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Olmesartan, but not Amlodipine, Improves Endothelium-dependent Coronary Dilation
in Hypertensive Patients

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Short title: Effects of ARB vs. CCB on coronary vasomotion

Key words: coronary endothelial function, olmesartan, amlodipine, hypertension,
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Abstract

Objectives: We aimed to compare the effects of angiotensin II receptor blocker (ARB) olmesartan versus calcium channel blocker (CCB) amlodipine on coronary endothelial dysfunction in patients with hypertension.

Background: ARB is thought to have greater beneficial effects on coronary vasomotion via directly blocking action of angiotensin II than CCB.

Methods: Twenty-six patients with untreated essential hypertension were prospectively assigned to the treatment with either olmesartan (27.7 ± 12.4 mg per day, $n=13$) or amlodipine (5.6 ± 1.5 mg per day, $n=13$) for 12 weeks. Changes of corrected myocardial blood flow (Δ MBF) and coronary vascular resistance (Δ CVR) from rest to cold pressor were measured by using ^{15}O -water and positron emission tomography before and after treatment. Blood biomarkers including lipids, glucose, insulin, hs-CRP, interleukin-6, tumor necrosis factor- α , and superoxide dismutase (SOD) were also measured.

Results: Olmesartan and amlodipine reduced blood pressure (BP) to the same extent (-28.7 ± 16.2 vs. -26.7 ± 10.8 mmHg). In olmesartan group, Δ MBF tended to be greater (-0.15 ± 0.19 vs. 0.03 ± 0.17 ml/g/min, $P=0.09$ by 2-way ANOVA) and Δ CVR was significantly decreased (7.9 ± 23.5 vs. -16.6 ± 18.0 mmHg/[ml/g/min], $P<0.05$) after treatment whereas they did not change in amlodipine group (Δ MBF: -0.15 ± 0.12 vs. -0.12 ± 0.20 ml/g/min; Δ CVR: 6.5 ± 18.2 vs. 4.8 ± 23.4 mmHg/[ml/g/min]). Serum SOD activity tended to increase (4.74 ± 4.77 vs. 5.57 ± 4.74 U/ml, $P=0.07$ by 2-way ANOVA) only in olmesartan group.

Conclusions: Olmesartan, but not amlodipine, improved endothelium-dependent

coronary dilation in hypertensive patients independently of BP lowering. These beneficial effects on coronary vasomotion might be via an antioxidant property of ARB.

Condensed Abstract

Olmesartan, but not amlodipine, improved coronary endothelial function in hypertensive patients, indicating that angiotensin II receptor blocker has greater beneficial effects on coronary endothelial function independently of blood pressure lowering.

Abbreviations and Acronyms

ARB = angiotensin II receptor blocker

BMI = body mass index

BP = blood pressure

CCB = calcium channel blocker

CPT = cold pressor test

CVR = coronary vascular resistance

HDL = high density lipoprotein

HOMA-IR = homeostasis model assessment for insulin resistance

HR = heart rate

hs-CRP = high-sensitivity C-reactive protein

IL-6 = interleukin-6

LDL = low density lipoprotein

LVMI = left ventricular mass index

MBF = myocardial blood flow

¹⁵O-water = oxygen 15-labeled water

PET = positron emission tomography

RPP = rate pressure product

SOD = superoxide dismutase

TNF- α = tumor necrosis factor- α

Introduction

Hypertension is a major risk factor of coronary artery disease (1). In hypertensive patients, coronary vasodilator response is impaired (2), which is caused not only by the elevation of blood pressure (BP) but also by inflammation and oxidative stress in the vascular wall induced by angiotensin II (3,4).

Angiotensin II receptor blocker (ARB) and calcium channel blocker (CCB) are highly used in the treatment of hypertension. ARB has been demonstrated to reduce inflammation (5) and oxidative stress (4) via directly blocking the action of angiotensin II. Therefore, the effects of antihypertensive drugs on endothelial function may differ between ARB and CCB.

Myocardial blood flow (MBF) could be measured by using oxygen-15 labeled (¹⁵O-) water positron emission tomography (PET). MBF and coronary vascular resistance (CVR) response to cold pressor test (CPT) are feasible and repeatable variables for the noninvasive evaluation of coronary endothelium-dependent function (6,7). The severity of coronary endothelial dysfunction has been demonstrated to be associated with the risk of developing cardiovascular events and poor prognosis (8). Thus, this study was performed to compare the effects of ARB and CCB on endothelium-dependent coronary dilation in patients with essential hypertension. Furthermore, the relation between blood biomarkers and coronary endothelial function was also evaluated.

Materials and Methods

Patients

Twenty-six consecutive untreated and uncomplicated patients with essential hypertension (12 males and 14 females; age 53.7 ± 11.0 [\pm SD] years) were studied from December 2004 to March 2006. They had systolic BP over 140 mmHg and/or diastolic BP over 90 mmHg by mercury sphygmomanometer, measured twice with an interval of one month. Patients with a history or clinical evidence of recent infection, malignancies, coronary artery disease, peripheral vascular disease, cerebrovascular disease, secondary hypertension, diabetes mellitus with HbA1c $> 5.8\%$, hyperlipidemia with total cholesterol > 260 mg/dl, wall motion abnormalities by echocardiography, and on medications were excluded. The patients were prospectively assigned to antihypertensive treatment with either olmesartan (27.7 ± 12.4 mg per day, n=13) or amlodipine (5.6 ± 1.5 mg per day, n=13) for 12 weeks.

Informed consent was obtained from each study patient. The study was approved by the institutional ethical committee, and the procedures were in accordance with institutional guidelines.

Treatment Protocol

BP was measured before and 4, 8, and 12 weeks after treatment. At least 2 measurements were made and the mean values of these measurements were used. Patients had either 20 mg olmesartan or 5 mg amlodipine daily. If systolic BP was ≥ 140 mmHg or diastolic BP was ≥ 90 mmHg after 1 month, the dose was doubled to 40 mg

olmesartan or 10 mg amlodipine. If systolic BP < 110 mmHg after 1 month, the dose was halved to 10 mg olmesartan or 2.5 mg amlodipine. No adverse effects of antihypertensive drugs were experienced.

Blood Chemical Analysis

Blood samples were obtained at the time of PET scans. Serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, blood sugar, insulin, high-sensitivity C-reactive protein (hs-CRP) and superoxide dismutase (SOD) activity, and plasma interleukin-6 (IL-6) and tumor necrosis factor (TNF)- α were measured. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated; $\text{HOMA-IR} = \text{fasting blood sugar} \times \text{insulin} / 405$.

Echocardiography

Left ventricular mass index (LVMI) was measured by using the M-mode guided echocardiogram according to the method recommended by the American Society of Echocardiography.

PET Scans

MBF at rest and during CPT were determined using ^{15}O -water and PET before and after treatments. All patients refrained from caffeine-containing beverages for at least 24 hours and from smoking for at least 12 hours before the PET study. All PET scans were performed with ECAT EXACT HR+ (Siemens/CTI, Knoxville, Tennessee) by modified methods as previously reported (9). CPT was performed as follows: The patient's right

foot was immersed in ice water up to the ankle. Sixty seconds later, PET scanning of ^{15}O -water was started, and the CPT was continued for 4 minutes.

Reconstruction of emission sinograms and quantification of MBF using semiautomatic program were performed according to the methods as previously reported (10).

MBF was corrected against rate pressure product (RPP) to account for individual differences in cardiac work as follow (9); MBF was divided by RPP and multiplied by 7,500, which is the average RPP at rest of healthy controls with age of 50.1 ± 9.7 years.

ΔMBF , an index of coronary endothelial function, was calculated as corrected MBF during CPT minus corrected MBF at rest (11). CVR was calculated by dividing mean BP by MBF to exclude the effects of coronary perfusion pressure as previously reported (11). CVR during CPT was also used as an index of coronary endothelial function (8,11). ΔCVR was calculated as CVR during CPT minus CVR at rest.

Statistical Analyses

All data were expressed as mean \pm SD. Baseline characteristics between groups were compared by an unpaired *t*-test. Within treatment groups, the changes of corrected MBF and CVR from rest to CPT were compared by a paired *t*-test. Between-group comparisons with regard to hemodynamic, blood biomarkers, ΔRPP , ΔMBF , and ΔCVR before and after treatment were performed by 2-way ANOVA with repeated measures followed by the Scheffé's test if the interaction was significant. Univariate analysis of the association between serum SOD activity and CVR during CPT was performed with the use of linear regression. A $P < 0.05$ was considered to be statistically significant.

Results

Study Patients

Table 1 shows the baseline clinical characteristic data for the study patients. Both olmesartan and amlodipine reduced BP 12 weeks after treatment ($P=0.51$ by 2-way ANOVA with repeated measures; Table 2) and the extent of BP reduction was the same between groups (-28.7 ± 16.2 vs. -26.7 ± 10.8 mmHg, $P=0.71$).

MBF Response to CPT

The increase of RPP from rest to CPT was comparable before and after treatment between groups (olmesartan: $2,410\pm 1,823$ vs. $2,523\pm 1,528$ mmHg/min; amlodipine: $2,925\pm 1,298$ vs. $2,639\pm 1,504$ mmHg/min, $P=0.49$ by 2-way ANOVA with repeated measures). Before treatment, corrected MBF was significantly decreased from rest to CPT in both groups. After treatment, corrected MBF did not change from rest to CPT in olmesartan group whereas it tended to decrease in amlodipine group (Figure 1).

Corrected MBF during CPT was significantly increased after treatment in olmesartan group, but not in amlodipine group (Figure 1). The increase of Δ MBF tended to be greater in olmesartan group than in amlodipine group ($P=0.09$ by 2-way ANOVA with repeated measures; Figure 2).

CVR Response to CPT

Before treatment, CVR did not change from rest to CPT in either group. After treatment, CVR significantly decreased from rest to CPT in olmesartan group, but not in

amlodipine group (Figure 3). CVR during CPT significantly decreased after treatment in olmesartan group, but not in amlodipine group. The decrease of Δ CVR was significantly greater in olmesartan group than in amlodipine group ($P < 0.05$ by 2-way ANOVA with repeated measures; Figure 4). Δ CVR significantly decreased after olmesartan, but not after amlodipine (Figure 4).

Blood Biochemical Markers

Blood biomarkers including total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood sugar, insulin, HOMA-IR, TNF- α , IL-6, and hs-CRP were comparable between groups (Table 3). Serum SOD tended to increase in olmesartan group compared with amlodipine group ($P = 0.07$ by 2-way ANOVA with repeated measures). There was a significant negative correlation between the changes of serum SOD activity and CVR during CPT in olmesartan group, whereas no such correlation was observed in amlodipine group (Figure 5).

Discussion

The present study demonstrated that 12-week treatment of hypertensive patients with olmesartan, but not amlodipine, improved endothelium-dependent coronary dilation despite comparable BP reduction. Serum SOD activity tended to increase only in the olmesartan group. Notably, there was a significant relationship between the improvement of coronary endothelial dysfunction and the increase of serum SOD by olmesartan.

Previous studies demonstrate that CCB improves the vasodilation of the epicardial coronary arteries in hypertensive patients (12). However, in the case of non-obstructed coronary arteries, MBF is not regulated by the conduit epicardial coronary arteries, but rather by the coronary microcirculation as is the largest part of the resistance of the coronary tree. Therefore, the present study suggested that ARB, but not CCB, might improve the endothelial function in coronary microcirculation, which is most prone to be affected by damaging cardiovascular risk factors such as hypertension (2). Consequently, any treatment strategy mostly targeting coronary microcirculation would be expected to prevent early episodes of myocardial ischemia by keeping coronary resistance as low as possible during high flow demand situations. The present study has thus provided a direct evidence to suggest that ARB has such beneficial effects on coronary microcirculation.

Some groups previously reported the similar effects of ACE inhibitors on MBF in response to dipyridamole (13). However, they compared the effects of ACE inhibitor to those by placebo, which did not allow us to comment on any effects beyond BP

lowering. In addition, a previous study found a beneficial effect of an ACE inhibitor, lisinopril, but not ARBs, losartan, on MBF response to dipyridamole (14). However, first, not all ARBs have the same effects on coronary microcirculation; i.e. olmesartan seems to have such an effect but not losartan. Second, the present study used the CPT, which is an established stimulus mostly dependent on endothelial function (6,7,11), while the previous study used dipyridamole, which is less endothelium-dependent.

The present study demonstrated that the augmentation of serum SOD by olmesartan might be involved in the improvement of coronary endothelial function. In addition, ARB can directly inhibit angiotensin II-mediated superoxide production (15). These results suggest that the antioxidant effects of olmesartan are specific for this ARB and differ from unspecific effects of vitamin C. More importantly, these effects of olmesartan can explain the contrasting results, in which ARB losartan failed to improve MBF response to dipyridamole (14) whereas olmesartan could exert beneficial effects on coronary microcirculation as seen in the present study.

Study Limitations

First, the present study was not a blinded, randomized study. However, the characteristics of the study patients were well matched between the two groups (Table 1-3). Importantly, MBF, CVR, and blood biomarkers were measured and analyzed by another group of investigators who were blinded to the treatment groups. Second, central BP measurement as in the CAFE study (16), which might affect MBF more effectively than peripheral BP, was not available in the present study. Therefore, a further study is clearly needed to evaluate the relation between the central BP and MBF.

Conclusions

ARB olmesartan, but not CCB amlodipine, improved endothelium-dependent coronary dilation assessed by using ^{15}O -water PET in hypertensive patients independently of BP lowering. These beneficial effects might contribute to the cardioprotective benefits of ARB in the treatment of hypertension, which warrants further investigation.

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Figure Legend

Figure 1

Corrected MBF in response to CPT before and after treatment with olmesartan (n=13; left panel) and amlodipine (n=13; right panel). The central bar on the vertical bars represents the mean \pm SD.

Figure 2

Δ MBF from rest to CPT before and after treatment with olmesartan (n=13) and amlodipine (n=13).

Figure 3

CVR in response to CPT before and after treatment with olmesartan (n=13; left panel) and amlodipine (n=13; right panel). The bars represent the mean \pm SD.

Figure 4

Δ CVR from rest to CPT before and after treatment with olmesartan (n=13) and amlodipine (n=13).

Figure 5

Relationship between the changes of CVR during CPT and serum SOD activity after treatment with olmesartan (n=13; panel A) and amlodipine (n=13; panel B).

Table 1

Characteristics of the Study Patients at Baseline

	Olmesartan (n = 13)	Amlodipine (n = 13)	P value
Age (years)	53.5 ± 12.1	53.9 ± 9.1	0.92
Sex (M/F)	7/6	5/8	0.43
BMI (kg/m ²)	25.7 ± 4.1	24.5 ± 4.6	0.50
Smoking [No (%)]	2 (15)	2 (15)	0.99
Duration of HT (yr)	3.5 ± 3.6	3.4 ± 3.4	0.98
LVMI (g/m ²)	101.4 ± 19.5	99.7 ± 18.9	0.82

BMI: body mass index, HT: hypertension, LVMI: left ventricular mass index

Data are expressed as mean ± SD

Table 2 BP and HR at Rest Before and After Treatment

Olmesartan (n = 13)				
	Before	4 weeks after	8 weeks after	12 weeks after
SBP (mmHg)	154 ± 14	140 ± 14	134 ± 15	125 ± 10
DBP (mmHg)	100 ± 14	88 ± 12	84 ± 11	82 ± 11
HR (bpm)	65 ± 7	-	-	65 ± 7

Amlodipine (n = 13)				
	Before	4 weeks after	8 weeks after	12 weeks after
SBP (mmHg)	152 ± 15	134 ± 14	128 ± 12	125 ± 10
DBP (mmHg)	101 ± 8	88 ± 7	85 ± 7	85 ± 8
HR (bpm)	64 ± 9	-	-	64 ± 8

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure

-: not measured

Data are expressed as mean ± SD

Table 3

Blood Biochemistry Before and After Treatment

	Olmesartan (n = 13)		Amlodipine (n = 13)	
	Before	After	Before	After
Total cholesterol (mg/dl)	209.1 ± 32.8	204 ± 33.7	194.1 ± 33.1	210 ± 47.8
HDL cholesterol (mg/dl)	66.5 ± 21.8	67.6 ± 23.3	59.0 ± 10.1	65.2 ± 17.0
LDL cholesterol (mg/dl)	123.5 ± 30.5	118 ± 25.9	119.7 ± 31.7	128 ± 47.9
Triglycerides (mg/dl)	116.6 ± 55.9	134 ± 105.2	124.8 ± 105	120 ± 96.4
Blood sugar (mg/dl)	101.4 ± 8.5	99.7 ± 7.5	98.9 ± 7.7	97.2 ± 9.4
Insulin (mU/L)	6.47 ± 2.93	8.3 ± 5.94	6.98 ± 5.36	5.3 ± 3.10
HOMA-IR	1.61 ± 0.71	2.07 ± 1.48	1.74 ± 1.36	1.32 ± 0.87
IL-6 (pg/ml)	2.65 ± 4.02	1.68 ± 2.68	1.63 ± 1.64	1.35 ± 1.17
TNF- α (pg/ml)	1.11 ± 0.29	1.06 ± 0.34	1.12 ± 0.37	1.17 ± 0.38
hs-CRP (ng/ml)	998 ± 1,433	880 ± 1,055	760 ± 935	815 ± 896
SOD activity (U/ml)	4.74 ± 4.77	5.57 ± 4.74	3.09 ± 3.09	3.09 ± 1.26

HOMA-IR: hemeostasis model assessment for insulin resistance, IL-6: interleukin-6

TNF- α : tumor necrosis factor- α , hs-CRP: high sensitivity C-reactive protein

SOD: superoxide dismutase

Data are expressed as mean \pm SD

Figure 1 Corrected MBF in Response to CPT Before and After Treatment

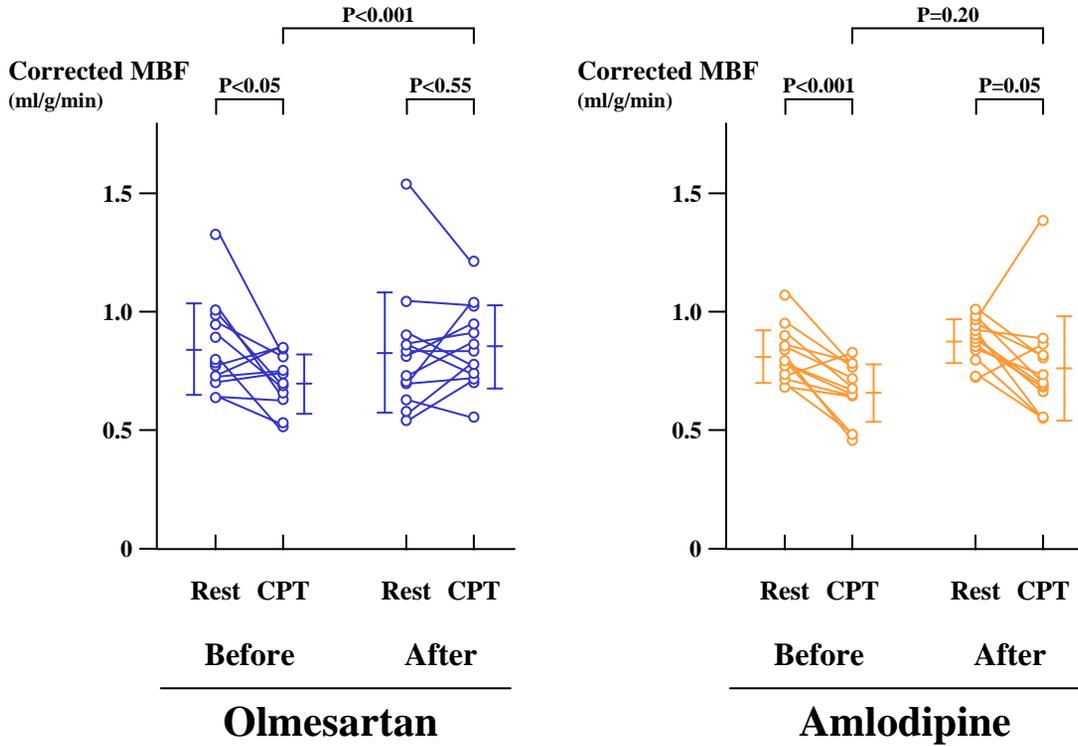
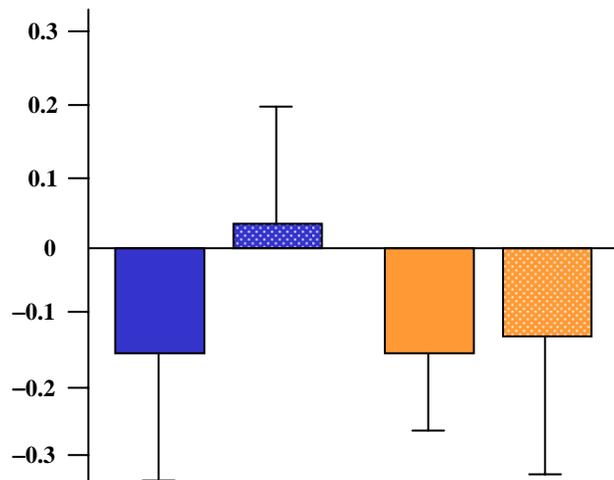


Figure 2 Δ MBF in Response to CPT Before and After Treatment

Δ MBF from rest to CPT
(ml/g/min)



Before After
Olmesartan

Before After
Amlodipine

Figure 3 CVR in Response to CPT Before and After Treatment

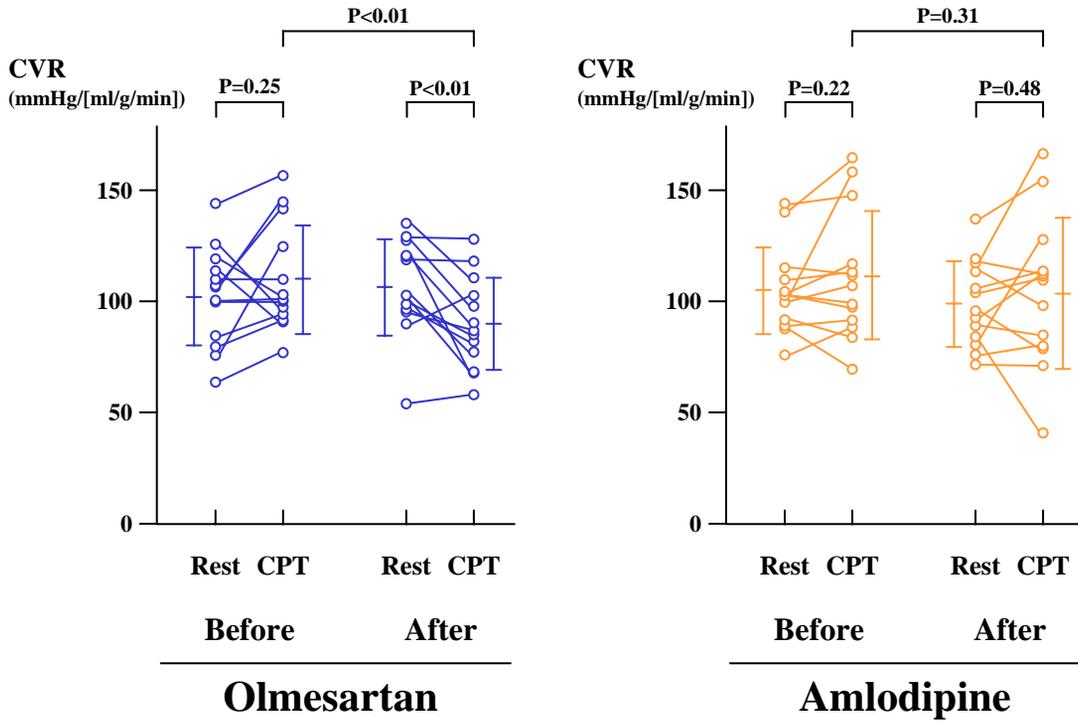


Figure 4 Δ CVR in Response to CPT Before and After Treatment

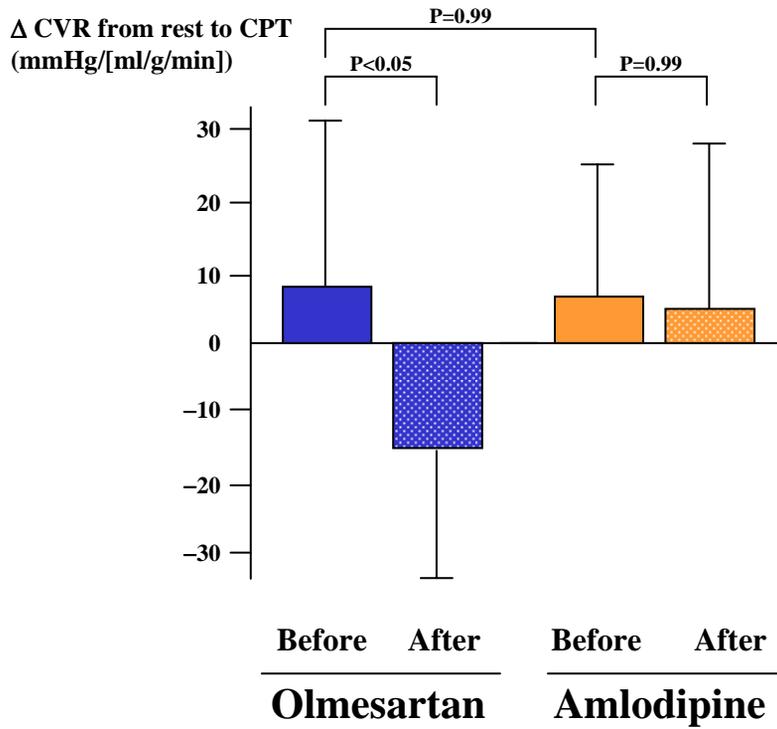
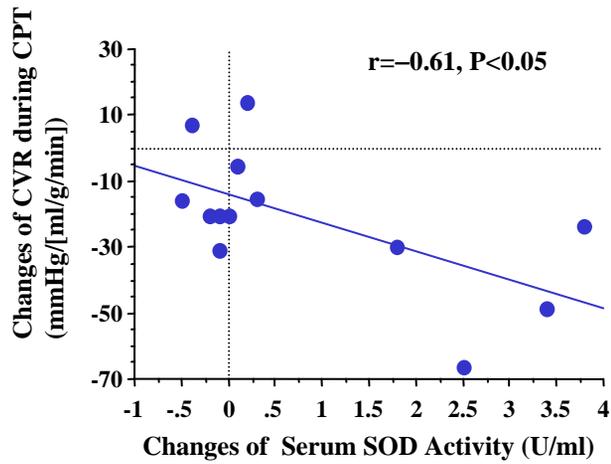


Figure 5 Relationship Between the Changes of CVR during CPT and Serum SOD Activity After Treatment

A

Olmesartan



B

Amlodipine

