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Comparative Hemodynamic and Neurohormonal Effects of Intravenous Captopril and Digoxin and Their Combinations in Patients With Severe Heart Failure

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The effects of intravenous captopril and intravenous digoxin given separately and in combination on rest and exercise hemodynamics were studied in 16 patients with severe heart failure and sinus rhythm. When given separately, both captopril and digoxin decreased the pulmonary capillary wedge pressure by, respectively, 24% ($p = 0.003$) and 34% ($p = 0.004$) and systemic vascular resistance by 23% ($p = 0.09$) and 20% ($p = 0.03$). Only digoxin increased cardiac index by 23% ($p = 0.03$) and stroke work index by 52% ($p = 0.01$).

During maximal exercise, captopril alone decreased systemic vascular resistance by 28% ($p = 0.0002$) and increased cardiac index by 33% ($p = 0.02$). Digoxin alone decreased pulmonary capillary wedge pressure by 11% ($p = 0.04$) and increased stroke work index by 44% ($p = 0.01$). The combination of captopril and digoxin resulted in a decrease in pulmonary capillary wedge pressure and systemic vascular resistance and an increase in cardiac index and stroke work index both at rest and during exercise that was greater than values observed with either drug given alone.

Cardiac index response to the combination of captopril and digoxin correlated with baseline serum aldosterone concentration ($r = 0.81$, $p < 0.001$) and plasma renin activity ($r = 0.74$, $p < 0.0002$). A significant decrease in norepinephrine concentration was noted after digoxin was administered alone or added to captopril.

These findings demonstrate that in patients with severe heart failure, the acute administration of captopril and digoxin has an independent salutary hemodynamic effect. The combination of these agents, however, has an adjunctive effect on cardiac function at rest and during exercise.

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The role of digitalis preparations in the treatment of patients with heart failure and sinus rhythm remains controversial (1,2). Because of the increased systemic vasoconstriction occasionally seen with the use of a cardiac glycoside, its inotropic effect may not always be translated into a beneficial hemodynamic or clinical response (3–7). Angiotensin-converting enzyme inhibitors improve cardiac function by reducing both arterial and venous resistance (8,9) by attenuating the neurohormonal imbalance observed in heart failure (10). During the last decade, clinical studies (11–17) of angiotensin-converting enzyme inhibitors in patients with heart failure who were maintained on digoxin therapy demonstrated both hemodynamic and clinical benefit. A recent double-blind study (18) concluded that both captopril and digoxin, when used separately, were useful in patients with heart failure; however, only digoxin significantly increased the ejection fraction when compared with captopril, and only captopril resulted in a significant increase in exercise time and improvement in functional class when compared with results after placebo.

Because angiotensin-converting enzyme inhibitors (in particular, captopril) prevent some of the peripheral vasoconstrictive effects of digitalis preparations (19), it is possible that the combination of digoxin and captopril may be more beneficial in the treatment of heart failure than is either drug used alone. This study examines the hemodynamic and neurohormonal effects of the intravenous administration of these agents given separately and in combination to patients with severe heart failure and sinus rhythm.

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Table 1. Clinical Characteristics and Baseline Hemodynamics in 16 Patients

Patient No.	Age (yr) & Gender	Etiology of Heart Failure	NYHA Class	Prior Therapy*			RNEF (%)	CI (liters/min per m^2)	PCWP (mm Hg)
				Dig	Acei	S Vas			
Group 1 (captopril followed by digoxin)									
1	36M	DCM	III	No	No	No	9	2.4	22
2	73M	DCM	IV	Yes†	No	No	13	1.4	25
3	61M	CAD	III	Yes†	No	No	13	1.0	40
4	33M	DCM	III	No	Yes†	No	13	1.4	40
5	81M	DCM	IV	No	No	No	17	2.3	26
6	52M	CAD	III	No	Yes†	No	12	2.2	30
7	71M	CAD	III	No	No	No	12	1.6	28
8	59M	CAD	III	No	No	No	19	1.8	24
9	58M	DCM	III	No	No	No	25	1.8	28
Mean	58						15	1.8	29
±SD	10						5	0.5	7
Group 2 (digoxin followed by captopril)									
10	69M	CAD	IV	No	No	No	17	2.4	42
11	49M	CAD	III	Yes†	No	No	34	2.7	20
12	59M	CAD	III	No	No	No	21	2.0	32
13	71M	DCM	III	No	No	No	40	2.3	44
14	41M	DCM	III	No	Yes†	No	11	1.9	35
15	54M	DCM	III	No	No	Yes	25	1.6	30
16	59M	DCM	III	Yes†	No	Yes	19	1.5	40
Mean	57						23	2.1	35
±SD	5						10‡	0.4	8‡

*All patients were receiving a constant dose of diuretic drug (furosemide); †discontinued at least 7 days before study; ‡differences between Groups 1 and 2 ($p < 0.05$). Acei = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease; CI = cardiac index; DCM = dilated cardiomyopathy; Dig = digoxin; M = male; NYHA class = New York Heart Association functional class; PCWP = pulmonary capillary wedge pressure; RNEF = radionuclide ejection fraction; S Vas = systemic vasodilators.

Methods

Patient selection. Patients enrolled in this study were among those admitted to Henry Ford Hospital between July 1986 and May 1987 with a diagnosis of severe chronic heart failure due to ischemic or primary myocardial disease. All had normal sinus rhythm.

Exclusion criteria were therapy with digitalis or systemic vasodilators other than nitrates 7 days before entering the study; heart failure resulting primarily from uncontrolled hypertension or congenital, valvular, pericardial, hypertrophic or restrictive heart disease; myocardial infarction within the previous 2 months; history of atrial arrhythmias other than premature atrial complexes and significant pulmonary, renal, hepatic or hematologic disease. The protocol was approved by the Project Research and Human Rights Committee of Henry Ford Hospital. Participants were fully informed and provided written informed consent.

Study patients (Table 1). The study group consisted of 16 men with severe heart failure due to ischemic (7 patients) or dilated idiopathic (9 patients) cardiomyopathy. The mean age was 57 years (range 33 to 81). Prior medication and baseline hemodynamic characteristics are shown in Table 1. All had New York Heart Association functional class III or IV heart failure symptoms 30 to 60 days before admission and received a constant dose of diuretic drug in the hospital for several days before study.

Study Protocol

Baseline studies and measurements. To assure hemodynamic stability and prevent hemodynamic changes that may be induced by the instrumentation (20), the day before study, a balloon-tipped fiberoptic triple lumen thermodilution catheter (Swan-Ganz Oximetry, American Edwards; or Oximetrix, Abbott Laboratories) was advanced into the pulmonary artery, and a short plastic cannula (3.0F, Cook) was inserted percutaneously into the radial artery.

On the morning of the study, diuretic drugs were withheld and patients were maintained on a liquid diet. After hemodynamic stabilization (<10% variability in cardiac index or pulmonary capillary wedge pressure), supine radionuclide ejection fraction at rest, heart rate and systemic arterial, pulmonary capillary wedge and right atrial pressures were determined, as previously described (21), and recorded on a multichannel physiologic recorder (Hewlett-Packard). Cardiac output was measured in triplicate by the thermodilution

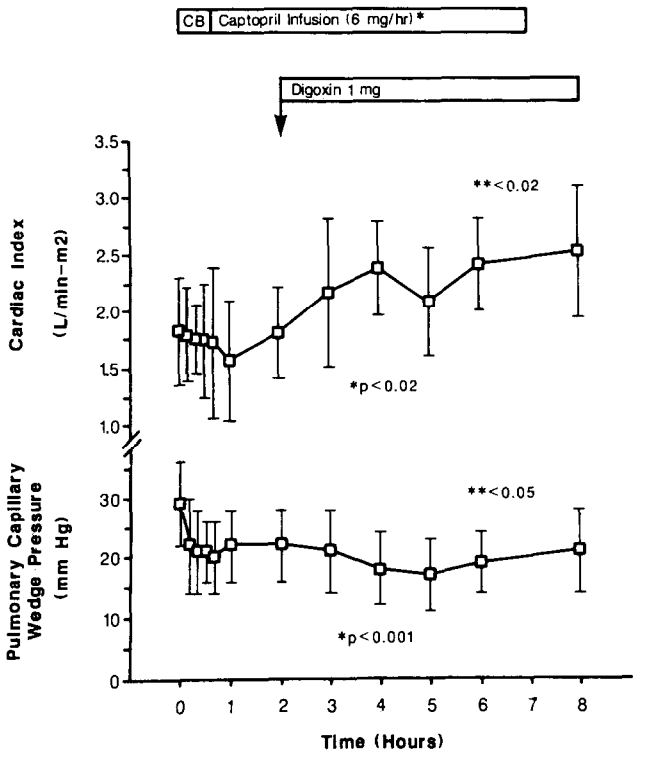


Figure 1. Serial changes in cardiac index and pulmonary capillary wedge pressure in Group 1 (nine patients; captopril preceding digoxin). *Analysis of variance for repeated measurements over time in response to the combination of captopril and digoxin; **comparison of the summary of mean hemodynamic values in each patient after the administration of captopril bolus injections (CB) and constant infusion compared with the sum of all mean values obtained after the addition of digoxin to captopril.

method (Oximeter cardiac output computer and Co Set, American Edwards). Mean arterial pressure, cardiac index, stroke work index and systemic vascular resistance were calculated using standard formulas. Blood samples were drawn, and serum digoxin, aldosterone concentration and plasma renin activity were determined by standard radioimmunoassay technique. Plasma norepinephrine measurements were available in only 12 patients, and were determined with use of high performance liquid chromatography.

Thirteen patients performed maximal exercise in a sitting position using a chair exercise bicycle (Pedalmate, Collins) with an electronic brake ergometer. The initial load of 25 W was increased by 25 W every 3 min. Heart rate, central hemodynamics and cardiac output were measured every 2 min and at maximal exercise. When heart rate and pressures had returned to baseline, patients were considered to be at time 0.

Drug intervention. *The first nine consecutive patients studied constituted Group 1.* Each patient received an initial dose of 1 mg of intravenous captopril (provided by E.R. Squibb & Sons Pharmaceutical). The dose was doubled approximately every 10 min until a total dose of 15 mg was given, unless the systolic blood pressure decreased to <80 mm Hg or the heart rate was increased to 120 beats/min. The maximal dose of 15 mg was given to eight patients, and the remaining patient (Patient 8) received only 1 mg. All but one patient (Patient 8 receiving 1 mg/h) then received a continuous and constant infusion of captopril (6 mg/h) for the next consecutive 6 h. The initial dose of 1 mg was selected because it was reported (22) to cause a marked reduction (within minutes) in angiotensin II and angiotensin-converting

Table 2. Rest Hemodynamics in Group 1*

	HR (beats/min)			AP (mm Hg)			PCWP (mm Hg)			RA (mm Hg)			CI (liters/min per m²)			SWI (g·m/m²)			SVR (dynes·s·cm⁻⁵)		
Pt	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD
1	98	92	86	98	83	90	22	20	18	4	12	8	2.4	2.0	2.5	25	19	29	1,635	1,535	1,396
2	74	58	57	73	65	60	25	18	18	7	3	0	1.4	1.8	2.0	13	20	20	2,031	1,503	1,333
3	102	89	91	87	67	65	40	25	24	15	13	11	1.0	2.5	3.0	7	16	18	3,032	939	800
4	110	95	96	78	73	90	40	32	28	14	15	15	1.4	1.6	2.8	7	9	25	1,505	1,261	932
5	84	77	84	93	90	83	26	16	10	5	8	2	2.3	2.2	2.7	23	29	31	1,892	1,731	1,518
6	94	84	74	74	69	58	30	26	24	14	10	7	2.2	2.2	2.5	13	13	12	1,069	913	912
7	86	88	85	80	77	92	28	22	25	12	14	14	1.6	1.5	1.8	14	13	19	1,935	2,016	2,066
8	89	95	84	71	83	73	24	24	17	10	8	3	1.8	1.9	2.0	13	17	17	1,581	1,609	1,410
9	62	57	84	104	65	95	28	12	14	5	4	6	1.8	1.6	2.4	32	20	32	1,980	1,294	1,230
Mean	89	82	82	84	75	78	29	22	20	10	10	7	1.8	1.9	2.4	16	17	23	1,851	1,422	1,289
±SD	15	15	11	12	9	15	7	6	5	4	4	5	0.5	0.4	0.4	9	6	9	537	360	387
p Value†		0.02	NS		0.08	NS		0.003	0.0004		NS	NS		NS	0.02		NS	0.01		0.09	0.04
p Value‡			NS			NS			NS			0.02			0.003			0.03			0.008

*Group 1 consisted of nine consecutive patients who first received captopril followed 2 h later by 1 mg of intravenous digoxin. Measurements obtained at baseline and 2 and 6 h after baseline in response to captopril alone and to the combination of captopril and digoxin. †p compared with baseline; ‡p compared with captopril. AP = mean systemic arterial pressure; B = baseline; C = captopril; CD = captopril and digoxin; HR = heart rate; Pt = patient; RA = mean right atrial pressure; SVR = systemic vascular resistance; SWI = stroke work index; other abbreviations as in Table 1.

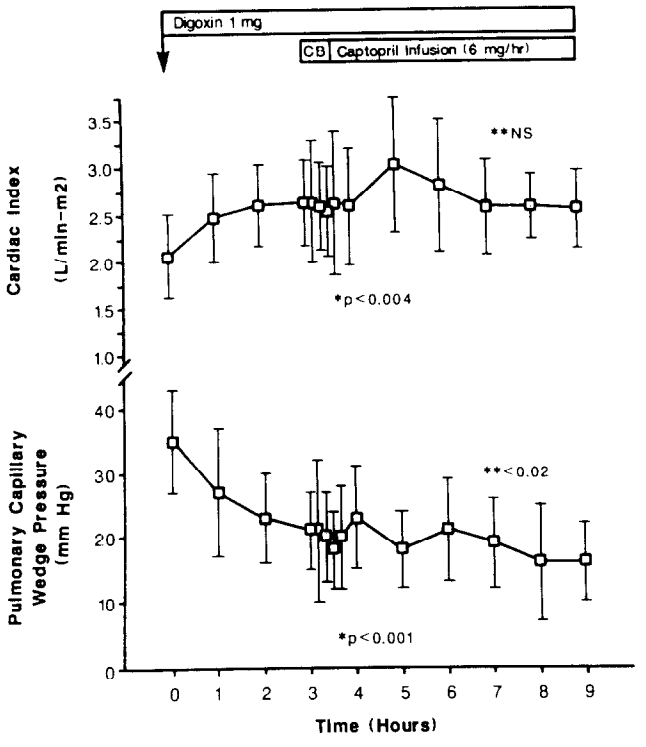


Figure 2. Serial changes in cardiac index and pulmonary capillary wedge pressure in Group 2 (seven patients; digoxin preceding captopril). *Analysis of variance for repeated measurements over time; **comparison of the summary of mean hemodynamic values in each patient after the administration of digoxin compared with the summary of all mean values obtained after the addition of captopril bolus injections (CB) and the constant infusion.

enzyme levels. Given the fact that the bioavailability of oral captopril is 62% (Squibb Institute on Medical Research, data on file), the total 15 mg of intravenous bolus injections represented the usual oral dose of 25 mg. The infusion rate was calculated to produce the same blood level of captopril as produced by the total loading dose. The assumption made in the calculation included a volume of distribution of 0.2 liter/kg for the central compartment, 2 liters/kg for the elimination phase and a total body clearance of 0.8 liter/kg per h (22).

Two hours after the start of the captopril infusion, 1 mg of intravenous digoxin was given over 30 min. Rest hemodynamic values were obtained 5 to 10 min after each bolus injection of captopril, serially thereafter for 6 h and at 8 h after the start of captopril infusion. Exercise hemodynamics were obtained at 2 h (immediately before digoxin administration) and 6 h.

Group 2 consisted of seven consecutive patients. Each patient received 1 mg of intravenous digoxin given over 30 min. Three hours later, intravenous captopril was titrated in the same manner as for the first group, and a constant infusion continued for approximately 6 consecutive h. All seven patients tolerated the total 15 mg of captopril bolus injections and then a continuous infusion of 6 mg/h. Rest hemodynamic values were obtained 5 to 10 min after each bolus injection of captopril and serially thereafter for 9 h. Exercise hemodynamic values were obtained at 2 and 6 h.

In both groups, 2 and 6 h after the first drug intervention, blood specimens were obtained for determination of norepinephrine concentration. In addition, at 6 h, digoxin and aldosterone concentrations and plasma renin activity were determined, and rest radionuclide angiography repeated.

Statistical analysis. Values are represented as mean values ±SD. Sequential changes in hemodynamic and hormonal variables were analyzed using paired *t* tests, with Bonferroni's multiple comparison adjustment. Probability (p) values <0.05 were considered indicative of a meaningful

Table 3. Rest Hemodynamics in Group 2*

	HR (beats/min)			AP (mm Hg)			PCWP (mm Hg)			RA (mm Hg)			CI (liters/min per m²)			SWI (g·m/m²)			SVR (dynes·s·cm⁻⁵)		
Pt	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC
10	95	82	80	85	86	90	42	24	26	10	10	10	2.4	2.0	2.7	15	17	30	1,117	1,163	1,101
11	96	95	96	101	90	86	20	15	12	6	4	8	2.7	3.1	3.4	31	33	33	1,310	1,047	865
12	88	82	92	80	75	72	32	23	20	12	10	6	2.0	2.9	3.0	15	25	23	1,097	833	829
13	96	103	90	115	105	112	44	28	30	14	10	8	2.3	2.6	3.4	23	26	42	1,701	1,397	1,187
14	97	87	73	82	80	80	35	12	12	6	2	4	1.9	3.0	3.4	13	32	42	1,670	1,108	962
15	91	86	86	92	110	108	30	26	15	16	10	12	1.6	2.1	2.0	15	28	30	1,865	1,882	1,930
16	106	99	105	97	88	92	40	30	32	13	8	8	1.5	2.4	1.9	11	19	15	1,931	1,159	1,385
Mean	96	91	89	93	91	91	35	23	21	11	8	8	2.1	2.6	2.8	17	26	31	1,527	1,227	1,180
±SD	6	8	10	12	13	14	8	7	8	4	3	3	0.4	0.4	0.7	7	6	10	348	334	383
p Value†		0.09	NS		NS	NS		0.004	0.0004		0.005	0.04		0.03	0.004		0.01	0.01		0.03	0.02
p Value‡			NS			NS			NS			NS			NS			NS			NS

*Group 2 consisted of seven consecutive patients who received digoxin first and captopril 3 h later. Measurements obtained at baseline and 2 and 6 h after baseline in response to digoxin alone and to the combination of digoxin and captopril. †p = compared with baseline; ‡p = compared with digoxin. D = digoxin; DC = digoxin and captopril; other abbreviations as in Tables 1 and 2.

Table 4. Exercise Hemodynamics in Group 1*

	HR (beats/min)			AP (mm Hg)			PCWP (mm Hg)			RA (mm Hg)			CI (liters/min per m^2)			SWI (g·m/m^2)			SVR (dynes·s·cm^{-5})			ET (s)		
Pt	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD	B	C	CD
1	107	120	93	133	103	90	28	28	20	4	8	6	2.2	2.4	5.8	28	19	59	2,279	1,689	622	585	600	660
2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3	153	115	104	97	91	100	38	34	34	18	12	10	1.7	2.7	3.0	9	19	27	2,039	1,290	1,333	252	360	420
4	120	121	121	97	102	107	40	38	24	14	—	10	2.2	2.5	3.0	14	18	27	1,274	—	1,069	450	562	835
5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6	117	105	105	113	88	98	46	44	42	20	14	14	2.7	4.5	3.1	21	25	23	1,466	688	1,111	191	236	190
7	125	132	118	118	107	115	48	38	38	—	22	24	1.4	2.1	3.0	11	15	27	—	1,937	1,427	371	311	246
8	98	106	100	109	77	102	30	36	20	4	16	0	2.0	2.0	2.8	20	10	33	2,159	1,251	1,500	200	252	276
9	100	135	120	122	95	103	30	18	18	5	0	0	2.5	3.6	3.8	26	27	37	1,547	886	897	246	375	489
Mean	117	119	109	113	95	102	37	34	28	11	12	9	2.1	2.8	3.5	18	19	33	1,794	1,290	1,137	328	385	445
±SD	19	12	11	13	10	8	8	8	10	7	7	8	0.5	0.9	1.0	7	6	12	417	470	312	147	144	236
p Value†		NS	NS		0.01	NS		NS	0.001		NS	0.03		0.02	0.01		NS	0.005		0.0002	0.02		0.06	NS
p Value‡			0.03			NS			0.07			NS			NS			0.03			NS			NS

*Group 1 consisted of seven patients who received captopril first and 1 mg of intravenous digoxin 2 h later. Measurements obtained at baseline and 2 and 6 h after baseline in response to captopril alone and to the combination of captopril and digoxin. †p compared with baseline; ‡p compared with captopril. ET = exercise time; other abbreviations as in Tables 1 and 2.

change, whereas p values <0.02 were considered statistically significant. Repeated measures analysis of variance (ANOVA) was used to analyze for overall change across time (23). In addition, for each patient, the mean value for hemodynamic changes over the specified time was taken as the summary measure of response to digoxin or captopril given separately and compared with the summary measure in response to the combination of captopril and digoxin (24).

Results

Hemodynamic measurements at rest. Baseline comparison of the two groups (Table 1) showed a higher pulmonary capillary wedge pressure and left ventricular ejection fraction in Group 2 than in Group 1 ($p < 0.05$ for both). No significant differences were noted between groups in regard to age, New York Heart Association functional class, prior medication, heart rate, systemic, pulmonary and right atrial pressures, cardiac index, stroke work index and systemic vascular resistance.

The serial changes after captopril and digoxin administration in mean cardiac index and pulmonary capillary wedge pressure for all patients in Group 1 are shown in Figure 1. Captopril alone did not produce a significant change in cardiac index. The addition of digoxin to the

Table 5. Exercise Hemodynamics in Group 2*

	HR (beats/min)			AP (mm Hg)			PCWP (mm Hg)			RA (mm Hg)			CI (liters/m per m^2)			SWI (g·m/m^2)			SVR (dynes·s·cm^{-5})			ET (s)		
Pt	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC	B	D	DC
10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
11	136	129	137	131	122	123	40	32	30	8	6	4	3.3	5.3	6.0	33	52	52	1,447	842	750	279	250	251
12	119	99	120	104	97	100	42	31	32	20	18	16	3.6	3.3	4.0	26	32	30	882	909	790	351	358	338
13	108	108	100	122	138	142	48	46	38	16	10	12	3.3	3.3	3.5	31	38	50	1,243	1,491	1,415	151	207	225
14	127	129	127	105	113	108	36	34	22	6	4	1	4.8	6.3	6.3	36	52	58	878	745	719	693	780	860
15	106	99	110	110	117	138	36	36	40	28	16	22	1.1	3.2	2.6	11	36	32	3,051	1,293	1,788	147	248	320
16	120	130	130	130	133	130	57	50	40	24	16	16	2.9	3.1	3.9	24	27	37	1,266	1,307	1,049	364	417	550
Mean	119	116	121	117	120	124	43	38	34	17	12	12	3.1	4.0	4.4	27	39	43	1,461	1,098	1,085	331	377	424
±SD	11	15	14	12	15	17	8	8	7	9	6	8	1.2	1.4	1.5	9	10	12	811	304	433	201	213	242
p Value†		NS	NS		NS	NS		0.04	0.02		0.02	0.005		0.09	0.02		0.01	0.001		NS	NS		0.07	0.06
p Value‡			NS			NS			NS			NS			NS			NS			NS			NS

*Group 2 consisted of six patients who first received digoxin and captopril 3 h later. Measurements were obtained at baseline and 2 and 6 h after baseline in response to digoxin alone and to the combination of digoxin and digoxin and captopril. †p compared with baseline; ‡p compared with captopril. Abbreviations as in Tables 1 to 4.

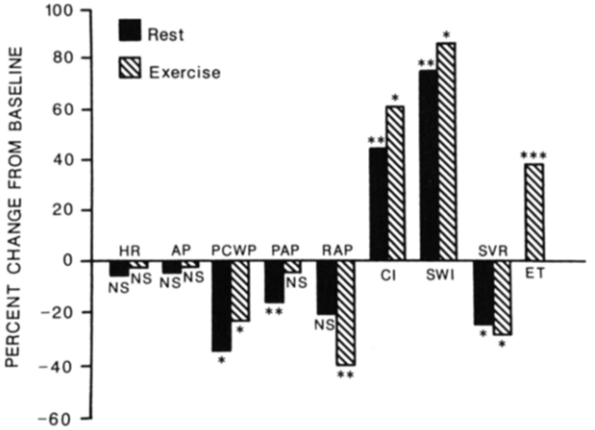


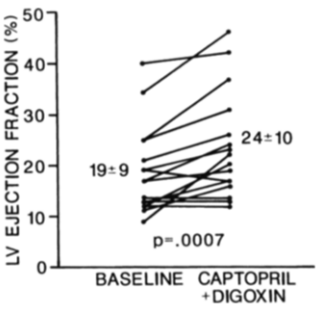
Figure 3. Percent change in mean rest hemodynamics (16 patients), exercise hemodynamics (13 patients) and exercise time in response to the combination of captopril and digoxin when compared with baseline measurements. AP = systemic arterial pressure; CI = cardiac index; ET = exercise time; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SVR = systemic vascular resistance; SWI = stroke work index. *$p < 0.001$; **$p < 0.005$; ***$p < 0.01$.

constant infusion of captopril was associated with a significant increase in cardiac index that persisted at 6 h.

Pulmonary capillary wedge pressure decreased with the initial bolus injection of 1 mg of captopril. No further significant changes were noted in response to additional bolus injections or with the constant infusion of captopril. The addition of digoxin caused a further decrease in pulmonary capillary wedge pressure.

The hemodynamic changes from baseline at 2 and 6 h in response to captopril alone and in combination with digoxin are shown in Table 2. Captopril alone resulted in a decrease in pulmonary capillary wedge pressure and systemic vascular resistance of 24% ($p = 0.003$) and 23% ($p = 0.09$), respectively. No significant changes were noted in cardiac index or stroke work index. The addition of digoxin to captopril resulted in a 26% increase in cardiac index ($p = 0.003$) and a 35% increase in stroke work index ($p = 0.03$), accompanied by a 9% decrease in systemic vascular resistance ($p = 0.008$).

Figure 4. Left ventricular (LV) ejection fraction in 16 patients before and 6 h after the administration of captopril and digoxin combination.



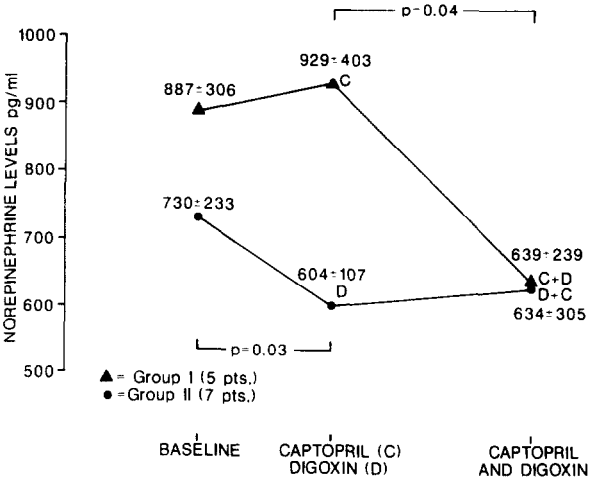


Figure 5. Plasma norepinephrine concentration changes in 12 patients in response to captopril (C), digoxin (D) and their combination.

The response to the administration of digoxin followed by captopril in Group 2 is shown in Figure 2. Digoxin alone resulted in both a significant increase in cardiac index and a decrease in pulmonary capillary wedge pressure. The addition of captopril resulted in a further decrease in pulmonary capillary wedge pressure without a significant increase in cardiac index.

The hemodynamic changes from baseline at 2 and 6 h in response to digoxin and the combination of digoxin and captopril are shown in Table 3. The administration of digoxin alone resulted in a decrease in pulmonary capillary wedge pressure and systemic vascular resistance of 34% ($p = 0.004$) and 20% ($p = 0.03$), respectively. Cardiac index increased by 23% ($p = 0.03$) and stroke work index by 52% ($p = 0.01$). The addition of captopril to digoxin caused a further increase in cardiac index and stroke work index and a decrease in pulmonary capillary wedge pressure and systemic vascular resistance, none of which reached statistical significance.

Hemodynamic measurements at maximal exercise. The administration of captopril alone (Table 4) resulted in a 33% increase in cardiac index ($p = 0.02$), a 28% decrease in systemic vascular resistance ($p = 0.0002$) and a 15% increase in systemic arterial pressure ($p = 0.01$) compared with baseline maximal exercise values. The addition of digoxin resulted in a further 25% increase in exercise cardiac index (p = NS) and 75% increase in stroke work index ($p = 0.03$). A significant decrease ($p = 0.001$) in pulmonary capillary wedge pressure compared with baseline was observed only with the combination of digoxin and captopril.

At maximal exercise (Table 5), digoxin alone resulted in

an increase in stroke work index of 44% ($p = 0.01$), a trend toward an increase in cardiac index of 24% ($p = 0.09$) and a decrease in pulmonary capillary wedge pressure of 11% ($p = 0.04$). Although cardiac index increased with both captopril and digoxin, only with captopril did it reach statistical significance. This finding may have been related to a higher cardiac index observed at baseline in the patients in Group 2. The addition of captopril to digoxin resulted in a further increase in stroke work index and a decrease in pulmonary capillary wedge pressure, neither change reached statistical significance.

Hemodynamic response to the combination of digoxin and captopril. The combination of digoxin and captopril (Fig. 3) had a greater hemodynamic effect compared with the effect of each drug given separately. At rest, pulmonary capillary wedge pressure decreased by 35% ($p = 0.0001$), pulmonary artery pressure by 17% ($p = 0.004$) and systemic vascular resistance by 24% ($p = 0.0002$). Cardiac index increased by 43% ($p = 0.003$) and stroke work index by 75% ($p = 0.002$). During exercise, pulmonary capillary wedge pressure decreased by 24% ($p = 0.0001$), right atrial pressure by 40% ($p = 0.006$) and systemic vascular resistance by 29% ($p = 0.0009$). Cardiac index increased by 61% ($p = 0.0008$) and stroke work index by 87% ($p = 0.0004$). The rest radionuclide ejection fraction (Fig. 4) increased from 19 ± 9% to 24 ± 10% ($p = 0.0007$).

Although an increase in maximal exercise time was noted in response to digoxin and captopril alone, this increase reached statistical significance only with the combination of digoxin and captopril (Fig. 3; Tables 3 and 4).

Neurohormonal changes. At baseline, there was no significant difference between groups 1 and 2 in the increase of plasma norepinephrine concentration. The norepinephrine concentration did not change significantly in response to captopril; however, a significant decrease was observed after the administration of digoxin alone and when added to captopril (Fig. 5). The decline in norepinephrine concentration correlated with the increase in stroke work index ($r = 0.90$; $p = 0.02$) and cardiac index ($r = 0.70$; $p = 0.09$).

In response to the combination of digoxin and captopril, the aldosterone concentration decreased from a mean of 22.2 ± 32.5 to 5.9 ± 3.2 pg/ml ($p = 0.002$). Plasma renin activity increased from 6.2 ± 8 to 10.5 ± 13 ng/ml per h ($p = 0.004$). The degree of increase in cardiac index in response to the combination of captopril and digoxin correlated with baseline levels of aldosterone ($r = 0.81$, $p < 0.001$) and plasma renin activity ($r = 0.74$, $p < 0.0002$).

Digoxin concentrations. The serum digoxin concentration was below the limits of the assay in all patients during the control period. Six hours after the administration of 1 mg of digoxin, the serum digoxin concentration averaged 1.7 ng/ml (range 1 to 3).

Discussion

In this study of patients with severe heart failure in sinus rhythm, the short-term administration of captopril and digoxin given separately resulted in a significant and different hemodynamic improvement. Both drugs decreased pulmonary capillary wedge pressure; only digoxin increased cardiac and stroke work index. The combination of digoxin and captopril, however, produced an improvement in hemodynamic variables, both at rest and during maximal exercise, that was greater than that observed with either drug given alone. A significant decrease in plasma norepinephrine concentration was associated only with digoxin administration.

Acute hemodynamic effects of intravenous digitalis preparations. This study is in general agreement with those of others (21,25–29) who found an increase in cardiac index and stroke work index associated with a decrease in pulmonary capillary wedge pressure when digitalis preparations were administered intravenously in patients with severe heart failure in sinus rhythm. However, when digitalis preparations were administered to patients with heart failure whose hemodynamic status was normalized with diuretic drugs and vasodilators (21) or to normal subjects (3–5), no significant changes in hemodynamic variables were observed.

It has been suggested that in patients with a lesser degree of heart failure (21), intravenous digoxin could increase systemic vascular resistance, thereby preventing an increase or even causing a decrease (7) in cardiac output. In contrast, in our patients with stable but very abnormal hemodynamics, the administration of digoxin was associated with a reduction in systemic vascular resistance. Similarly, Mason et al. (30) observed a decrease in peripheral resistance in patients with severe heart failure in response to ouabain.

Acute hemodynamic responses to captopril. Rademaker et al. (31) studied the effects of the addition of incremental doses of intravenous captopril in patients with chronic heart failure already receiving digoxin. Like others (14–17), they observed a reduction in systemic vascular resistance and pulmonary capillary wedge pressure associated with an increase in cardiac output. The maximal hemodynamic effect was obtained when a cumulative dose of 5 mg of intravenous captopril was reached. In our study, intravenous captopril alone, although decreasing pulmonary capillary wedge pressure and systemic vascular resistance, did not increase cardiac index. Because angiotensin enzyme inhibitors are not known to have a positive inotropic effect (32), it is possible that in some patients with heart failure already receiving digoxin, the addition of captopril may augment the inotropic effect of the glycoside by attenuating some of its peripheral vasoconstrictive effects (19).

Comparison of digoxin and captopril. There are no previously reported studies comparing the short-term hemodynamic effects of captopril and digoxin when administered separately. Although both digoxin or captopril decreased

pulmonary capillary wedge pressure at rest, only digoxin was associated with a significant increase in cardiac index.

The combination of captopril and digoxin had a marked and, in some respects, additive effect in improving cardiac function both at rest and during exercise. This suggests that these agents achieve hemodynamic improvement by separate mechanisms: captopril by decreasing vascular resistance and digoxin by enhancing contractility. It is possible that in some patients, the salutary effects of digoxin can be potentiated by captopril, which blocks the activation of angiotensin II observed with digitalis preparations (19). That the effects were not always additive suggests that when hemodynamic variables or neurohormonal abnormalities are attenuated by a drug, one is less likely to observe significant changes in response to the addition of a second drug.

Only two studies have compared the long-term effects of captopril and digoxin. Alicandri et al. (33), using isometric exercise, examined the effects of captopril and digoxin in patients with chronic heart failure and concluded that both drugs are beneficial. Similarly, in a multicenter trial (18) comparing the effects of captopril and digoxin in patients with moderate heart failure, digoxin alone caused an increase in ejection fraction, compared with that obtained with captopril and placebo, without significantly increasing exercise time or improving functional class. Captopril increased exercise tolerance, in comparison with results after placebo, without affecting ejection fraction.

Neurohormonal changes. Published reports (34–37) on the effects of angiotensin-converting enzyme inhibitors on circulating catecholamines are not consistent. In our short-term study, no significant change in plasma norepinephrine was noted after the administration of captopril. In agreement with the observations of Ribner et al. (29), we observed a reduction in norepinephrine concentrations after intravenous digoxin alone and when added to captopril that correlated with the increase in cardiac output. It is possible that these changes in norepinephrine concentration reflect acute modifications of cardiac function that are different from those observed during prolonged therapy. This is in keeping with the observations (12) that indicate that physiologic improvement in exercise performance occurs over a 12 week period.

The degree of increase in cardiac index with the combination of digoxin and captopril was correlated with aldosterone levels and plasma renin activity at baseline study. These observations support the concept that the response of patients with heart failure to various medical interventions may be related to the degree of neurohormonal abnormalities (38), and may provide a more rational approach to the selection of therapy.

Limitations of the study. This study was neither randomized nor blinded and patients served as their own control. It is possible that some of the changes in hemodynamic variables were due to spontaneous variation (20,39). However, to minimize these variations, patients underwent instrumentation 1 day before study, vasoactive substances were withheld and each patient was placed on a clear liquid diet.

It is not known if the short-term additive salutary effects, including the increase in exercise time, observed with the combination of digoxin and captopril are sustained. Packer et al. (40) reported that the effect of the first dose of captopril is usually sustained, but in some patients this effect may initially be attenuated or delayed. This triphasic response suggests that a complex relation may exist between the early and late hemodynamic effects of vasoactive drugs in patients with heart failure.

Clinical implications. In this group of patients with severe heart failure, the short-term administration of digoxin and captopril independently caused salutary hemodynamic effects. The combination of captopril and digoxin had an adjunctive effect in improving cardiac function at rest and during exercise. Further clinical studies appear warranted to determine whether these short-term effects are sustained.

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