Comparative Effects of Candesartan and Enalapril on Augmented Vasoconstrictive Responses to Endothelin-1 in Coronary Vessels of Spontaneously Hypertensive Rats

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Background: The aim of this study was to compare the effect of angiotensin type-1 receptor blockade (ARB) on augmented vasoconstrictive response to endothelin-1 (ET-1) in coronary vessels of hypertensive hearts with angiotensin converting enzyme (ACE) inhibitor, candesartan cilexetil (CAN) or enalapril was administered for 3 weeks in spontaneously hypertensive rats (SHR).

Methods: We used SHR (9 to 12 weeks old, n=18) and Wistar-Kyoto (WKY) rats (n=6). Systolic blood pressure was measured once a week. Spontaneously hypertensive rats were divided into three groups. Enalapril malate (10 mg/day) or CAN (10 mg/day) was administered orally in each of six SHR in each group receiving treatment for 3 weeks. The control group (n=6) received no treatment. At the end of this experiment, the hearts were isolated. Isolated hearts mounted on a Langendorff apparatus after weighing were then perfused with modified Krebs-Henseleit buffer at constant pressure (75 mm Hg). The coronary perfusion pressure and coronary flow were measured during perfusion of isolated hearts. Coronary vascular resistance (CVR; mm Hg/mL/min/100 g) was calculated.

Results: The ET-1 elicited increases in CVR dose-dependently in both normotensive and hypertensive rat hearts. However, the responses were significantly greater in SHR than in WKY rat. Chronic treatment with enalapril or candesartan inhibited the development of hypertension and cardiac hypertrophy equally in SHR. Augmented vasoconstrictive responses to ET-1 were significantly reduced in treated SHR. There was no difference in these effects between enalapril and candesartan.

Conclusion: These findings suggest that both ACE inhibitors and ARB can equally inhibit augmented coronary vascular response to ET-1 in hypertensive hearts. Am J Hypertens 2002; 15:286–290 © 2002 American Journal of Hypertension, Ltd.

Key Words: AII antagonist, ACE inhibitor, endothelin-1, coronary circulation, hypertensive hearts.

Coronary vascular impairment has been associated with the hypertensive heart. This impairment often occurs with no coronary artery stenosis detectable by angiography, and it is reported to be due to structural and functional changes of coronary vessels. Structural changes consist of changes in the walls of coronary vessels, whereas functional changes have been shown to be a reduced endothelium-mediated relaxation in coronary vessels. Functional changes include vascular responsiveness to a vasoconstrictive substance. Endothelin-1 (ET-1) is a strong vasoconstrictive peptide released from the endothelium that elicits vasoconstriction in coronary arteries. Vascular response to ET-1 is augmented in hypertension. Thus, it may be possible that the augmented coronary response to ET-1 contributes to the impairment of coronary circulation. However, coronary response to ET-1 in hypertension has not been clarified. In some studies the response to ET-1 by coronary vessels in hypertensive hearts is greater than that in normotensive hearts; on the other hand, another study reported that coronary response to ET-1 was not augmented. Recently we reported that the response to ET-1 in coronary vessels...
of spontaneously hypertensive rats (SHR) was augmented. Moreover it is reported that angiotensin converting enzyme (ACE) inhibitors reduced the augmented response to ET-1. However, it is not known whether ARB can decrease the response to ET-1 in hypertensive coronary circulation.

The present study examines whether vasoconstrictive responses to ET-1 are augmented in the coronary circulation of hypertensive hearts, and compares the effect of ARB on vasoconstrictive responses to ET-1 with ACE inhibitor.

Material and Methods

Subgroups

A total of 24 SHR (9 to 12 weeks old) and age-matched Wistar-Kyoto (WKY) rats were used. The SHR were divided into three groups: a control group with no treatment, a group administered candesartan cilexetil (CAN) (10 mg/day by gavage), and a group administered enalapril malate (10 mg/day dissolved in water).

Protocol

After 3 weeks of treatment, vasoconstrictive responses to endothelin-1 in isolated rat hearts were compared. Systolic blood pressure (BP) was measured by the tail-cuff method (UR 5000; UEDA, Tokyo, Japan) once a week. Hearts were excised under anesthesia with sodium pentobarbital (50 mg/kg body weight, intraperitoneally), and the isolated hearts were perfused with a Langendorff apparatus (LWS-1; Technical Supply Co. Ltd., Osaka, Japan) at a constant pressure (75 mm Hg).

The perfusion solution consisted of a 37°C Krebs-Henseleit buffer (NaCl 118 mmol/L), KCl 4.7 mmol/L, CaCl₂ 2.5 mmol/L, MgSO₄ 1.2 mmol/L, KH₂PO₄ 1.2 (mmol/L), NaHCO₃ 25 (mmol/L), Na₂ EDTA 0.5 (mmol/L), glucose 11.1 mmol/L continuously infused with 95% O₂ and 5% CO₂. Hearts were paced at a rate of 300 beats/min using an electric stimulator.

Measurements

Coronary perfusion pressure was recorded with a pressure transducer (Statham; P23XL Hugo Sachs Elektronik-Harvard, March-Hugstetten, Germany), and coronary perfusion flow was measured using a digital drop counter (DCBF-1; Technical Supply Co. Ltd.). Coronary vascular resistance (CVR) was calculated from coronary pressure and flow. Minimal coronary vascular resistance is expressed as coronary flow during adenosine (10⁻³ mmol/L) infusion. N⁶-monomethyl-L-arginine (10⁻⁴ mmol/L), ET-1 (1.5 × 10⁻¹⁰, 1.5 × 10⁻⁹, 3 × 10⁻⁹ mmol/L) were infused in the perfusate by means of a syringe pump (A-99, Eazel, Kyoto, Japan). Total heart wet weights and left ventricle (LV) wet weights were measured.

Statistics

Data are given as mean ± SEM. For statistical analysis (analysis of variance was used, followed by the Fisher Protected least significant difference) test for repeated measurements. A two-tailed value of P < .05 was considered statistically significant.

Results

Antihypertensive Effect of Candesartan and Enalapril in SHR

Systolic BP was less in SHR treated with CAN or enalapril malate than in nontreated SHR. After 3 weeks of treatment, systolic BP was reduced. There was no difference in antihypertensive effect in either drug treatment. In treated SHR, BP was almost the same as that of WKY rats (Fig. 1). Body weights were not different in the three SHR groups after the treatment (254 ± 3.784, 245 ± 3.213 v

FIG. 1. Antihypertensive effect of candesartan cilexetil (CAN) and enalapril malate (EN) in spontaneously hypertensive rats (SHR). *P < .001.
250 ± 2.584, control SHR vs. candesartan-SHR vs. enalapril-SHR, NS).

**Effects of Candesartan and Enalapril Reduction on Cardiac Hypertrophy and Minimum Coronary Vascular Resistance**

Cardiac weights were significantly greater in SHR than in WKY rats. However, hearts of SHR treated with CAN or enalapril malate were significantly smaller than those of the control SHR (0.075 ± 0.008 vs. 0.678 ± 0.025 vs. 0.698 ± 0.024, control SHR vs. candesartan-SHR vs. enalapril-SHR, *P* < .05). Basal CVR was not different among the three groups (7.494 ± 0.613, 7.648 ± 0.616 vs. 7.298 ± 0.598, control-SHR vs. candesartan-SHR vs. enalapril-SHR, NS), whereas minimum coronary vascular resistance (MCVR) was increased in SHR compared with those of WKY and candesartan or enalapril treatment restored MCVR in SHR (Fig. 2).

**Effects of Candesartan and Enalapril on Augmented Vasoconstrictive Responses to Endothelin-1 in SHR**

The ET-1 infusion increased CVR in both SHR and WKY rats. The increased responses to ET-1 were significantly greater in SHR than in WKY rats (Fig. 3). However, CVR responses were not augmented in SHR treated with CAN or enalapril malate (Fig. 3).

**Discussion**

Our results show that angiotensin blockade by ACE inhibitor or an angiotensin II receptor antagonist (AIIA)
inhibited equally augmented vasoconstrictive responses of the coronary artery to ET-1 with a resulting antihypertensive effect in SHR. Previously it was reported that enalapril prevents augmented response to ET-1 in coronary vessel of SHR. In a study using the aortic ring of SHR, losartan reduces constrictor responses to endothelin-1. Present results show AIIA (losartan) also inhibited augmented responses to ET-1 in coronary vessel same as ACE inhibitor (enalapril). This result indicates that angiotensin II may be involved in the augmented response to ET-1 in the coronary vessel of hypertensive hearts. Several findings have been reported about the relation between angiotensin II and endothelin. One is that angiotensin II stimulates ET production. On the other hand, ET inhibits renin release, because ET receptor blockade stimulates renin release. The AT1 receptor may enhance vasoconstrictive response to ET-1, since AT1 receptor unmasks a vasodilator response to ET antagonist. Thus, angiotensin blockade may affect the vasoconstrictive response to ET-1. Coronary vascular remodeling and attenuated coronary flow reserve is associated with left cardiac hypertrophy (LVH) of hypertension. Even without LVH, reduced coronary flow reserve and increased minimal coronary resistance are detectable in hypertensive patients. AIIA regressed cardiac hypertrophy and improved capillarity of the left ventricular wall. ACE inhibitor and AIIA both improved systemic and coronary hemodynamics. Thus, ACE inhibitor and AIIA improve coronary circulation. The effect of losartan and enalapril on the vasoconstrictive responses to ET-1 may act partly as the underlying mechanism, which is improved in the coronary circulation of the hypertensive heart. Use of ACE inhibitor reduces coronary artery wall hypertrophy, and AIIA inhibits perivascular fibrosis. These improvements may change vascular reactivity to ET-1. On the other hand, we recently found that vasoconstrictive responses to ET-1 in coronary arteries of hypertensive hearts were dependent on reduced nitric oxide (NO) release. Coronary circulation is impaired in SHR, and this impairment is partly due to reduced NO release.

Candesartan treatment in SHR improved NO release in coronary vessels in SHR. Enalapril also accelerated NO release in coronary arteries. Losartan and captopril improves endothelial dysfunction including NO release in SHR. These findings suggest that the effect of candesartan and enalapril on attenuation of vasoconstrictive responses to ET-1 may be due to the release of NO from coronary vessels.

In this study, ACE inhibitor and AIIA attenuated equally the vasoconstrictive responses to ET-1 in coronary vessel of SHR. Maeso et al showed that AIIA and losartan inhibited constrictor responses to ET-1 in the aortic ring from SHR, but captopril did not; this inhibition is mediated by the release of NO. This shows AIIA is different from ACE inhibitor in the attenuated effect on vasoconstrictive responses to ET-1.

Our results indicate that AIIA and ACE inhibitor did not show any difference from ET-1 in their effects on vasoconstriction in the coronary vessels of hypertensive hearts. One reason may be the difference in the materials study, namely, coronary vessels and aortic rings. However, Nunez et al showed that losartan is stronger than enalapril in the improvement of coronary circulation in SHR. Therefore, the difference between our results and others is not clear.

In hypertension, the ET receptor antagonist fails to prevent the development of hypertension. However, ET-1 levels may be higher than in normotension, because several studies have suggested that this peptide is increased in hypertension. Therefore, endogeneous ET-1 may contribute to impaired coronary circulation in hypertensive hearts. Recently, it has been demonstrated that enalapril malate can improve impaired coronary reserve in hypertensive patients without coronary artery stenosis and losartan also improve coronary flow reserve in SHR.

The ACE inhibitors and angiotensin receptor antagonists might not only reduce high BP but may also improve impaired coronary vasomotion.

References


