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Effects of Afterload-Reducing Drugs on Pathogenesis of Antioxidant Changes and Congestive Heart Failure in Rats

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Objectives. **The present study sought to evaluate the effects of the afterload-reducing drugs captopril and prazosin on changes in antioxidants as well as oxidative stress in relation to hemodynamic function in congestive heart failure (CHF) subsequent to myocardial infarction (MI).**

Background. **Afterload reduction therapy has been shown to reduce morbidity and mortality in patients with MI. CHF subsequent to MI in rats is associated with a decrease in myocardial endogenous antioxidants and an increase in oxidative stress.**

Methods. **The left anterior descending coronary artery in male Sprague-Dawley rats was ligated. Sham and experimental (post-MI [PMI]) animals were assessed for hemodynamic function as well as lung and liver weights at 1, 4 and 16 weeks after operation. At 4 weeks, some rats were also treated with captopril (2 g/liter in drinking water daily) or prazosin (0.2 mg/kg body weight subcutaneously daily) and assessed at 16 weeks. Hearts were isolated to study the activity of superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and catalase as well as for thiobarbituric acid reactive substances (TBARS).**

Results. **CHF at 4 and 16 weeks in the infarcted rats was indicated by an increase in left ventricular end-diastolic pressure and wet/dry weight lung and liver ratios and depressed left ventricular systolic pressure and dyspnea. All these changes were attenuated in both the captopril- and prazosin-treated groups. SOD, GSHPx and catalase activity in the untreated PMI groups was decreased at 4 and 16 weeks. However, treatment with captopril resulted in a significant improvement in SOD, GSHPx and catalase activity in the 16-week PMI group. With prazosin, only SOD activity was improved in the treated 16-week PMI group. Lipid peroxidation as indicated by TBARS was significantly increased in the 16-week PMI group, and both captopril and prazosin modulated this increase.**

Conclusions. **Occurrence of an antioxidant deficit and an increase in oxidative stress in the myocardium may play a role in the pathogenesis of CHF subsequent to MI. Attenuation of these changes in antioxidant activity with vasodilator (or antioxidant?) therapy mitigates the process of heart failure.**

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Although the clinical syndrome of congestive heart failure (CHF) has long been recognized, and significant advances have been made in its management, the pathophysiology of this syndrome remains poorly understood. Irrespective of etiology, several biochemical processes, including the production and utilization of high energy phosphates, excitation–contraction coupling and calcium metabolism, have been reported (1,2) to be defective in CHF. Whether any or all these changes are the result of the CHF condition, or whether in fact these may be causal, remains unknown. Recent data from experimental studies (3,4) have suggested that CHF in rats subsequent to myocardial infarction (MI), as well as in guinea pigs subjected to chronic pressure overload, may be caused by a decrease in myocardial endogenous antioxidants and an increase in oxidative stress. The latter has been shown (5,6) to cause myocardial cell damage and loss of contractile function in ex vivo studies. Direct evidence in support of this hypothesis has been provided by in vivo studies (7) in which the transition from myocardial hypertrophy to CHF was attenuated by vitamin E therapy. Analysis of breath pentane in patients with coronary artery disease has also provided evidence of increased lipid peroxidation and thus oxidative stress in CHF (8). The occurrence of myocardial antioxidant deficit as well as increased oxidative stress subsequent to MI may be intimately linked to CHF.

Although the efficacy of vasodilators in the management of hypertension and CHF in patients has been well documented, their effects on myocardial endogenous antioxidants remain to be studied. Both captopril and prazosin have been shown (9–14) to improve hemodynamic function in CHF subsequent to MI. Captopril (10), but not prazosin (15), has also been shown to reduce mortality. Whether this improved prognosis with vasodilator therapy is associated with the modulation of antioxidant changes remains to be determined. The present study was therefore designed to test the hypothesis that improved hemodynamic function with afterload reduction in

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Abbreviations and Acronyms

CHF = congestive heart failure
GSHPx = glutathione peroxidase
LVEDP = left ventricular end-diastolic pressure
LVPSP = left ventricular peak systolic pressure
MI = myocardial infarction
NADP = nicotinamide adenine dinucleotide phosphate
NADPH = nicotinamide adenine dinucleotide phosphate, reduced
PMI = post–myocardial infarction
SOD = superoxide dismutase
TBARS = thiobarbituric acid-reactive substances

the treatment of CHF may also involve an improvement in myocardial endogenous antioxidant status. Changes in myocardial antioxidant activity, oxidative stress, hemodynamic variables and tissue weight were examined at 1, 4 and 16 weeks postoperatively. Captopril and prazosin therapy was started at 4 weeks after operation, and the studies were repeated at 16 weeks.

Methods

Animal model and study groups. Male Sprague-Dawley rats weighing (mean ± SE) 150 ± 10 g were maintained on standard rat chow and water ad libitum unless otherwise indicated. MI was produced by occlusion of the left anterior descending coronary artery (16,17). The animals were anesthetized with 2% isoflurane, and the skin was then incised along the left sternal border. The third and fourth ribs were cut proximal to the sternum, with the subsequent insertion of retractors. The pericardial sac was perforated, and the heart was exteriorized through the intercostal space. The left main coronary artery was ligated ~1 to 2 mm from its origin with a 6-0 silk thread. After ligation, the heart was gently repositioned in the chest. Excess air was drawn into a syringe, and the chest was closed. Closure of the incision was accomplished by a purse-string suture. The rats were maintained on a positive pressure ventilation delivering 2% isoflurane mixed with oxygen throughout the operation. The entire surgical procedure was carried out under sterile conditions. Control animals were similarly treated, except that the suture around the coronary artery was not tied, and the thread was passed only through the muscle.

There were five experimental groups, each with its own age-matched sham control group as follows: group 1 = 1-week after MI (PMI) and 1-week sham control; group 2 = 4-week PMI and 4-week sham control; group 3 = 16-week PMI and 16-week sham control; group 4 = 16-week PMI and 16-week sham control, both treated with captopril; group 5 = 16-week PMI and 16-week sham control, both treated with prazosin. In groups 4 and 5, captopril (2 g/liter in drinking water) or prazosin (0.2 mg/kg body weight subcutaneously daily) treatment, respectively, was started 4 weeks after the operation and was continued up to 16 weeks. Animals were monitored daily for general behavior and food and water intake.

Hemodynamic studies. Rats were anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally). A miniature pressure transducer catheter (Millar Micro-Tip, model PR 249) was inserted into the right carotid artery and then advanced into the left ventricle. Left ventricular end-diastolic (LVEDP) and left ventricular peak systolic (LVPSP) pressures were recorded on a computer for an on-line analysis (Axotape acquisition data program and Acqknowledge 3.0). After these assessments, the rats were killed, and the heart and other organs were removed for further studies.

Tissue weight determination. To obtain the wet/dry weight ratio of the lungs and liver, these organs were removed and freed from adhering tissues. In each case, the sample tissue was weighed, chopped into smaller pieces and placed in the oven at 65°C until a constant weight was obtained, which was usually after ~24 h.

Biochemical assays. For the studies of antioxidants and lipid peroxidation, only viable portion of the ventricles were utilized, as follows: *Superoxide dismutase.* Superoxide dismutase (SOD) activity in the hearts was determined by a previously described method (18). Hearts were homogenized (1:10) in 50 mmol/liter Tris-HCl, pH 8.20, containing 1 mmol/liter diethylenetriamine pentaacetic acid. The homogenate was centrifuged at 20,000*g* for 20 min. The supernatant was aspirated and assayed for total SOD activity by following the inhibition of pyrogallol auto-oxidation. Pyrogallol (24 mmol/liter) was prepared in 10 mmol/liter HCl and kept at 4°C before use. Catalase, 30 μmol/liter stock solution was prepared in an alkaline buffer (pH 9.0). Aliquots of supernatant (150 μg protein) were added to Tris-HCl buffer containing 25 μl of pyrogallol and 10 μl of catalase. Changes in absorbance at 420 nm were recorded at 1-min intervals for 5 min. SOD activity was expressed as units per milligram protein derived from an SOD standard curve of pyrogallol autoxidation obtained in the presence of commercially available SOD.

Glutathione peroxidase. Glutathione peroxidase (GSHPx) activity was determined in whole heart as previously described (19). Hearts were homogenized (1:10) in 75 mmol/liter phosphate buffer (pH 7.0). Homogenate was centrifuged at 20,000*g* for 25 min, and the supernatant was aspirated and assayed for total cytosolic GSHPx activity. GSHPx activity was assayed in a 3-ml cuvette containing 2.0 ml of 75 mmol/liter phosphate buffer (pH 7.0). The following solutions were then added: 50 μl of 60 mmol/liter glutathione, 100 μl of glutathione reductase solution (30 U/ml), 50 μl of 0.12 mol/liter NaN_3, 100 μl of 15 mmol/liter Na_2 EDTA, 100 μl of 3.0 mmol/liter nicotinamide adenine dinucleotide phosphate, reduced (NADPH) and 100 μl of cytosolic fraction. The reaction was started by the addition of 100 μl of 7.5 mmol/liter H_2O_2, and the conversion of NADPH to nicotinamide adenine dinucleotide phosphate (NADP) was monitored by continuous recording of the change in absorbance at 340 nm at 1-min intervals for 5 min. GSHPx activity was expressed as nanomoles of reduced NADPH oxidized to NADP per minute per milligram protein, with a molar extinction coefficient for NADPH at 340 nm of 6.22×10^6.

Table 1. Lung and Liver Wet/Dry Weight Ratios in Sham and Infarcted Rats at 1, 4 and 16 Weeks After Operation and Effect of Afterload Reduction Therapy at 16 Weeks

Postoperative Period	Lung		Liver	
	Sham Control Group	PMI Group	Sham Control Group	PMI Group
No therapy				
1 wk	4.76 ± 0.19	4.78 ± 0.22	3.19 ± 0.02	3.20 ± 0.51
4 wk	4.66 ± 0.27	4.97 ± 0.58	3.21 ± 0.54	3.42 ± 0.11
16 wk	4.64 ± 0.19	6.20 ± 0.32*	3.22 ± 0.17	4.04 ± 0.28†
Therapy‡				
Captopril (16 wk)	4.21 ± 0.27	4.71 ± 0.17§	3.47 ± 0.3	2.91 ± 0.5§
Prazosin (16 wk)	4.28 ± 0.39	4.43 ± 0.57§	2.95 ± 0.46	3.12 ± 0.1§

*$p < 0.05$ versus sham control group by analysis of variance (ANOVA) followed by Bonferroni test. †$p < 0.05$ versus sham control group by ANOVA. ‡Captopril or prazosin therapy was started at 4 weeks and continued up to 16 weeks, as described in Methods. §$p < 0.05$ versus 16-week untreated post–myocardial infarction (PMI) group by ANOVA. Data presented are mean value ± SE of five to eight experiments.

Catalase. Catalase activity in the hearts was determined as previously described (20). Hearts were homogenized in (1:10) 50 mmol/liter potassium phosphate buffer (pH 7.4). Homogenate was centrifuged at 40,000*g* for 30 min. Fifty microliters of supernatant was added to a 3-ml cuvette that contained 2.95 ml of 19 mmol/liter hydrogen peroxide in 50 mmol/liter potassium phosphate buffer (pH 7.4). Changes in absorbance at 240 nm were continuously monitored for 5 min. Catalase activity was expressed as units per milligram protein.

Thiobarbituric acid reactive substances. Lipid peroxide content in hearts was determined by measuring the thiobarbituric acid reactive substances (TBARS) as previously described (21). Hearts were homogenized in (10% wt/vol) 0.2 mol/liter Tris, 0.16 mol/liter KCl buffer (pH 7.4) and incubated at 37°C for 1 h. After 1 h, a 2-ml aliquot was collected from the incubation mixture and poured into a Corning culture tube. To this tube, 2.0 ml of 40% trichloroacetic acid and 1.0 ml of 0.2% thiobarbituric acid (TBA) were added; 100 μl of 2% butylated hydroxy toluene was added to the thiobarbituric reagent mixture to minimize peroxidation during the assay procedure. The mixture was then boiled for 15 min and allowed to cool on ice for 5 min; 2 ml of 70% trichloroacetic acid was then added, and the tubes were allowed to stand for 20 min. After 2 min, the sample was centrifuged at 800*g* for 20 min. The developed color was read at 532 nm. Commercially available malondialdehyde was used as the standard.

Proteins and statistical analysis. Proteins were determined by the method described by Lowry et al. (22). Results are expressed as mean value ± SEM. For statistical analysis of the data, group means were compared by one-way analysis of variance and a Bonferroni test. A value of $p < 0.05$ were considered significant.

Results

General characteristics and mortality. No unusual changes in general appearance or behavior were observed in any of the sham control or the 1- and 4-week PMI groups. In the 16-week untreated PMI group, rats showed clear signs of dyspnea. The mortality rate in the coronary ligated animals during or immediately after the operation was 20%. Another 12% of the rats died within 24 h of the operation. There was no difference between control and experimental rats with respect to food and water intake at 1, 4 and 16 weeks.

Lung and liver wet/dry weight ratios. There was no change in lung and liver wet/dry weight ratios in the PMI groups at 1 and 4 weeks (Table 1). However, at 16 weeks in the PMI groups, the ratios for the liver and lungs were ~25% and 33% higher, respectively, than those in the 16-week sham control group, and these differences were statistically significant. In the 16-week treated PMI group, captopril and prazosin treatment significantly attenuated the wet/dry weight ratios for both the lungs and the liver. Neither drug had any effect on these ratios in the sham control rats (Table 1).

Hemodynamic variables. In the untreated PMI groups, LVPSP was unchanged at 1 week, marginally reduced at 4 weeks and significantly depressed at 16 weeks (Table 2); LVEDP was unchanged at 1 week but was significantly elevated at 4 and 16 weeks (Table 2). In the 16-week treated PMI groups, both captopril and prazosin attenuated the increase in LVEDP, and LVPSP was significantly higher than that in the untreated 16-week PMI group (Table 2).

Antioxidant enzymes. SOD activity remained unchanged in the 1-week PMI and sham control groups (Table 3) but decreased ~19% and 45% in the 4- and untreated 16-week PMI groups, respectively, compared with their respective sham control groups, and these changes were statistically significant. GSHPx activity was marginally higher in the 1-week PMI group relative to sham control values, but the change was not significant (Table 3). However, in the 4-week and untreated 16-week PMI groups, GSHPx activity was depressed by 30% and 37%, respectively, relative to sham control values. A similar trend was seen with respect to catalase activity (Table 3): There was no change in catalase activity in the 1-week PMI group but a significant decrease in the 4-week and 16-week untreated PMI groups of ~27% and ~40%, respectively.

Captopril or prazosin therapy resulted in an improvement in SOD activity in the treated versus the untreated 16-week

Table 2. Left Ventricular Pressure in Sham and Infarcted Rats at 1, 4 and 16 Weeks After Operation and Effect of Afterload Reduction Therapy at 16 Weeks

Postoperative Period	LVEDP (mm Hg)		LVPSP (mm Hg)	
	Sham Control Group	PMI Group	Sham Control Group	PMI Group
No therapy				
1 wk	2.0 ± 0.28	2.2 ± 1.4	125.7 ± 6.7	130.7 ± 5.9
4 wk	2.6 ± 0.63	6.5 ± 0.9†	124.5 ± 8.3	109.5 ± 1.7
16 wk	3.3 ± 0.60	27.5 ± 1.2*	128.7 ± 4.6	88.6 ± 2.8*
Therapy‡				
Captopril (16 wk)	3.2 ± 0.4	10.8 ± 0.2†§	129.3 ± 6.2	103.2 ± 4.7†§
Prazosin (16 wk)	2.8 ± 0.5	8.2 ± 1.6†§	125.2 ± 6.2	115.6 ± 4.6§

*$p < 0.05$ versus sham control group by analysis of variance (ANOVA) followed by Bonferroni test. †$p < 0.05$ versus sham control group by ANOVA. ‡Captopril or prazosin therapy was started at 4 weeks and continued up to 16 weeks, as described in Methods. §$p < 0.05$ versus 16-week post–myocardial infarction (PMI) group by ANOVA. Data presented are mean value ± SE for six to eight rats. LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure.

PMI group (Table 3). GSHPx activity in captopril-treated 16-week PMI group was higher than that in the untreated 16-week PMI group but remained unchanged in the prazosin-treated group compared with the untreated 16-week PMI group. Catalase activity was significantly higher in the captopril-treated 16-week PMI group that in the untreated 16-week PMI group and showed some increase in the prazosin-treated 16-week PMI group over that in the untreated 16-week PMI group, but the change was not statistically significant.

Lipid peroxidation. Lipid peroxidation was assessed in the 1-, 4- and 16-week sham and PMI groups by evaluating myocardial TBARS (Table 3). TBARS in the 1-week PMI group remained unchanged relative to its respective sham control group but increased by 12% and 48%, respectively, in the 4-week and untreated 16-week PMI groups relative to their respective sham control groups. The increase in the untreated 16-week PMI group was statistically significant.

TBARS in the 16-week sham control groups treated with captopril or prazosin remained unchanged relative to the 16-week untreated PMI group (Table 3). However, TBARS was significantly lower in the captopril- and prazosin-treated 16-week PMI groups than the untreated 16-week PMI group.

Discussion

To our knowledge, the present study demonstrates for the first time that improved hemodynamic function subsequent to afterload reduction therapy in rats after MI is associated with an increase in antioxidant levels and a decrease in oxidative stress in the heart. The study supports the hypothesis that antioxidant deficit may have a role in the pathogenesis of CHF subsequent to MI.

Progressive CHF subsequent to MI. In untreated rats at 1 week PMI, there was no change in LVPSP and LVEDP. Signs of lung and liver congestion were also not apparent, indicating 1 week PMI to be a "nonfailure" stage. However, at 4 weeks

Table 3. Antioxidant Enzyme Activity and Lipid Peroxidation in Sham and Infarcted Rats at 1, 4 and 16 Weeks After Operation and Effect of Afterload Reduction Therapy at 16 Weeks

Postoperative Period	Antioxidant Enzyme Activity						Lipid Peroxidation (TBARS [nmol/g wet wt])	
	SOD (U/mg protein)		GSHPx (nmol/mg protein)		Catalase (U/mg protein)			
	Sham Control Group	PMI Group	Sham Control Group	PMI Group	Sham Control Group	PMI Group	Sham Control Group	PMI Group
No Therapy								
1 wk	35.2 ± 3.1	38.1 ± 2.7	86.4 ± 1.9	96.6 ± 6.9	26.9 ± 1.7	29.4 ± 2.8	74.7 ± 5.3	72.1 ± 0.8
4 wk	34.8 ± 5.1	28.2 ± 4.2*	84.6 ± 1.6	60.3 ± 1.9*	30.8 ± 2.6	22.3 ± 1.7*	70.2 ± 2.9	78.1 ± 4.5
16 wk	33.1 ± 5.3	18.1 ± 4.7†	78.6 ± 2.8	49.5 ± 3.6†	29.7 ± 2.3	18.4 ± 3.5*	71.1 ± 3.1	104 ± 7.5*
Therapy								
Captopril (16 wk)	35.1 ± 2.7	24.2 ± 10.5‡	76.1 ± 6.7	69.2 ± 0.5§	32.3 ± 3.8	38.5 ± 2.5§	72.1 ± 2.7	80 ± 2.8§
Prazosin (16 wk)	35.2 ± 10.1	29.2 ± 7.6‡	82.9 ± 2.5	46.3 ± 4.7*	29.1 ± 1.9	22.4 ± 1.7*	71.4 ± 1.4	89.6 ± 2.4§

*$p < 0.05$ versus sham control group by analysis of variance (ANOVA). †$p < 0.05$ versus sham control group by ANOVA followed by Bonferroni test; captopril or prazosin therapy was started at 4 weeks and continued up to 16 weeks, as described in Methods. ‡$p < 0.05$ versus the 16-week untreated post–myocardial infarction (PMI) group by ANOVA. Data presented are mean value ± SE for six to eight rats. GSHPx = glutathione peroxidase; SOD = superoxide dismutase; TBARS = thiobarbituric acid reactive substances.

PMI, LVEDP was significantly elevated, whereas LVPSP was slightly depressed, but the change was not significant. Pulmonary edema and liver congestion were also absent in this experimental group. Thus, 4 weeks PMI was considered to be a "mild failure" and functionally compensated stage. At 16 weeks PMI, LVEDP increased along with a significant depression in LVPSP. Lung and liver wet/dry weight ratios were significantly higher. All these features, along with respiratory distress, in these animals suggested 16 weeks PMI be in a "severe failure" stage. The increase in LVEDP and congestion of lung and liver seen in our study at 16 weeks have also been previously reported by several other studies using this animal model (3,9,17). Heart failure appears to worsen with duration of the postoperative period.

Afterload reduction and attenuation of heart failure. Because the early signs of CHF were evident at 4 weeks, vasodilatory therapy was started at this stage. Data for the captopril- and prazosin-treated groups demonstrated not only improved hemodynamic function at 16 weeks PMI but also the absence of any signs of respiratory distress as well as lung and liver congestion. Normalization of hemodynamic variables in the infarcted rats after prolonged treatment with captopril has been reported (9). In the SAVE trial (23) in humans with left ventricular dysfunction, captopril was reported to improve survival and reduce morbidity and mortality. In another study in patients with symptomless left ventricular dysfunction after MI (24), treatment with captopril attenuated ventricular enlargement and prevented further deterioration of ventricular performance. In a canine model of MI, treatment with captopril, enalapril and isosorbide dinitrate improved left ventricular geometry and function after both anterior and inferior infarctions (25,26). In contrast, prazosin has been shown (12–15) to improve morbidity but not mortality. In a long-term follow-up study (13), prazosin was found to improve New York Heart Association functional class (3.7 to 2.2, $p < 0.001$) and to be effective in the ambulatory management of CHF. Thus, previous studies have clearly demonstrated the beneficial effects of both drugs in patients as well as in experimental models. However, the subcellular mechanisms for improvement at the myocardial level have not been precisely defined. In this regard, loss of myocytes (27) as well as subcellular abnormalities in individual myocytes may play an important role.

Antioxidant deficit and heart failure. Findings of the present study as well as other published data (3,7,8) suggest that the improved "antioxidant reserve" (28,29) may form an important part of the attenuation of subcellular changes leading to CHF. In our model of CHF, characteristic changes in SOD, GSHPx and catalase activity were seen at different time points after MI. Antioxidant activity showed either no change or a slight trend toward an increase at 1 week after MI; a significant depression at 4 weeks after MI; and an even greater reduction at 16 weeks after MI. Antioxidant decrease in CHF subsequent to MI has been previously documented (3). In the present study, the presence of depressed antioxidant reserves or increased oxidative stress at 16 weeks was also suggested by an increase in lipid peroxidation. Increased lipid peroxidation has been reported in experimental models of CHF, such as CHF due to pressure overload in guinea pigs (4), subsequent to MI in rats (3) and in cardiomyopathic hamsters (30). An increase in lipid peroxidation, measured by breath pentane content, is also known to occur in patients with CHF (8,31). Thus, the present study suggests that poor cardiac function or CHF may in fact be linked to the decrease in antioxidant activity and an increase in lipid peroxidation.

Improved antioxidant reserves and attenuation of heart failure. The present study also showed that long-term treatment with captopril not only improved hemodynamic function, but also resulted in better maintenance of antioxidant enzyme activity. As a result, oxidative stress in the captopril-treated 16-week PMI group was significantly less than that in the untreated 16-week PMI group, as was evidenced by a decrease in myocardial lipid peroxidation in the drug-treated groups. Thus, our data as well as the findings reported by others suggest that a relative deficit in antioxidant activity and an increase in oxidative stress may play an important role in the pathogenesis of CHF (28,29,32). Because of the other humoral and tissue level effects of angiotensin-converting enzyme and angiotensin II, the exact mechanism by which angiotensin-converting enzyme inhibition with captopril treatment improves left ventricular function is not yet defined. In this regard, sulfydryl groups in captopril may act as free radical scavengers (8,33), and some component of protection may also result from a direct antioxidant effect of the drug. Vasodilatory effects of captopril through mechanisms other than modifying angiotensin II levels have also been reported (34). Captopril has been shown to increase the activity of bradykinin, a potent vasodilator (34), and to stimulate the production and release of prostacyclin (35). However, prazosin, another vasodilator with no known antioxidant property, significantly improved cardiac function and alleviated signs of CHF. Prazosin reduced myocardial lipid peroxidation as measured by TBARS and also improved levels of SOD. There is also a clinical evidence of reduced pulmonary venous congestion and enhanced exercise tolerance with prazosin (13,15,36,37).

Conclusions. To our knowledge, our study demonstrated for the first time that an afterload reduction was not only accompanied by an improvement in hemodynamic variables, but also by an increase in antioxidant activity and a decrease in oxidative stress. Because protection was seen with both vasodilators (captopril and prazosin), it is likely that the primary beneficial effect may be due to afterload reduction or a reduction in myocardial wall stress, which may then influence antioxidant activity and oxidative stress through a yet undefined mechanism. Afterload reduction is clearly beneficial in the treatment of CHF, and attenuation of antioxidant activity as well as oxidative stress changes that occur during CHF may play a role in this beneficial effect. An understanding of the molecular basis of the antioxidant changes subsequent to afterload reduction may lead to the use of an early and targeted gene therapy that can play an important role in preventing CHF.

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