Dissociation of Changes in Cardiovascular Mass and Performance With Angiotensin-Converting Enzyme Inhibitors in Wistar-Kyoto and Spontaneously Hypertensive Rats

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The effects of angiotensin-converting enzyme inhibitors on cardiovascular mass and function were measured in three groups of 22 week old male Wistar-Kyoto normotensive and spontaneously hypertensive rats treated with CGS-16617, cilazapril or quinapril. Left ventricular performance was assessed by electromagnetic flow meter during rapid whole blood infusion before and after arterial pressure increased abruptly with aortic snare; aortic distensibility also was assessed in vitro. The systemic hemodynamic effects of these three agents were similar, yet their structural effects varied. Although left ventricular and aortic masses diminished and right ventricular mass remained unchanged (with all three agents) in the spontaneously hypertensive rats, CGS-11617 and cilazapril also reduced left ventricular mass in the normotensive Wistar-Kyoto rats without changing aortic mass. All three agents improved aortic distensibility whether or not mass was decreased. Left ventricular structural changes were associated with variable changes in pumping ability. These data show that reduced mass associated with angiotensin-converting enzyme inhibitor treatment was not consistent in ventricles and aorta, that a dissociation exists between structural and functional changes and that reduction of cardiac mass alone does not relate to changes in chamber mass or in function. Thus, biologic and pharmacodynamic differences exist among angiotensin-converting enzyme inhibitors as well as between classes of antihypertensive agents.

Left ventricular hypertrophy develops over the natural history of hypertensive disease in humans with essential hypertension and in rats with spontaneous hypertension as a structural adaptation to the progressively increasing afterload, although it continues to progress even when arterial pressure stabilizes (1-4). It therefore serves an adaptive function in preventing the earlier emergence of left ventricular failure (1-4); however, this effect may be offset, at least in part, by the resultant independent risk of premature cardiovascular morbidity and mortality (5,6).

If used long enough, antihypertensive therapy will diminish left ventricular mass (7), although under special laboratory conditions certain pharmacologic agents will rapidly normalize left ventricular mass within 3 weeks in spontaneously hypertensive rats (8,9) and within 4 to 12 weeks in patients with essential hypertension (3,4,10-12). Determination of whether this pharmacologically induced decreased left ventricular mass corrects for the inherent risk of hypertrophy requires prospective studies in which pressure is allowed to return to pretreatment levels so that the benefit from reduced left ventricular mass itself can be dissociated from the effect of the antihypertensive therapy. This is a difficult proposition in light of the clinical ethical issues involved (4).

In two earlier studies from our laboratory (13,14), the pumping ability of the left ventricle that had undergone reduction in mass with methyldopa or with captopril was assessed at both pharmacologically reduced as well as pretreatment levels. Improvement of left ventricular pumping ability was not shown either at the pharmacologically induced normalized arterial pressures or at its pretreatment hypertensive pressure levels. The present study assesses three additional angiotensin-converting enzyme inhibitors that use the identical experimental protocol reported earlier (13,14) and demonstrates qualitatively and quantitatively different responses among classes of antihypertensive agents.
as well as within the angiotensin-converting enzyme inhibitor group.

**Methods**

**Experimental rats.** Sixty spontaneously hypertensive rats and 60 Wistar-Kyoto normotensive control male rats (Charles River Co.) were divided into three equal subgroups of 20 rats each for the two strains. Before treatment we confirmed the existence of hypertension or normotension in all spontaneously hypertensive rats and Wistar-Kyoto rats, respectively, by tail-cuff plethysmography (15). All rats were maintained thereafter three to a cage and were fed standard rat chow and tap water as desired and they were of the same body weight. The protocol was approved previously by our institutional animal care committee.

**Drug dosing.** The effects of the three angiotensin-converting enzyme inhibitors (that is, CGS-16617, cilazapril and quinapril) were determined on cardiac mass and left ventricular pumping performance, as well as on aortic mass and distensibility (the latter in vitro). With each drug evaluation 20 Wistar-Kyoto and 20 spontaneously hypertensive rats were divided into two subgroups; 10 rats received the respective vehicle (thereby serving as a control) for each drug and 10 the angiotensin-converting enzyme inhibitor. Treatment was begun at age 19 weeks of age and was administered once daily by gastric Savage for 3 weeks with the following dosages: CGS-16617, 10 mg; cilazapril, 10 mg/kg and quinapril 3 mg/kg body weight per day. After 3 weeks of daily treatment each rat was studied hemodynamically.

**Systemic hemodynamics.** Two days before the conclusion of the 3 week treatment period, a polyethylene tubing (PE-90) was inserted into the right jugular vein so that whole blood could be infused rapidly to determine mean arterial pressure and pulse pressure directly by a Statham (P23Db) transducer. This permitted continuous measurement of arterial pressure in the conscious state. At the conclusion of the treatment period, mean arterial pressure and heart rate were recorded 6 h after final administration of the angiotensin-converting enzyme inhibitor or vehicle. Subsequently, under light ether anesthesia another polyethylene catheter (PE-90) was inserted into the right jugular vein so that whole blood could be infused rapidly to determine left ventricular pumping ability (13,14,16-18). Another polyethylene catheter (PE-50) was placed into the right carotid artery to record mean arterial pressure and pulse pressure directly by a Statham (P23Db) transducer. This permitted continuous recording of arterial pressure even during aortic constriction (see following sections) (13,14).

Tracheal intubation was accomplished with PE-240 tubing to permit artificial ventilation with a small animal respirator (Harvard model 680). The chest was then entered by electric cautery through a medial sternal incision and positive end-expiratory pressure was maintained by submerging the respirator outflow catheter tip under 1.0 to 1.5 cm of water to prevent pulmonary atelectasis. Another polyethylene catheter (PE-50) was inserted into the left ventricle through the left atrium to permit continuous measurement of left ventricular end-diastolic pressure. Ascending aortic blood flow was measured as cardiac output with a precalibrated Statham electromagnetic flow probe (diameter 2.3 mm) whose electric signal was fed into the Beckman recorder (type 9583A) by a Statham electromagnetic flowmeter (SP 2202). The zero line of aortic blood flow was adjusted to the flat portion of the flow wave during the diastolic phase of flow. This zero line was confirmed at the conclusion of each study with use of a blood-filled aortic arch preparation. In this manner and under continuous ether anesthesia, baseline systemic hemodynamic values were recorded for at least 10 min after the conclusion of all surgical procedures and then only when the rat was recognized to be physiologically stable. Heart rate was determined from a beat to beat analysis of the aortic flow curve using a Beckman cardiotachometer (type 9587B). Cardiac index was calculated by dividing cardiac output by body weight, stroke index by dividing cardiac index by heart rate and total peripheral resistance index by dividing mean arterial pressure by cardiac index.

**Left ventricular pumping ability.** Whole blood obtained from donor rats of the same strain and maintained at 37°C was infused rapidly into the jugular vein (as an acutely raised preload) over a 1 min period with a Harvard infusion pump (model 945). This infusion volume had been quantified previously to be 40 ml/min per kg body weight. In this fashion cardiac index, stroke index, left ventricular end-diastolic pressure, heart rate, mean arterial pressure and pulse pressure could be determined at any time during the rapid volume loading. Left ventricular performance curves were subsequently constructed by plotting stroke index against left ventricular end-diastolic pressure during the rapid 1 min volume loading (13,14,17,18).

After all rapid whole blood volume infusion measurements for left ventricular pumping ability were obtained, the precise volume of blood that had been infused was withdrawn. Then all hemodynamic indexes were permitted to return to their original preinfusion levels in all rats treated with an angiotensin-converting enzyme inhibitor and control rats. When physiologic stability was achieved, a snare that had been previously placed around the descending thoracic aorta was occluded abruptly to elevate mean arterial pressure to pretreatment (but with anesthesia) pressure levels. This intervention permitted comparison of left ventricular (pumping) performance of the treated rats at the same mean arterial pressure as in the untreated rats.

**In vitro aortic distensibility.** At the conclusion of the hemodynamic studies, each rat was killed by exsanguination and the heart was removed carefully. The aorta then was
Table 1. Comparison of Systemic Hemodynamics of Untreated and Angiotensin-Converting Enzyme-Treated Normotensive Wistar-Kyoto (WKY) and Spontaneously Hypertensive (SHR) Rats

<table>
<thead>
<tr>
<th>Hemodynamic Index</th>
<th>Agents</th>
<th>Control</th>
<th>Treated</th>
<th>Control</th>
<th>Treated</th>
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</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>CGS-16617</td>
<td>92 ± 2</td>
<td>76 ± 1*</td>
<td>144 ± 3†</td>
<td>113 ± 2*</td>
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<td>Cilazapril</td>
<td>99 ± 1</td>
<td>76 ± 4*</td>
<td>146 ± 2†</td>
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<td>Quinapril</td>
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<td>78 ± 2*</td>
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<td>Heart rate (beats/min)</td>
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<td>263 ± 5</td>
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<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>CGS-16617</td>
<td>5.8 ± 0.2</td>
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<td>5.0 ± 0.1†</td>
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<td>5.2 ± 0.1</td>
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<td>Cardiac index (mL/min per kg)</td>
<td>CGS-16617</td>
<td>296 ± 6</td>
<td>249 ± 8*</td>
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<td>226 ± 7</td>
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<td>Stroke index (mL/beat per kg)</td>
<td>CGS-16617</td>
<td>1.05 ± 0.02</td>
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<td>Total peripheral resistance index (0-kg)</td>
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<td>0.31 ± 0.01</td>
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<td>0.58 ± 0.02†</td>
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</tbody>
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*p < 0.05 versus respective control rats; †p < 0.05 versus control WKY rats. Each group consists of 10 rats. Data are presented as mean values ± SEM.

ligated at two places, at the base of the ascending aorta and at that portion of the aorta where its first intercostal arterial branch began. The left carotid and left subclavian arteries were also ligated. The PE-50 tubing that previously had been inserted into the right carotid artery was connected to a Statham P23Db pressure transducer to record intraaortic arch pressure. Thus, this closed aortic arch preparation permitted plotting of aortic pressure-volume curves. To construct this curve, whole blood was infused at the rate of 3.4 µl/s during which time the intraaortic pressure varied from 0 to 250 mm Hg. The volume changes were expressed as a percent increase from the original volume that was determined at the 0 mm Hg point of intraaortic pressure. In this manner, in vitro aortic distensibility could be assessed and compared with in vivo aortic distensibility. 

Cardiac and aortic arch weights. Both atria were excised carefully from the removed heart and the free wall of the right ventricle was separated from the left ventricular chamber, this was considered as right ventricular mass. The intraventricular septum remained with the left ventricle. The aortic arch was also removed carefully after determining the in vitro aortic distensibility. Wet weights of the blotted ventricles and aortic arch were determined carefully on a grammatic balance both as absolute weight and as the ratio of the respective ventricular and aortic weights to total body weight (and expressed as mg/g or mg/kg).

Statistical methods. All calculated data are expressed as the mean (± 1 SEM). A two-way analysis of variance with repeated measures was applied to analyze both the left ventricular performance and aortic distensibility curves (19,20). Baseline hemodynamic data and cardiac and aortic weights were analyzed statistically using a one-way analysis of variance and they subsequently subjected to Newman-Keuls testing for multiple comparison (21). Statistical significance was established at the 95% confidence level.

Results

Systemic hemodynamics. Mean arterial pressure was significantly greater in each spontaneous hypertensive rat group than in its respective Wistar-Kyoto group before administration of the three angiotensin-converting enzyme inhibitors and it was reduced significantly in both strains with angiotensin-converting inhibitor treatment (Table 1). Thus, with CGS-16617, cilazapril and quinapril mean arterial pressure was reduced by 17%, 23% and 19%, respectively, in the Wistar-Kyoto and by 21%, 24% and 17%, respectively, in the spontaneously hypertensive rats. This mean arterial pressure decrease was associated with a 21% and 28% reduction in reduced total peripheral resistance index in the spontaneously hypertensive rats with the use of CGS-16617 and cilazapril but with only a 13% reduction with the use of quinapril. Changes in total peripheral resistance index in the Wistar-Kyoto rats were more variable, not decreasing with CGS-16617 but falling more variably with cilazapril and quinapril (by 21% and 10%, respectively). The mean arterial pressure and total peripheral resistance index changes after administration of these angiotensin-converting enzyme in-
hematases were not associated with compensatory increases in heart rate or cardiac index in either rat strain; however, after administration of CGS-16617 cardiac index declined by 16%, thereby explaining the lack of reduction in calculated total peripheral resistance index with the decline in mean arterial pressure. This reduction in cardiac index after CGS-16617 was associated with a 17% fall in left ventricular end-diastolic pressure. This reduction in cardiac index after CGS-16617 was associated with a 17% fall in left ventricular end-diastolic pressure; however, cardiac index did not decline in association with a similar reduction in left ventricular end-diastolic pressure (of 19%) after treatment with cilazapril. There was no change in left ventricular end-diastolic pressure in either strain after administration of quinapril.

**Cardiovascular mass.** Both total and left ventricular mass indexes and aortic arch weight were significantly greater in the untreated spontaneously hypertensive rats with respect to the Wistar-Kyoto rats (Table 2); right ventricular mass did not differ between the rat strains at this age. Each of the angiotensin-converting enzyme inhibitors reduced left ventricular and aortic mass in the spontaneously hypertensive rats but only CGS-16617 and cilazapril reduced the mass of the nonhypo- trophied left ventricle in the Wistar-Kyoto rats. Moreover, only cilazapril reduced aortic arch weight in the Wistar-Kyoto rats. Right ventricular mass remained unchanged with all three angiotensin-converting enzyme inhibitors (Table 2).

**Left ventricular pumping ability.** To express a function curve for the left ventricle in response to increased filling, stroke index was plotted against increasing left ventricular end-diastolic pressure during the 1 min rapid infusion of whole blood (Figs. 1A to C) (16-18). With CGS-16617 treatment left ventricular pumping ability in the Wistar-Kyoto rats was depressed downward (p < 0.05), but with increased left ventricular afterload this curve shifted no further (Fig. 1A). In contrast to these responses in the Wistar-Kyoto rats, the function curves of the spontaneously hypertensive rats remained unchanged with treatment, although on abruptly increasing afterload the function curve did shift downward (p < 0.05) (Fig. 1A).

There were no significant differences among the untreated, treated and treated-afterloaded left ventricles of the Wistar-Kyoto groups given quinapril (Fig. 1B). These findings were quite similar to those curves obtained with the Wistar-Kyoto groups given CGS-16617. In contrast to these responses in the Wistar-Kyoto rats, quinapril shifted the curves upward in the spontaneously hypertensive rats, although the function curve for the treated-afterloaded left ventricle fell between the untreated and treated function curves (Fig. 1B).

With cilazapril the left ventricular pumping ability of both Wistar-Kyoto and spontaneously hypertensive rats improved, the curves shifting upward and to the right, but when left ventricular afterload was increased abruptly, the curves became depressed, especially at the higher left ventricular end-diastolic pressures. However, this shift was depressed below those curves of the untreated or treated Wistar-Kyoto and spontaneously hypertensive rats (Fig. 1C).

**Aortic distensibility.** When evaluated by our in vitro assessment (Fig. 2, A to C), aortic distensibility was significantly reduced in the untreated spontaneously hypertensive rats with respect to the Wistar-Kyoto rats (at least p < 0.05). This impaired aortic distensibility (with respect to the Wistar-Kyoto rats) persisted with treatment with all three angiotensin-converting enzyme inhibitors in the spontaneously hypertensive rats, although each of the three agents significantly improved their respective in vitro distensibility curves (Fig. 2, A to C).

**Discussion**

In this study the three angiotensin-converting enzyme inhibitors had similar systemic hemodynamic effects, but they produced different cardiovascular structural and func-
tional responses to the volume and pressure-volume interventions. All three agents reduced arterial pressure through arteriolar dilation that decreased total peripheral resistance. These changes were achieved without a compensatory increase in heart rate or in cardiac index, and left ventricular end-diastolic pressure did not increase with treatment. These hemodynamic responses were similar to those reported earlier in patients with hypertension (10-12,22,23). Associated with these very similar hemodynamic effects was a diminished left ventricular and aortic mass in all spontaneously hypertensive rat groups, although there were variable effects in the normotensive Wistar-Kyoto rats without ventricular hypertrophy or increased vascular wall mass. Right ventricular mass did not change in either the hypertensive or the normotensive rats.

Structural-functional dissociation. The structural changes produced by angiotensin-converting enzyme inhibitors were associated with some changes in the pumping ability of the left ventricle but these do not necessarily relate to the changes in cardiovascular mass produced by the antihypertensive agents. Thus, a structural and functional dissociation was again demonstrated to be associated with reversal of cardiovascular mass with antihypertensive agents (1-4,8,9,13,14,24-30). In this study CGS-16617 reduced the mass of the nonhypertrophied left ventricle in the Wistar-Kyoto rats and this effect was associated with decreased pumping ability. However, this functional response was not aggravated when an increased afterload was superimposed on the volume loading conditions. In the spontaneously hypertensive rats with left ventricular hypertrophy, mass was reduced by approximately the same amount but the performance curve was not further diminished until the increased afterload was superimposed.

In contrast to these responses with CGS-16617, in both normotensive and hypertensive rats cilazapril improved the pumping ability of both the Wistar-Kyoto and spontaneously hypertensive rat left ventricles that had undergone similar, and perhaps greater, reduction in mass. Moreover, when the increased afterload was imposed on these left ventricles that had undergone diminution in mass from their once hypertro-
phied or nonhypertrophied state, pumping ability became diminished. However, this reduced performance was not significantly different from that shown from those function curves of treated or untreated spontaneously hypertensive rats. Finally, with quinapril, which did not decrease left ventricular mass in the Wistar-Kyoto rats and had the least effect in diminishing left ventricular mass in the spontaneously hypertensive rats, there was no alteration of left ventricular pumping ability in the Wistar-Kyoto rats, and the function curve improved in the spontaneously hypertensive rats.

Comparison with previous studies. These findings are in striking contrast with those from our studies of methyldopa (13) and captopril (14) in which we followed the identical protocol in male Wistar-Kyoto and spontaneously hypertensive rats of the same age. In those studies methyldopa and captopril produced systemic hemodynamic effects qualitatively and quantitatively similar to the effects obtained with the three angiotensin-converting enzyme inhibitors in this study. However, in contrast to the structural effects produced by these three agents, methyldopa reduced right ventricular mass in both the Wistar-Kyoto and spontaneously hypertensive rats but did not affect ascending aortic-arch mass (13). Moreover, CGS-16617 and cilazapril, like methyldopa, diminished left ventricular mass in the Wistar-Kyoto rats, although quinapril did not. In contrast to the three agents in the present study, captopril reduced left ventricular mass in both the Wistar-Kyoto and spontaneously hypertensive rats but reduced right ventricular mass only in the spontaneously hypertensive rats (14).

These findings underscore our earlier observations of a dissociation between the systemic hemodynamic and structural responses that takes place with the development (or reversal) of left ventricular hypertrophy in humans with essential hypertension as well as in animals with experimental forms of hypertension (1-4,28,29). The present findings extend the thesis by demonstrating that this dissociation also occurs with respect to the hemodynamic and structural responses of nonhypertrophied ventricles and aorta in normotensive rats with diminished ventricular mass associated with administration of pharmacologic agents. This concept is supported further by our recent observation of increased

Figure 2. In vitro aortic distensibility curves of ligated aortic segments in which measured increments of whole blood are added as pressure is measured in Wistar-Kyoto (WKY) (O) and spontaneously hypertensive (SHR) (■) rats treated with CGS-16617 (A), cilazapril (B) or quinapril (C). Symbols connected by solid lines represent untreated rats and those connected by interrupted lines, treated rats. There are 10 rats in each group; statistical significance is indicated.

[Graph A: Intra-aortic pressure (mmHg) vs. % increase of Aortic Volume]

[Graph B: Intra-aortic pressure (mmHg) vs. % increase of Aortic Volume]

[Graph C: Intra-aortic pressure (mmHg) vs. % increase of Aortic Volume]
right ventricular mass in Wistar-Kyoto rats and some spontaneously hypertensive rats associated with treatment with one of several calcium antagonists (30).

Mechanisms. At present it is not possible to define the mechanism or mechanisms responsible for the reduced cardiovascular mass or for the variable functional responses to these structural changes. Hemodynamic events are of major importance in producing left ventricular hypertrophy (1,2) and nonhemodynamic mechanisms must also participate to a greater or lesser extent in the situations that occur experimentally or clinically (1-4,28,31,32). Reduced left ventricular and aortic mass result from pharmacotherapy with a variety of antihypertensive agents (such as beta-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors or calcium antagonists) (1-4), and mass does not decrease with other effective hypotensive agents (such as directly acting smooth muscle vasodilators and alpha-adrenergic receptor blockers) (9,25,27) favoring participation of nonhemodynamic factors (28,29).

Among those factors that have been incriminated are intramyocytic protooncogenes (4,33), events involving the intramyocytic renin-angiotensin system (35) and changes in the intracellular calcium ionic milieu (4,26,37). Confounding the complexity of these possibilities are the obvious pharmacologic considerations of cellular penetration by the various antihypertensive drugs due to their pharmacodynamic and pharmacokinetic properties and the responsiveness of the aforementioned intracellular systems to these agents.

Therapeutic implications. The importance of the present study concerns the differences in the effects of the various antihypertensive agents on cardiovascular structure not only from one antihypertensive drug class to another, but also within the same class of pharmacologic agents (such as the angiotensin-converting enzyme inhibitors reported herein).

It is necessary to mention the clinical implications of the role of antihypertensive agents in diminishing the mass of the hypertrophied ventricles. Retrospective and prospective studies have shown that left ventricular hypertrophy in itself confers an independent risk of increased cardiovascular morbidity and mortality (5,6,38). It is not known what mechanisms account for this increased risk nor whether pharmacologically induced reversal of the hypertrophic process can reduce it. Until prospective studies demonstrate that risk has been reduced (after hypertrophy is reversed when the antihypertensive and antiarrhythmic effects of the drugs have dissipated), it seems wise to withhold further clinical, scientific and commercial speculation.

References


34. Re R. The myocardial intracellular renin-angiotensin system. Am J Cardiol 1987;59(suppl AI):56A-8A.


