groups; however, the response was significantly attenuated in ACEI compared with control groups ($*P < 0.05$; $**P < 0.01$, respectively). These differences were completely abolished in the ACEI + HOE-140 group.

PRA, Serum ANP, ANG II, and Aldosterone Levels

Baseline values of PRA, ANP, ANG II, and aldosterone were not significantly different. PRA levels increased significantly after Iso infusion in the control (14.4 ± 4.1 to 32.9 ± 4.8 $ng \cdot ml^{-1} \cdot h^{-1}$; $P < 0.01$) and ACEI (14.9 ± 3.2 to 33.8 ± 2.3 $ng \cdot ml^{-1} \cdot h^{-1}$; $P < 0.01$; Fig. 6) groups. In contrast, the increases in PRA were not significant in the ARB group (15.1 ± 2.6 to 18.8 ± 3.6 $ng \cdot ml^{-1} \cdot h^{-1}$) and were significant but relatively attenuated in the ACEI + HOE-140 group (16.5 ± 3.0 to 26.9 ± 2.0 $ng \cdot ml^{-1} \cdot h^{-1}$; $P < 0.05$). ANP levels were significantly higher after Iso infusion in the control (11.2 ± 2.1 to 45.1 ± 10.1 pg/ml; $P < 0.01$) and ACEI (13.0 ± 2.5 to 44.9 ± 6.5 pg/ml; $P < 0.01$) groups. The increases in ANP levels were not significant in the ARB group (12.1 ± 2.6 to 22.1 ± 8.9 pg/ml) and were significant but relatively attenuated in the ACEI + HOE-140 group (10.8 ± 2.3 to 38.0 ± 6.1 pg/ml; $P < 0.01$). Peak values for both PRA and ANP were significantly lower in the ARB than the control and ACEI groups, respectively ($P < 0.05$; Fig. 6).

Serum ANG II levels were significantly higher after Iso infusion in all groups and particularly in the ARB group (control, 3,354 ± 1,183; ARB, 5,410 ± 1,788; ACEI, 723 ± 220; and ACEI + HOE-140, 936 ± 478 pg/ml; $P < 0.05$ vs. baseline, respectively). Serum aldosterone levels were significantly decreased after Iso infusion only in the ARB group (176.5 ± 23.1 to 107.5 ± 17.5 pg/ml; $P < 0.01$). The nadir of serum aldosterone levels was significantly lower in the ARB compared with the control group (107.5 ± 17.5 vs. 204.2 ± 21.4 pg/ml; $P < 0.05$).

Serum LPO Levels

The baseline levels for serum LPOs were not significantly different among all groups. The LPO levels were significantly higher after Iso infusion only in the control group (1.3 ± 0.1 to 3.2 ± 0.4 nmol/ml; $P < 0.01$). The peak value for LPO levels

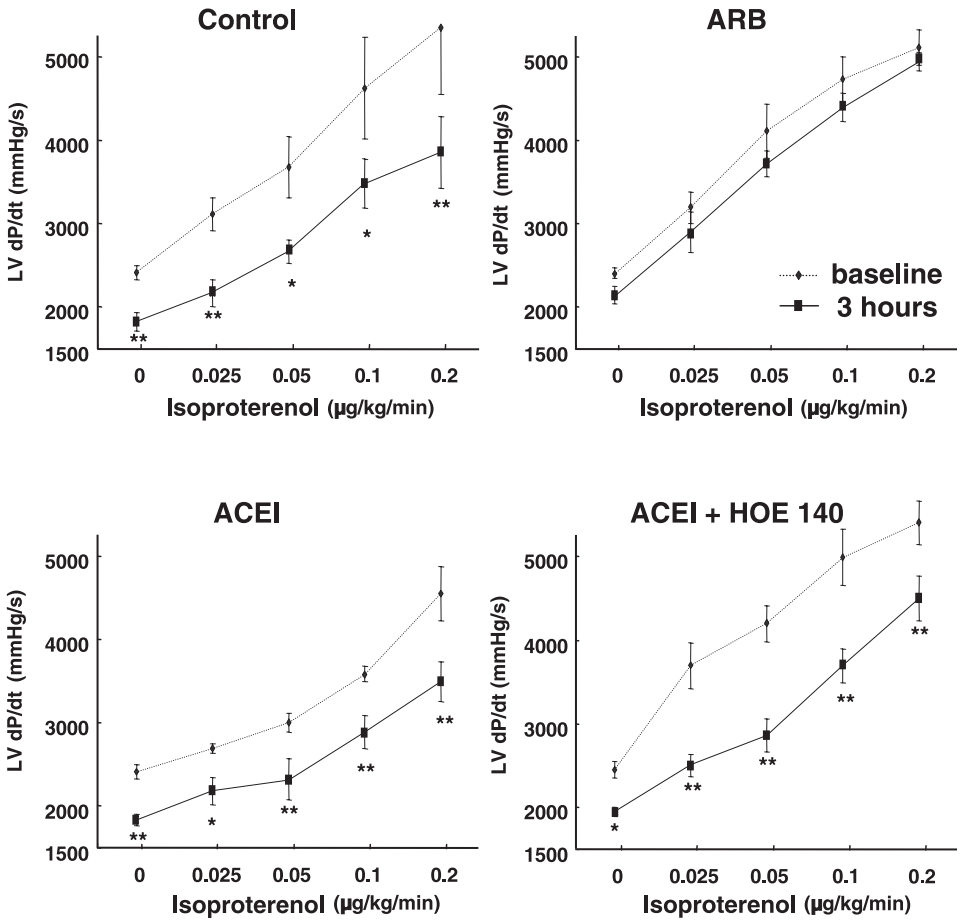

Fig. 5. Dose responses of LV dP/d*t* to test Iso applications were compared at baseline and 3 h after excess Iso infusion. Responses were significantly attenuated 3 h after Iso infusion in the control group (*top left*) as well as in the ACEI group (*bottom left*). Responses were not restored in ACEI + HOE-140 group 3 h after excess Iso infusion (*bottom right*). In contrast, responses were almost totally preserved in ARB group (*top right*). *$P < 0.05$; **$P < 0.01$ vs. baseline.

was significantly lower in the ARB compared to the control group (1.8 ± 0.4 vs. 3.2 ± 0.4 nmol/ml; $P < 0.01$; Fig. 6).

DISCUSSION

We introduced an experimental model of acute LV dysfunction induced by infusion of a large Iso dose in dogs. The β-adrenergic stimulation activates the RAS, which causes myocardial damage mainly through AT_1 receptors (25), and ANG II stimulates release of norepinephrine from the adrenal medulla and sympathetic nervous terminals (8, 44). The vicious circle of activation of the β-adrenergic system and the RAS aggravates heart failure. Thus the breaking of this circle is a potential strategy for the treatment of heart failure.

In the present study, we found a significant difference between the effects of ACEI and ARB on acute cardiac dysfunction. ARB almost totally but ACEI only partially prevented acute cardiac dysfunction induced by a large-dose Iso infusion. More interestingly, ACEI significantly attenuated responses to Iso administration.

The cardioprotective effects of ACEI in heart failure have been mainly attributable to inhibition of bradykinin degradation in addition to inhibition of ACE (29, 30). Bradykinin facilitates the generation of NO and prostacyclin, both of which are also known to be beneficial in the treatment of myocardial ischemia and heart failure. However, this concept may not be applicable to the acute phase of cardiac dysfunction that is induced by excess β-adrenergic stimulation. In the case in which we applied ACEI with HOE-140 (a bradykinin B_2 receptor antagonist), the effect was partially improved but it compared significantly with the effect of ACEI alone. The dose of HOE-140 that we used in the present study was determined to completely abolish the depressor effects of a 2.0 μg/kg bradykinin injection (an approximately −50-mmHg decrease in systemic blood pressure) while not affecting systemic blood pressure. Thus the inferior effect of ACEI compared with ARB is attributable at least in part to the bradykinin pathway.

It is noteworthy that ACEI markedly suppressed the positive inotropic response to Iso at baseline, which was not observed in the ARB group and was completely restored by coadministration of HOE-140. NO released by bradykinin is known to inhibit myocardial contractility in vivo as well as in vitro and particularly in pathological conditions (7, 18, 20, 42, 43). Importantly, the positive inotropic response to β-adrenergic stimulation is known to be suppressed by NO (18, 42, 43). We have previously demonstrated that LV dysfunction is indirectly aggravated even with inhaled NO in heart failure (32).

More directly, bradykinin itself has been reported to inhibit myocardial contraction independent of NO or prostacyclin (5, 17, 37). One plausible mechanism for the negative inotropic action of bradykinin is based on cytochrome *P*-450 metabolites, which are a major candidate for an endothelial-derived hyperpolarizing factor (11, 21). Rastaldo et al. (37) demonstrated that the negative inotropic response to bradykinin was abolished by cytochrome *P*-450 inhibitors and was not affected by NO and cyclooxygenase inhibitors in isolated perfused rat heart. The positive inotropic response to Iso at baseline was

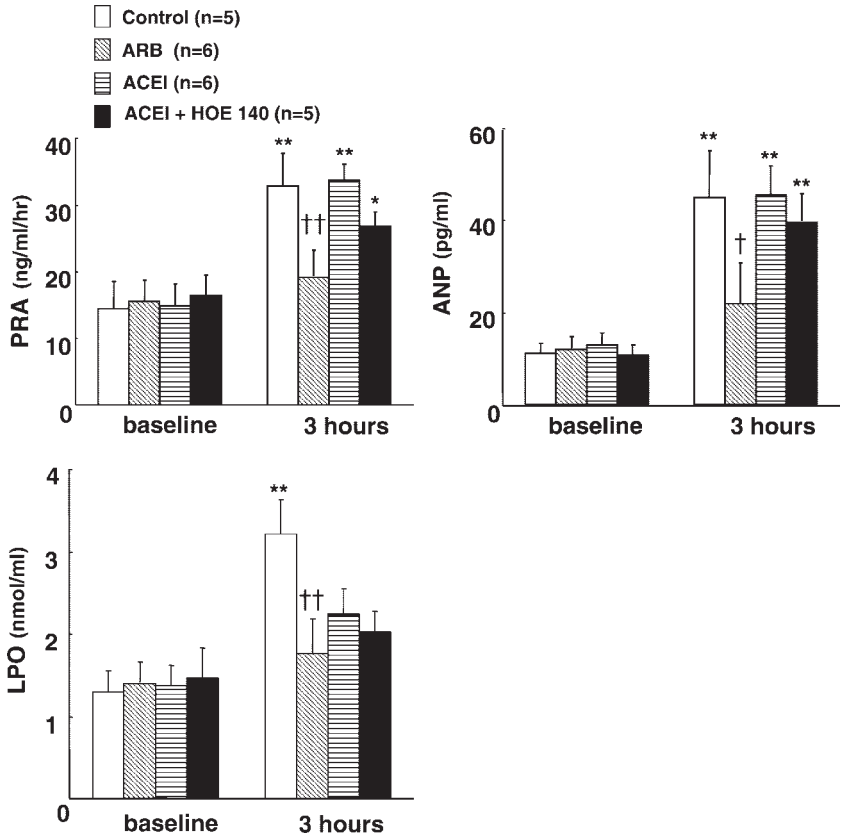

Fig. 6. Plasma rennin activity (PRA; *top left*), atrial natriuretic peptide (ANP; *top right*), and lipid peroxide (LPO; *bottom*) levels at baseline and 3 h after Iso infusions. PRA and ANP were significantly increased in control and ACEI groups. These changes were attenuated slightly in ACEI + HOE-140 group and were significantly abolished in ARB group. LPO levels were significantly increased in control group; however, the changes were attenuated in all other groups particularly in ARB compared with the control group. $*P < 0.05$; $**P < 0.01$ vs. baseline; $\dagger P < 0.05$; $\dagger\dagger P < 0.01$ vs. control.

significantly suppressed by ACEI through the bradykinin pathway in the present study. However, this inotropic response was no longer restored 3 h after infusion of a large dose of Iso. This was probably because the cardiac dysfunction induced by excess β-adrenergic stimulation for 3 h was too serious to be affected by HOE-140.

We found an intriguing coincidence between our results and those of the two major clinical trials that queried the beneficial effects of ACEI in the acute phase of heart failure. CONSENSUS II (40) and the subanalysis of GISSI-3 (3) both demonstrated that ACEI therapies initiated early after the onset of acute myocardial infarction failed to improve the survival rate. Their results were ascribed to the harmful hypotensive reaction of ACEI and inhibition of the myocardial healing process mediated by ANG II (3, 40). In addition to these, the negative inotropic action of bradykinin, which we found in the present study (conducted with constant afterload and heart rate), is another potentially deleterious factor in the treatment of the acute phase of cardiac dysfunction with ACEI. In contrast, there are few clinical data on ARB. The Optimal Trial in Myocardial Infarction with ANG II Antagonist Losartan (14) and the Valsartan Acute Myocardial Infarction Trial (33) demonstrated that ARB is as effective as ACEI in acute myocardial infarction that is treated >12 h from onset. There are no data available regarding ARB and the very early phase of acute myocardial infarction. In clinical settings, it may be possible that the clinical course of the very early phase of acute cardiac dysfunction differs depending on which drug, ACEI or ARB, that patients have taken as antihypertensive agents before the onset of the event. This concept has never been studied in a major clinical trial.

Numerous experimental studies of myocardial infarction and heart failure conducted in rats suggest that the cardioprotective effects of ARB are equivalent or inferior to those of ACEI (23, 41). ANG II is exclusively produced by ACE in rats (4). In contrast, it is also produced through alternative pathways such as via chymase in humans and dogs (2, 4); for this reason, we used dogs in the present study. Theoretically, the effects of ANG II might be completely suppressed by ARB, whereas the effects are not suppressed by ACEI in humans and dogs. We believe this could be an important explanation for the differences in effects between ARB and ACEI in the present study.

The serum LPO levels were increased by excess Iso administration and were prevented by ARB and ACEI. Oxidative stress is known to be enhanced and to cause deterioration of cardiac function in heart failure (22, 26, 27). Reduction of oxidative stress is one of the potential mechanisms of cardioprotective action for ARB and ACEI in this model. Excess Iso infusion activated the RAS and enhanced ANP release. The increase in serum ANP levels was significantly suppressed only by ARB. These results suggest that ARB potently suppressed the RAS and provided greater cardioprotective effects than ACEI in this acute cardiac dysfunction model.

Study Limitations

We examined the acute effects of ARB and ACEI in this study. The deterioration of the animal's condition is extremely serious after excess Iso infusion, and therefore we were unable to continue experiments with Iso infusion longer than the studied periods. It is possible that the chronic effects of ARB and ACEI could be different from the acute effects.

We selected and examined the maximum doses of ACEI and ARB that did not significantly affect systemic blood pressure but did sufficiently suppress pressor effects of ANG I and ANG II, for ACEI and ARB, respectively. We then compared those maximum doses of ARB and ACEI in the present study. It is possible that different doses of agents, and particularly different doses of ACEI, would modify the results. However, even at baseline, ACEI at the dose used markedly suppressed the responses to the test application of Iso, which was totally restored by HOE-140; this clearly suggests that bradykinin was the major factor responsible for the attenuated responses to Iso by ACEI.

The experimental model of cardiac dysfunction used in the present study does not fully represent the acute phase of myocardial infarction. Therefore, additional study is required to confirm the clinical significance of the difference between ARB and ACEI that was observed in this study, particularly in the very early phase of acute myocardial infarction.

In conclusion, LV dysfunction and β-adrenergic desensitization induced by excess β-adrenergic stimulation were prevented almost totally by ARB and partially by ACEI. Activating bradykinin pathways by ACEI administration may not be beneficial in the very early phase of heart failure. Additional investigation is required to clarify the differences between ACEI and ARB in the very early phase of acute heart failure, which is accompanied with a storm of sympathetic activation.

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