Regional and Systemic Metabolic Effects of Angiotensin-converting Enzyme Inhibition During Exercise in Patients with Severe Heart Failure

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SUMMARY **The acute hemodynamic and metabolic effects of captopril therapy were studied in 12 patients with severe heart failure during maximal exercise performed on an upright bicycle ergometer. During the control period, exhaustion occurred after 4.2 ± 2.7 minutes of exercise. Cardiac index increased from 1.54 ± 0.36 l/min/m^2 at rest to 3.39 ± 1.54 l/min/m^2 ($p < 0.001$) at exhaustion; systemic arteriovenous oxygen difference increased from 8.8 ± 2.1 to 12.8 ± 2.4 ml/100 ml ($p < 0.001$) and oxygen uptake from 3.4 ± 0.5 to 10.8 ± 3.0 ml/kg/min ($p < 0.001$). Pulmonary arterial oxygen content decreased from 7.3 ± 1.3 to 3.7 ± 1.5 ml/100 ml ($p < 0.001$) and femoral vein oxygen content from 5.0 ± 1.7 to 2.5 ± 1.2 ml/100 ml ($p < 0.001$). During captopril therapy, cardiac index significantly increased both at rest (1.83 ± 0.54 vs 1.54 ± 0.36 l/min/m^2, $p < 0.01$) and during maximal exercise (3.67 ± 1.51 vs 3.39 ± 1.54 l/min/m^2, $p < 0.01$). Systemic arteriovenous oxygen difference decreased significantly at rest, from 8.8 ± 2.1 to 7.7 ± 2.1 ml/100 ml ($p < 0.01$) and during maximal exercise from 12.8 ± 2.4 to 12.3 ± 2.2 ml/100 ml ($p < 0.01$). Pulmonary arterial oxygen content at exhaustion was significantly higher during captopril therapy than during the control period (4.1 ± 1.1 vs 3.7 ± 1.5 ml/100 ml, $p < 0.05$), while femoral venous blood content was unchanged. Captopril therapy did not significantly increase maximal oxygen uptake or exercise duration. Thus, the acute administration of captopril to patients with severe heart failure does not increase exercise capacity despite improved cardiac performance. Moreover, captopril therapy does not acutely result in metabolic benefits to the skeletal muscles during exercise.**

ACUTE INHIBITION of the angiotensin-converting enzyme with captopril improves resting cardiac performance in patients with severe congestive heart failure.[1-7] Such improvement supports the contention that the renin-angiotensin system plays a role in the excessive level of vasoconstriction at rest in this condition.[8-10] Whether acute inhibition of the angiotensin-converting enzyme might also exert beneficial hemodynamic and metabolic effects during maximal exercise is not known. Since the release of renin is increased during exercise in patients with heart failure,[11] one might anticipate a greater hemodynamic improvement during exercise than at rest with captopril therapy. Furthermore, as demonstrated in patients with hypertension,[12] angiotensin II is more important in maintaining systemic arterial pressure during physical activity than at rest.

The present study was undertaken to investigate the hemodynamic and metabolic effects of acute angiotensin converting-enzyme inhibition with captopril during exercise in patients with severe congestive heart failure. Special attention was taken to evaluate the regional and systemic metabolic effects of captopril.

Methods

Patients

Eleven men and one woman with severe and chronic congestive heart failure were studied. The average patient age was 65.2 ± 10.1 years (range 47–81 years). Heart failure was caused by coronary artery disease in seven patients and idiopathic cardiomyopathy in five. All patients were severely limited in physical activity by dyspnea or fatigue despite optimal therapy with digoxin and diuretics, and were in New York Heart Association functional class III or IV. No patient had had angina or a myocardial infarction within 3 months of the study. Left ventricular ejection fraction determined by gated radionuclide measurements was less than 30% in all patients. All patients were in sinus rhythm, except one patient who was in atrial fibrillation. Patients were maintained on their usual doses of digoxin and diuretics, while nitrates were discontinued 2 days before the study. Mean digoxin level immediately before the study was 0.8 ± 0.4 mg/ml. During hospitalization, digoxin and diuretics were administered at night. Each patient was maintained on a 2-g sodium diet. Studies were conducted in the coronary care unit. The risks and potential benefits of the study were fully explained to the patients, who then gave informed consent.

Hemodynamics

One day before the study, right-heart catheterization was performed in all patients using a triple-lumen, flow-directed, balloon-tipped thermodilution catheter (Swan-Ganz). On the day of the study, an intraarterial indwelling catheter was inserted percutaneously into a radial artery for measurement of systemic arterial pressure (SAP) and withdrawal of blood samples. SAP and pulmonary arterial and pulmonary capillary wedge pressures (PAP and PCWP) were determined using Gould Statham P23ID transducers and recorded on an Electronics for Medicine Photographic recorder. Heart rate (HR) was recorded continuously from a bedside

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electrocardiographic monitoring device. Cardiac output was determined in triplicate by thermodilution using iced 5% dextrose, and confirmed by the Fick method using determination of oxygen consumption and pulmonary artery and radial artery oxygen contents. Resting hemodynamics were measured with patients sitting in the upright position on the bicycle ergometer. The pressure transducers were positioned at the level of the fourth intercostal space. Two sets of similar resting measurements were taken every 10 minutes. During the control period of exercise, PAP, mean SAP and HR were monitored and measurements of cardiac output repeated continuously. At the end of each work load, as well as at the end of exercise, PCWP was measured. After captopril therapy, the exercise protocol was repeated to exhaustion, and hemodynamic measurements were performed as before. Derived hemodynamic values were calculated by standard methods.

Oxygen Uptake

Measurements of mixed expired oxygen, mixed expired carbon dioxide, expired volume, expired gas temperature (C°) and barometric pressure were performed at rest while patients were sitting on the bicycle and every 30 seconds throughout exercise using a metabolic measurement cart (Beckman Instruments). Oxygen uptake was calculated using standard formulas.[13] Patients were breathing through a mouthpiece and a low-resistance, non-rebreathing, three-way valve with a nose clamp. The oxygen analyzer (OM-11 Beckman Instruments) and carbon dioxide analyzer (LB-2 Beckman Instruments) were calibrated using an analyzed mixture of approximately 4% carbon dioxide and 16% oxygen in nitrogen. This calibration was made within 1 hour of testing.

Oxygen Contents

All samples were evaluated in triplicate for oxygen content (vol/unit) using a Lex-O_2 CON-TL oxygen analyzer (Lexington Instruments) Multiple temperature and barometric pressure corrections were made throughout each study, and calibration of the Lex-O_2 CON-TL was considered optimal if three consecutive readings for dry air were within ± 0.1 ml/100 ml. During the control period of exercise, systemic arterial and pulmonary arterial oxygen contents (SAO_2 and PAO_2) were measured at rest, at the end of each work load and at exhaustion. They were also measured during exercise during captopril therapy. Arteriovenous oxygen difference (A-VO_2) was calculated as (SAO_2 − PAO_2).

In five patients, femoral venous oxygen contents (FVO_2) were also determined at rest, at the end of each work load and at exhaustion during the control period and during exercise performed during captopril therapy. One hour before exercises, retrograde catheterization of the femoral vein was performed using a #7F USCI catheter introduced percutaneously with the Seldinger technique,[14] and advanced 10 cm distally into the femoral vein. The catheter was used to withdraw blood samples, and was removed immediately after each exercise period.

Plasma Renin Activity

Blood samples were taken to measure plasma renin activity during the control period and after captopril therapy. After the patient rested in the supine position for 30–60 minutes, mixed venous blood was withdrawn from the indwelling thermodilution catheter into chilled collection tubes that contained EDTA. Specimens were immediately centrifuged and the plasma was removed and maintained at 4°C. Plasma renin activity was measured by radiommunoassay.[15]

Exercise Protocol

Exercise testing was performed with the patient upright on an electronically braked bicycle ergometer (Warren E. Collins, Inc.) with feet secured to the pedals. Two exercise tests had been performed within 72 hours of the control period of exercise to determine reproducibility and to familiarize the patient with the apparatus. Patients were tested in the postabsorptive state at least 8 hours after their dose of furosemide. The initial work load was 25 W for 3 minutes, and this load was increased every 3 minutes by 12.5 W until exhaustion. Patients pedaled at a frequency of at least 35 rpm. During captopril therapy, exercise testing was repeated using a protocol similar to that during the control period.

Captopril Administration

After baseline determinations of hemodynamics in the supine position, an initial dose of 25 mg of captopril was administered orally to all patients. Hemodynamic measurements were repeated at 30-minute intervals for 2 hours and hourly thereafter until values returned to baseline levels. Captopril was subsequently administered in ascending doses of 25, 50 and 75 mg at 8-hour intervals to obtain an increase in cardiac output of at least 20%. A reduction of SAP greater than 15 mm Hg or below 80 mm Hg or a reduction in left ventricular filling pressure to less than 12 mm Hg, was considered a contraindication to increasing the dose of captopril. After 24 hours of captopril therapy at the optimal dose, resting hemodynamic and metabolic measurements were made 2 hours after the last dose while patients were sitting upright on the bicycle. The exercise protocol was then repeated.

Statistical Analysis

The results are expressed as mean ± SD. Hemodynamic and metabolic changes were assessed using a two-factor, within-subject analysis of variance model. Each patient was assessed at rest and during maximal exercise both before and after administration of captopril, for a total of four observations. Hemodynamic and metabolic variables were analyzed as a function of the effect of exercise (rest vs maximal exercise), the effect of the drug (control vs captopril administration) and the interaction of the two factors. In the presence of exercise drug interactions, F tests for the single

TABLE 1. *Hemodynamic and Metabolic Measurements During Exercise in the Control State and During Acute Captopril Therapy*

Pt		Hgb (g/100 ml)	HR (beats/min) R	HR (beats/min) Ex	CI (l/min/m²) R	CI (l/min/m²) Ex	SAP (mm Hg) R	SAP (mm Hg) Ex	PCWP (mm Hg) R	PCWP (mm Hg) Ex	SVR (units) R	SVR (units) Ex
1	CON	16.0	100	134	1.51	2.38	82	105	28	55	29.0	25.7
	CAP		96	122	1.93	2.77	72	80	22	45	19.8	15.4
2	CON	13.0	110	132	1.24	2.70	93	125	38	55	37.2	22.9
	CAP		96	130	1.32	2.73	90	120	12	55	33.7	21.7
3	CON	12.0	115	150	1.21	2.14	110	115	32	52	58.8	34.8
	CAP		94	150	1.36	2.26	95	105	18	40	45.2	30.2
4	CON	13.5	90	110	1.18	1.22	85	115	40	54	42.3	55.3
	CAP		80	110	1.55	1.78	76	90	28	45	30.9	29.7
5	CON	13.5	58	100	1.73	3.32	113	127	12	35	39.9	23.2
	CAP		70	105	2.53	3.87	97	110	10	35	23.4	17.3
6	CON	11.5	100	130	1.40	3.50	130	150	30	45	54.9	25.2
	CAP		98	135	1.54	3.35	110	130	18	40	41.9	22.8
7	CON	12.7	110	180	1.45	3.07	80	80	30	50	29.5	15.8
	CAP		100	180	1.53	3.62	74	73	12	40	28.8	12.3
8	CON	10.5	72	131	2.06	5.29	100	140	25	52	28.6	15.6
	CAP		64	131	2.09	5.37	76	135	15	32	21.3	14.8
9	CON	11.9	92	130	2.36	3.76	62	75	15	50	16.4	12.5
	CAP		90	130	2.59	4.80	58	78	15	50	14.0	10.2
10	CON	12.5	105	150	1.35	2.84	74	80	18	45	33.5	16.2
	CAP		106	140	1.46	2.97	50	60	20	45	20.2	11.6
11	CON	15.4	80	150	1.38	3.30	85	100	20	50	35.7	18.3
	CAP		65	150	1.75	3.25	75	90	15	40	25.9	15.8
12	CON	15.7	100	154	1.61	7.18	87	125	14	36	27.2	10.1
	CAP		90	150	2.36	7.25	80	120	16	40	17.2	9.6
Mean	CON	13.2	94.3	137.6	1.54	3.39	91.8	111.4	25.2	48.3	36.1	23.0
±SD			±17.0	±21.1	±0.36	±1.54	±18.7	±24.1	±9.4	±6.8	±11.9	±12.2
Mean	CAP	1.7	87.4	136.1	1.83	3.67	79.4	99.3	16.8	42.3	26.9	17.6
±SD			±14.2	±20.2	±0.46	±1.51	±16.7	±24.2	±4.9	±6.2	±9.7	±7.1
p (CAP vs CON)			<0.05	NS	<0.01	<0.01	<0.001	<0.001	<0.01	<0.01	<0.001	<0.001

Abbreviations: Hgb = hemoglobin; HR = heart rate; SAP = mean systemic arterial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; A-VO_2 = arteriovenous oxygen difference; VO_2 = oxygen uptake; CON = control state; CAP = captopril therapy; R = rest; Ex = exercise to exhaustion.

effects of the drug during maximal exercise were performed using orthogonal contrasts.

Results

During the control period, while resting upright on the bicycle, cardiac index averaged 1.54 ± 0.36 l/min/m² and PCWP was 25.2 ± 9.4 mm Hg. Exercise was sustained for 4.9 ± 2.7 minutes, at which point the cardiac index increased to 3.39 ± 1.54 l/min/m² ($p < 0.001$) (table 1). Stroke volume index increased from 17.3 ± 6.7 to 24.8 ± 10.7 ml/m² ($p < 0.05$), while PCWP reached 48.3 ± 6.8 mm Hg ($p < 0.001$) (fig. 1). At the point of exhaustion, oxygen uptake had increased from 3.4 ± 0.5 ml/kg/min at rest to 10.8 ± 3.0 ml/kg/min ($p < 0.001$) and A-VO_2 had increased from 8.8 ± 2.1 to 12.8 ± 2.4 ml/100 ml ($p < 0.001$). Systemic and regional metabolic changes during exercise are detailed in table 2. PAO_2 at rest averaged 7.3 ± 1.3 ml/100 ml and decreased to 3.7 ± 1.5 ml/100 ml ($p < 0.001$) with exercise to exhaustion, while FVO_2, which was 5.0 ± 1.7 ml/100 ml at rest, decreased to 2.5 ± 1.2 ml/100 ml ($p < 0.001$) at exhaustion. PAO_2 was significantly greater than FVO_2 both at rest (7.3 ± 1.3 vs 5.0 ± 1.7 ml/100 ml, $p < 0.01$) and at the point of exhaustion (3.7 ± 1.5 vs 2.5 ± 1.2 ml/100 ml, $p < 0.01$).

Administration of captopril increased stroke volume index at rest from 17.3 ± 6.7 to 22.1 ± 8.1 ml/m² (p

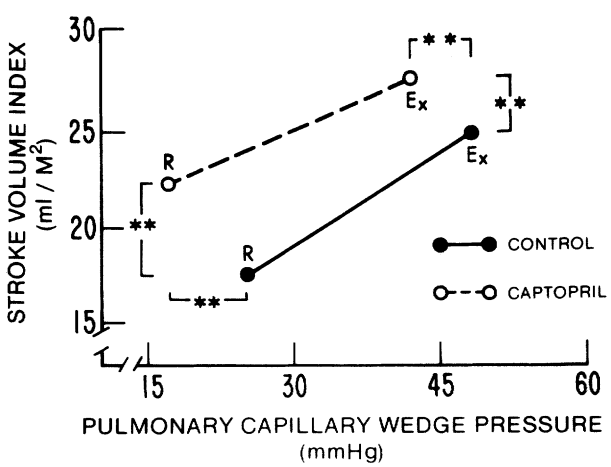

FIGURE 1. *Effects of captopril on stroke volume index and pulmonary capillary wedge pressure at rest (R) and during maximal exercise (EX).* **p < 0.01.

TABLE 1. (*Continued*)

VO_2 (ml/kg/min)		A-VO_2 (ml/100 ml)		Duration
R	Ex	R	Ex	(min)
4.3	10.5	11.0	15.8	4.6
4.0	10.2	8.0	14.1	4.0
3.5	10.0	11.6	15.0	6.0
3.7	10.1	11.5	15.2	6.0
2.8	7.3	8.4	12.4	3.0
2.7	7.4	7.2	11.9	3.0
2.8	4.8	8.5	13.8	2.5
2.9	6.1	7.2	12.3	3.0
3.1	10.4	7.0	12.1	5.0
3.3	10.6	5.1	12.0	5.0
3.4	11.4	8.6	11.4	3.5
3.6	11.0	8.4	11.6	4.0
4.2	12.9	10.4	14.6	6.0
4.0	14.0	10.5	14.0	6.0
3.4	13.4	5.3	8.0	3.0
3.4	13.8	5.2	8.0	3.5
3.0	8.5	5.4	9.5	2.5
3.1	9.6	5.1	8.5	3.0
4.0	11.8	10.4	13.8	5.0
4.0	11.9	9.3	13.1	5.0
3.5	11.8	10.0	14.9	5.3
3.6	11.8	8.6	14.3	5.5
3.2	16.3	9.4	12.3	12.5
3.2	16.4	6.5	12.5	13.0
3.4 ±0.5	10.8 ±3.0	8.8 ±2.1	12.8 ±2.4	4.9 ±2.7
3.5 ±0.4	11.1 ±2.8	7.7 ±2.1	12.3 ±2.2	5.1 ±2.7
NS	NS	<0.01	<0.01	NS

< 0.01) and reduced PCWP from 25.2 ± 9.4 to 16.8 ± 4.9 mm Hg ($p < 0.01$) (fig. 1). Captopril significantly decreased HR, from 94.3 ± 17.0 to 87.4 ± 14.2 beats/min ($p < 0.05$), and reduced mean SAP from 91.8 ± 18.7 to 79.4 ± 16.7 mm Hg ($p < 0.01$). Oxygen uptake at rest was not changed by captopril therapy while systemic A-VO_2 was reduced from 8.8 ± 2.1 to 7.7 ± 2.1 ml/100 ml ($p < 0.01$). SAO_2 was unchanged by captopril. PAO_2 was significantly increased by captopril therapy compared to the control state, while FVO_2 was unchanged, 8.4 ± 1.6 vs 7.3 ± 1.3 ml/100 ml ($p < 0.05$) and 4.9 ± 1.6 vs 5.0 ± 1.7 ml/100, respectively (fig. 2).

The dose of captopril varied in our patients from 25 to 75 mg (average 37.5 mg). Further dose increases were limited in patients 3, 6, 7 and 8 by substantial reductions in SAP and in patients 2 and 9 by reductions of PCWP to less than 12 mm Hg. In the remaining patients, a satisfactory augmentation of cardiac index of greater than 20% was produced.

During the control period, plasma renin activity averaged 20.7 mg/ml/hour (range 1.4–78.0 mg/ml/hour). After captopril therapy, plasma renin activity increased significantly, to 3.9 mg/ml/hour (range 2.0–199.0 mg/ml/hour, $p < 0.05$). Plasma renin activity during the control state did not correlate significantly with resting hemodynamics or with the changes in hemodynamics produced with captopril.

The improvement in cardiac performance produced by captopril during exercise was similar to that produced at rest. Stroke volume index at exhaustion was significantly increased and PCWP was reduced compared with the control period of exercise, 27.2 ± 10.7 vs 24.8 ± 10.7 ml/m^2 ($p < 0.01$) and 42.3 ± 6.2 vs 48.3 ± 6.8 mm Hg ($p < 0.01$), respectively (fig. 1). Mean SAP at the point of exhaustion was significantly reduced after captopril therapy, 99.3 ± 24.2 vs 111.4 ± 24.1 mm Hg ($p < 0.01$), while the maximum HR was similar, 136.1 ± 20.2 vs 137.6 ± 21.1 beats/min. Captopril therapy did not increase the duration of exercise to exhaustion or the maximum oxygen uptake compared with the control period of exercise, 5.1 ± 2.7 vs 4.9 ± 2.7 minutes and 11.1 ± 2.8 vs 10.8 ± 3.0 ml/kg/min, respectively. Indeed, the significant increase in cardiac index produced by captopril during exercise was accompanied by a reduction of systemic A-VO_2 reached at exhaustion, to 12.3 ± 2.2 from 12.8 ± 2.4 ml/1000 ml ($p < 0.01$) (fig. 3). PAO_2 at the point of exhaustion was significantly higher during captopril therapy than during the control period, 4.1 ± 1.1 vs 3.7 ± 1.5 ml/100 ml ($p < 0.05$), while FVO_2 reached at the point of exhaustion was unchanged, 2.4 ± 1.1 vs 2.5 ± 1.2 ml/100 ml (fig. 2).

Discussion

The present study demonstrates that the improvement in cardiac performance produced at rest by captopril is maintained during exercise in patients with severe congestive heart failure. The hemodynamic benefits in our patients at rest, sitting upright on a

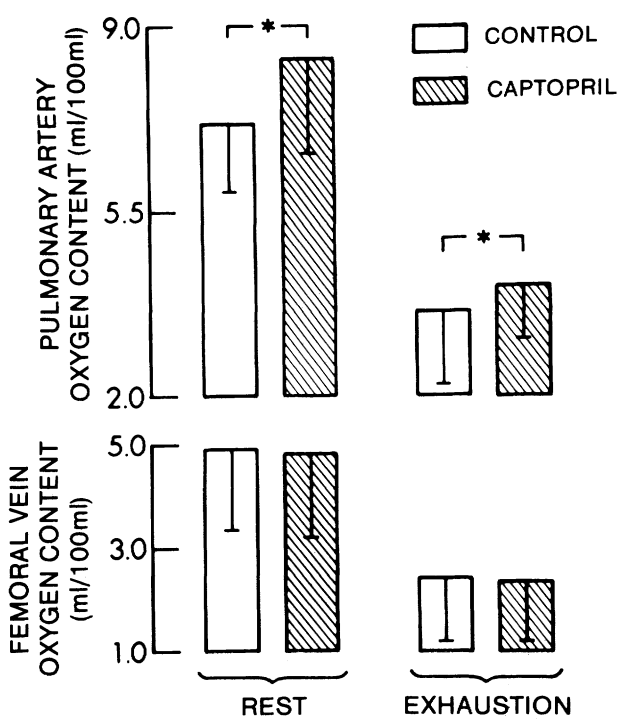

FIGURE 2. *Effects of captopril on systemic and regional venous oxygen content during maximal exercise.* *p< *0.05.*

TABLE 2. *Systemic and Regional Metabolic Effects of Captopril*

Pt		VO_2 (mg/kg)		A-VO_2 (ml/100 ml)		SAO_2 (ml/100 ml)		PAO_2 (ml/100 ml)		FVO_2 (ml/100 ml)	
		R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
8	CON	185	721	5.3	8.0	13.5	13.4	8.2	5.5	6.8	2.2
	CAP	186	732	5.2	8.0	13.4	13.4	8.3	5.5	6.5	2.1
9	CON	204	572	5.4	9.5	11.6	11.2	6.2	2.1	2.8	1.6
	CAP	211	653	5.1	8.5	11.8	11.8	6.5	3.1	2.9	1.9
10	CON	243	682	10.4	13.8	16.0	16.4	5.6	2.2	3.6	1.7
	CAP	236	676	9.3	13.1	16.1	16.3	6.7	3.1	3.3	1.4
11	CON	242	861	10.0	14.9	18.7	18.7	8.7	3.8	5.9	2.1
	CAP	263	813	8.6	14.3	18.2	18.5	10.1	4.4	5.4	2.2
12	CON	260	1519	9.4	12.3	17.0	17.0	7.6	4.7	5.8	4.7
	CAP	264	1560	6.5	12.5	17.0	16.9	10.5	4.5	6.2	4.2
Mean ±SD	CON	226.8 ±31.1	871.0 ±37.1	8.1 ±2.5	11.7 ±2.8	15.4 ±2.8	15.3 ±3.0	7.3 ±1.3	3.7 ±1.5	5.0 ±1.7	2.5 ±1.2
Mean ±SD	CAP	232.0 ±33.8	886.8 ±38.1	6.9 ±1.9	11.3 ±2.8	15.3 ±2.6	15.4 ±2.7	8.4 ±1.6	4.1 ±1.1	4.9 ±1.6	2.4 ±1.1
p (CAP vs CON)		NS	NS	<0.01	<0.05	NS	NS	<0.05	<0.05	NS	NS

Abbreviations: VO_2 = oxygen uptake; A-VO_2 = arteriovenous oxygen difference; SAO_2 = systemic arterial oxygen content; PAO_2 = pulmonary arterial oxygen content; FVO_2 = femoral venous oxygen content; R = rest; Ex = exercise to exhaustion; CON = control state; CAP = captopril therapy.

bicycle, were similar to those reported in patients resting supine.[1-7] Cardiac index was increased by an average of 20%, while left ventricular filling pressure and mean SAP were reduced by 33% and 14%, respectively. The augmentation of stroke volume and the reduction of mean systemic pressure produced by captopril during maximal exercise were of similar magnitude to the changes produced at rest. This differs from the response in hypertensive patients, in whom captopril effects a more substantial reduction of mean systemic pressure during exercise than at rest.[12] This also suggests that in patients with severe heart failure, in contrast to normal subjects,[16, 17] the renin released during exercise does not substantially contribute to arteriolar vasoconstriction. Moreover, release of renin during exercise is related to enhanced sympathetic activity,[18] which, in this condition, plays a predominant role in the vascular response to exercise.[19] However, the possibility cannot be eliminated that in our patients the angiotensin-converting enzyme was only partially inhibited and could, therefore, convert angiotensin I into angiotensin II during maximal exercise.

Although cardiac performance was improved during maximal exercise in our patients, maximal oxygen uptake and exercise duration were not increased by acute administration of captopril. Indeed, the augmentation of cardiac index produced at peak exercise by captopril was offset by a reduction of the A-VO_2 reached at exhaustion. Consequently, the maximum oxygen uptake was unchanged by captopril. Similar results have been found with acute administration of other vasodilator agents, such as hydralazine and prazosin.[20-22] A preferential distribution of the increased cardiac output toward the splanchnic and other non–metabolically active circulations, rather than to the exercising muscle, is probably responsible for the reduced systemic A-VO_2 while patients exercised during captopril therapy. Such an improvement in splanchnic blood flow during exercise has been demonstrated after infusion of nitroglycerin in a rat model of heart failure.[23]

Since maximum oxygen uptake was not increased, and patients could not exercise at higher work loads during captopril therapy, the observation that FVO_2 at exhaustion was not changed compared with control suggests that blood flow to the exercising muscle was not increased by captopril. During maximal exercise, the FVO_2 probably reflects predominantly blood flow from active skeletal muscle, with only a negligible

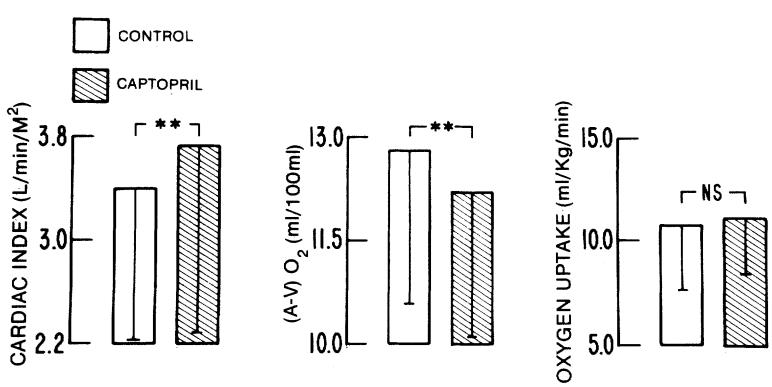

FIGURE 3. *Hemodynamic and metabolic effects of acute administration of captopril during maximal exercise. (A-V)O_2 = arteriovenous oxygen difference.* **p< *0.01.*

contribution from the skin, due to preferential cutaneous vasoconstriction in the exercising limb in severe heart failure.[24] A similar failure to improve the regional metabolic response to exercise has been demonstrated with hydralazine.[25] However, in contrast to hydralazine and prazosin, which improve blood flow to the limbs at rest,[26] captopril does not appear to augment resting limb flow. In our study, FVO_2 was low at rest and not increased by captopril therapy. One might have expected an increased FVO_2 if captopril had increased blood flow to the limb. The observation that in patients with severe heart failure, captopril therapy does not affect calf vascular resistance despite a substantial reduction in total systemic resistance is in complete agreement with our findings.[27] Furthermore, in conscious dogs, blood flow to skeletal muscle decreases after captopril.[28]

Failure to increase exercise capacity after acute captopril therapy does not preclude the development of functional improvement during chronic therapy in patients with severe heart failure.[24, 27, 29] The delayed benefit of captopril therapy on exercise capacity may be explained by a training effect of the skeletal muscles[30] induced by the improvement in cardiac performance and increased physical activity at submaximal levels of work, as well as an increased peripheral vasodilator response to exercise due to a decreased sodium content of the arteriolar wall.[31]

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