

# Antagonism of the acute hemodynamic effects of captopril in decompensated congestive heart failure by aspirin administration

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## Abstract

The concomitant use of angiotensin-converting enzyme inhibitors and aspirin may cause pharmacological antagonism. Hence we examined the effect of aspirin on the neurohormonal function and hemodynamic response to captopril in heart failure patients. Between April 1999 and August 2000, 40 patients were randomized into four equal groups: 1) captopril, 2) aspirin, 3) captopril-aspirin: captopril was given alone on the first day, followed by aspirin on the remaining days, and 4) aspirin-captopril: aspirin was given alone on the first day, followed by captopril on the remaining days. Hemodynamic, norepinephrine and prostaglandin measurements were performed pre- and post-medication for 4 days. Captopril (50 mg) was given orally every 8 h and 300 mg aspirin was given on the first day, and 100 mg/day thereafter. In the captopril group and only on the first day of captopril-aspirin, captopril produced increases in cardiac index ( $2.1 \pm 0.6$  to  $2.5 \pm 0.5$  l min<sup>-1</sup> m<sup>-2</sup>,  $P < 0.0001$ ), and reduced peripheral vascular resistance ( $1980 \pm 580$  to  $1545 \pm 506$  dyn s<sup>-1</sup> cm<sup>-5</sup>/m<sup>2</sup>,  $P < 0.0001$ ) and pulmonary wedge pressure ( $20 \pm 4$  to  $15 \pm 4$  mmHg,  $P < 0.0001$ ). In contrast, aspirin alone or associated with captopril showed no significant hemodynamic changes. Norepinephrine decreased ( $P < 0.02$ ) only in the captopril group. Prostaglandin levels did not differ significantly among groups. Thus, aspirin compromises the short-term hemodynamic and neurohormonal effects of captopril in patients with acute decompensated heart failure.

## Key words

- Pharmacological antagonism
- Aspirin
- Angiotensin-converting enzyme inhibitors
- Decompensated heart failure
- Hemodynamics and neurohormonal changes

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## Introduction

Angiotensin-converting enzyme (ACE) inhibitors are used extensively for the treatment of congestive heart failure. Several studies have documented their ability to reduce global and cardiovascular mortality,

reinfarction, and needs for rehospitalization following acute myocardial infarction (1,2). Aspirin (ASA) on the other hand, is also routinely used for the prevention of thrombotic events in patients with coronary artery disease (3). Thus, simultaneous therapy with both drugs is frequently recommended for

patients with ventricular dysfunction and coronary artery disease.

More recently, concern has been raised with respect to a potential antagonism between these two drugs (4). For instance, in the Consensus II study which included 6090 post-acute myocardial infarction patients, Nguyen et al. (5) found, in a retrospective analysis, that the effect of enalapril was less favorable among patients taking ASA at baseline than in those not taking it. On the other hand, Hall et al. (6) also reported that a single dose of ASA (325 mg) blunted the acute hemodynamic effect of enalaprilat in patients with severe heart failure.

The exact mechanism involved in this interaction is not completely understood. The vasodilatory effects of ACE inhibitors are attributed to inhibition of angiotensin II synthesis as well potentiation of bradykinin (BK)-induced vasodilation (7). Prostaglandin (PG) production is also stimulated by BK, and hence may contribute to vasodilation. ASA, on the other hand, being a cyclooxygenase inhibitor (8), could reduce, PG production at least in part and therefore diminish or eliminate its vasodilatory effect (9).

The issue is of considerable clinical importance, given the large number of patients with acute myocardial infarction and heart failure of ischemic origin who are potential candidates for both therapies (10). We determined whether or not a low ASA dose would interfere with the hemodynamic and neurohormonal effects of captopril in decompensated heart failure.

## Material and Methods

### Study patients

Forty consecutive patients with decompensated chronic congestive heart failure, functional classes III/IV (New York Heart Association), were studied over a period of six days in the Cardiovascular Intensive Care Unit. Patients with right-sided, acute, dia-

stolic, high-output, congenital and valvular heart failure were excluded. Patients with specific conditions that produce or exacerbate heart failure, such as infections, severe arrhythmias, pulmonary emboli, or significant pulmonary, renal, hepatic, hematological diseases and exposure to ASA or other nonsteroidal anti-inflammatory drugs for  $\leq 15$  days were also excluded. Informed consent was obtained from all subjects. The study was approved by the Scientific Committee of the Heart Institute (InCor), São Paulo, SP, Brazil.

### Hemodynamic measurements

A Swan-Ganz catheter was inserted through the subclavian vein for cardiac output measurement. Heart rate and mean arterial pressure were recorded by automatic non-invasive pressure monitoring with the Hewlett-Packard OmniCare Component Monitoring System; right atrial pressure and pulmonary and capillary wedge pressure were recorded through the Swan-Ganz catheter. Cardiac output (CO) was determined in triplicate by the thermodilution technique. The following parameters were derived according to the formulas indicated: cardiac index ( $l \text{ min}^{-1} \text{ m}^{-2}$ ) = CO/body surface area; systemic vascular resistance ( $\text{dyn s}^{-1} \text{ cm}^{-5}/\text{m}^2$ ) = mean arterial pressure  $\times 80/\text{CO}$ , and pulmonary vascular resistance ( $\text{dyn s}^{-1} \text{ cm}^{-5}$ ) = mean pulmonary capillary wedge pressure  $\times 80/\text{CO}$ .

### Neurohormonal analysis

All blood samples were collected from the Swan-Ganz catheter, except on the first day when the antecubital vein was used, and were taken with the patients at rest. For measurements of prostaglandin  $E_2$  ( $\text{PGE}_2$ ) and prostacyclin  $I_2$  ( $\text{PGI}_2$ ) (measured as 6-keto-prostaglandin  $F_{1\alpha}$  [6-keto- $\text{PGF}_{1\alpha}$ ], the stable breakdown product of  $\text{PGI}_2$ ) in plasma, 5 ml of blood was drawn into frozen tubes

with a mixture of EDTA and indomethacin, in the early morning at rest and every 8 h thereafter. Blood samples were centrifuged immediately at 2000 g for 15 min at 4°C and the supernatants were removed, frozen, and stored at -80°C until the time for assay. PGE<sub>2</sub> and PGI<sub>2</sub> were measured by the PGE<sub>2</sub> [<sup>125</sup>I]-RIA kit and 6-keto-PGF<sub>1α</sub> [<sup>125</sup>I]-RIA kit (NEN™, Life Science Products, Boston, MA, USA). Norepinephrine (NE) was sampled once a day, in the early morning at rest, in ice with EGTA as anticoagulant and glutathione solutions, and the samples were immediately centrifuged at 2000 g for 20 min at 4°C. The supernatants were removed, frozen, and stored at -20°C until assay by an electrochemical detection method after purification by HPLC.

### Study protocol

The study was carried out in two phases: the compensation phase, when patients were stabilized clinically, and the study phase, when hemodynamic measurements and neurohormonal analyses were performed over a period of 4 days. In the compensation phase, all patients received a standardized diet with fluid and salt restriction and fixed intravenous doses of lanatoside C, furosemide and nitroprusside for about 48 h without any ACE inhibitors until clinical stabilization or until they felt comfortable in the recumbent position. During the study, no vasoactive or anti-inflammatory drugs were given. Complete blood cell count and plasma glucose, creatinine, urea, sodium and potassium were measured on alternate days, by standard techniques. A Swan-Ganz catheter was inserted in the evening of the last day of the compensation phase. Sodium nitroprusside was interrupted 2 h before the study phase. Additional medications such as furosemide, 40 mg *iv* twice a day and digoxin, 0.25 mg a day, were given orally.

In the morning of the third day of hospitalization, at 7:00 h, patients were random-

ized into four groups of ten patients receiving the following medications: 1) captopril group: captopril was given orally at a daily dose of 50 mg three times a day for 4 days; 2) ASA group: ASA was given orally at a dose of 300 mg a day on the first day, and 100 mg on the subsequent three days; 3) captopril plus ASA group (Cap-ASA): captopril was given orally at a daily dose of 50 mg twice a day for 4 days in combination with 300 mg ASA on the second day, and 100 mg a day on the last 2 days; 4) ASA plus captopril group (ASA-Cap): ASA was given orally at a dose of 300 mg a day on the first day, and 100 mg on the subsequent 3 days, in combination with captopril at a daily dose of 50 mg twice a day on the last two days. Captopril and ASA were administered orally during fasting, and together in the ASA-Cap or Cap-ASA groups. Hemodynamic measurements were performed at baseline and 1 h after captopril or ASA.

### Statistical analysis

The groups were compared in terms of clinical, laboratory, echocardiographic, hemodynamic and neurohormonal variables. The chi-square test for categorical variables and the Student *t*-test for continuous variables were used. Differences between serial measurements were assessed by repeated-measures ANOVA and the Newman-Keuls multiple comparison test. Values are reported as mean ± SD and P<0.05 was considered to be statistically significant.

## Results

### Patient characteristics

The study was conducted on 24 men and 16 women with a mean age of 62 ± 13 years. All patients had been symptomatic for at least 1 year. Heart failure was due to hypertensive heart disease in most of them. Sinus rhythm was present in 34 patients (85%) and

chronic atrial fibrillation in 6 (15%). Enlarged cardiac silhouette, prominent pulmonary vasculature in the upper lung zones, alveolar edema and pleural effusions were the most common signs in the chest radiograph. The echocardiographic mean left ventricular ejection fraction was  $40 \pm 4.5\%$ . Patients were comparable in the four groups. Additional demographic characteristics, labo-

ratory and echocardiographic findings are shown in Tables 1 and 2.

### Clinical response

All patients were compensated within 48 h by the intravenous drug regimen. The daily dose of 150 mg captopril was well tolerated by most of them. Systolic arterial pressure lower

Table 1. Demographic characteristics of patients with stabilized heart failure.

	Captopril	Aspirin	Cap-ASA	ASA-Cap
Age (mean $\pm$ SD)	66 $\pm$ 12	60 $\pm$ 13	66 $\pm$ 10	63 $\pm$ 13
Sex, men	6	5	5	6
Clinical history				
Hypertension	9	9	7	9
CAD	3	1	3	3
Current smoker	1	2	2	3
Diabetes mellitus	2	2	4	3
Etiology				
Hypertensive disease	7	7	5	7
Ischemic heart disease	3	1	3	3
Dilated cardiomyopathy	1	3	2	1
NYHA functional class				
Class III	2	3	4	4
Class IV	8	7	6	6
Previous medication				
Diuretics	8	7	9	9
ACE inhibitors	9	7	8	8
Digoxin	9	8	9	9

CAD: coronary artery disease; NYHA: New York Heart Association; Cap-ASA: captopril plus aspirin group; ASA-Cap: aspirin plus captopril group; ACE: angiotensin-converting enzyme. There were no statistical differences among groups (N = 10 in each one) for any of the characteristics (repeated-measures ANOVA).

Table 2. Laboratory and echocardiographic findings.

	Captopril	Cap-ASA	Aspirin	ASA-Cap
Laboratory				
Creatinine (mg/dl)	1.4 $\pm$ 0.4	1.4 $\pm$ 0.8	1.6 $\pm$ 0.9	1.6 $\pm$ 0.6
Urea (mg/dl)	61.0 $\pm$ 31.0	56.0 $\pm$ 41.0	66.0 $\pm$ 30.0	67.0 $\pm$ 26.0
Norepinephrine (ng/dl)	1463.0 $\pm$ 1200.0	1075.0 $\pm$ 651.0	1220.0 $\pm$ 817.0	820.0 $\pm$ 401.0
Echocardiographic				
Ejection fraction (%)	36.0 $\pm$ 3.0	43.0 $\pm$ 4.0	42.0 $\pm$ 5.0	37.0 $\pm$ 3.0

Data are reported as mean  $\pm$  SD for 10 patients per group. Cap-ASA: captopril plus aspirin group; ASA-Cap: aspirin plus captopril group. Norepinephrine levels were obtained at baseline on the first day of the compensation phase. There were no statistically significant differences among groups for any of the parameters reported in the table (repeated-measures ANOVA).

Table 3. Hemodynamic parameters.

	1st day		2nd day		3rd day		4th day	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
HR (bpm)								
Captopril	83 ± 13	82 ± 12	80 ± 14	81 ± 14	81 ± 13	83 ± 13	79 ± 13	79 ± 12
ASA	85 ± 11	85 ± 10	84 ± 13	87 ± 10	82 ± 11	84 ± 12	82 ± 12	85 ± 15
Cap-ASA	96 ± 22	91 ± 19	91 ± 14	91 ± 12	89 ± 8	88 ± 9	89 ± 10	90 ± 11
ASA-Cap	86 ± 13	87 ± 14	86 ± 14	86 ± 14	89 ± 17	84 ± 15	89 ± 15	85 ± 14
MAP (mmHg)								
Captopril	93 ± 20	89 ± 23	91 ± 21	89 ± 20	91 ± 20	85 ± 15	83 ± 19	85 ± 23
ASA	92 ± 17	93 ± 19	88 ± 14	95 ± 13	92 ± 13	89 ± 15	94 ± 10	90 ± 21
Cap-ASA	90 ± 14	89 ± 13	90 ± 12	87 ± 12	90 ± 13	86 ± 11	92 ± 11	84 ± 13
ASA-Cap	106 ± 15	106 ± 16	105 ± 21	103 ± 19	103 ± 17	96 ± 21	101 ± 20	102 ± 18
CI (l min <sup>-1</sup> m <sup>-2</sup> )								
Captopril#	2.1 ± 0.5	2.5 ± 0.6**	2.0 ± 0.6	2.5 ± 0.7**	1.8 ± 0.5	2.3 ± 0.6**	2.0 ± 0.7	2.3 ± 0.7**
ASA	2.0 ± 0.5	1.9 ± 0.5	2.0 ± 0.5	2.0 ± 0.5	1.9 ± 0.5	1.8 ± 0.4	2.2 ± 0.4	2.1 ± 0.4
Cap-ASA	1.7 ± 0.6	2.2 ± 0.7**	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.5	2.0 ± 0.6	2.0 ± 0.5	2.0 ± 0.5
ASA-Cap	1.8 ± 0.5	1.9 ± 0.6	2.0 ± 0.3	1.8 ± 0.3	2.0 ± 0.2	2.0 ± 0.3	1.9 ± 0.3	2.0 ± 0.5
SVR (dyn s <sup>-1</sup> cm <sup>5</sup> /m <sup>2</sup> )								
Captopril+	1980 ± 580	1545 ± 506**	2157 ± 895	1684 ± 582**	2285 ± 791	1668 ± 574**	1839 ± 501	1686 ± 572**
ASA	2071 ± 558	2231 ± 517	2096 ± 599	2321 ± 607	2279 ± 563	2260 ± 446	1994 ± 453	2101 ± 564
Cap-ASA	2369 ± 830	1846 ± 542**	2267 ± 558	2226 ± 595	2320 ± 825	2040 ± 701	2110 ± 680	1880 ± 590
ASA-Cap	2486 ± 892	2485 ± 1126	2130 ± 612	2278 ± 575	2062 ± 536	1952 ± 656	2149 ± 573	2202 ± 637
MPAP (mmHg)								
Captopril	34 ± 6	34 ± 7	31 ± 6	28 ± 8	28 ± 9	28 ± 8	28 ± 7	27 ± 7
ASA	38 ± 7	36 ± 8	36 ± 8	35 ± 9	35 ± 10	33 ± 8	34 ± 7	35 ± 8
Cap-ASA	41 ± 11	38 ± 10	37 ± 6	36 ± 7	37 ± 9	37 ± 7	38 ± 4	38 ± 7
ASA-Cap	45 ± 13	44 ± 13	44 ± 14	43 ± 14	44 ± 14	40 ± 14	43 ± 13	41 ± 13
MRAP (mmHg)								
Captopril	9 ± 6	8 ± 4	7 ± 5	7 ± 5	7 ± 4	7 ± 5	7 ± 4	7 ± 4
ASA	8 ± 3	7 ± 4	6 ± 4	5 ± 3	6 ± 4	6 ± 5	6 ± 4	6 ± 4
Cap-ASA	11 ± 6	9 ± 5	9 ± 4	9 ± 4	10 ± 6	10 ± 5	10 ± 4	10 ± 4
ASA-Cap	10 ± 5	10 ± 5	10 ± 7	10 ± 7	9 ± 6	9 ± 7	9 ± 7	9 ± 7
PCWP (mmHg)								
Captopril*	20 ± 5	15 ± 5**	19 ± 6	15 ± 6**	20 ± 8	16 ± 6**	19 ± 7	15 ± 6**
ASA	21 ± 6	21 ± 6	20 ± 5	20 ± 6	20 ± 6	21 ± 5	21 ± 6	21 ± 6
Cap-ASA	19 ± 6	17 ± 5**	21 ± 6	19 ± 5	20 ± 4	19 ± 5	21 ± 4	21 ± 5
ASA-Cap	24 ± 6	24 ± 6	24 ± 6	23 ± 8	23 ± 6	20 ± 5	22 ± 7	21 ± 8

Values are reported as means ± SD for pre- and post-medication of four groups (N = 10 per group). HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; SVR, systemic vascular resistance; MPAP, mean pulmonary arterial pressure; MRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure.

\*P<0.04 vs ASA, Cap-ASA, and ASA-Cap groups. #P<0.002 vs ASA, Cap-ASA, and ASA-Cap groups. +P<0.009 vs ASA, Cap-ASA, and ASA-Cap groups. \*\*P<0.0001 vs pre-medication data.

than 100 mmHg occurred in one patient and was treated with intravenous saline. Only one patient showed a 30% increase in creatinine levels on the last day of study and was not excluded. Diuretic dosage was adjusted in 5 patients, but no other adjustments in medication were necessary. No cases of embolization, bleeding, cardiac arrhythmias or pneumothorax were observed. No patient died during the study.

### Hemodynamic effects

The average mean hemodynamic parameters of pre- and post-medication in each group are shown in Table 3. Captopril alone consistently produced significant increases in cardiac index ( $2.1 \pm 0.5$  to  $2.5 \pm 0.6$  l min<sup>-1</sup> m<sup>-2</sup>,  $P < 0.0001$ ), a response observed on all days of the study. The average increase was approximately 18% (Figure 1A). Similarly,

Figure 1. Changes in cardiac index (CI) before (open bar) and 1 h after (filled bar) administration of captopril (Cap), aspirin (ASA) or both. CI increased significantly in the captopril group (A) and on the first day of treatment in the Cap-ASA group (B) ( $P < 0.0001$ , repeated-measures ANOVA). Introduction of aspirin in the Cap-ASA group on the second day prevented further increases in CI. The CI remained unchanged in the ASA (C) and ASA-Cap groups (D).

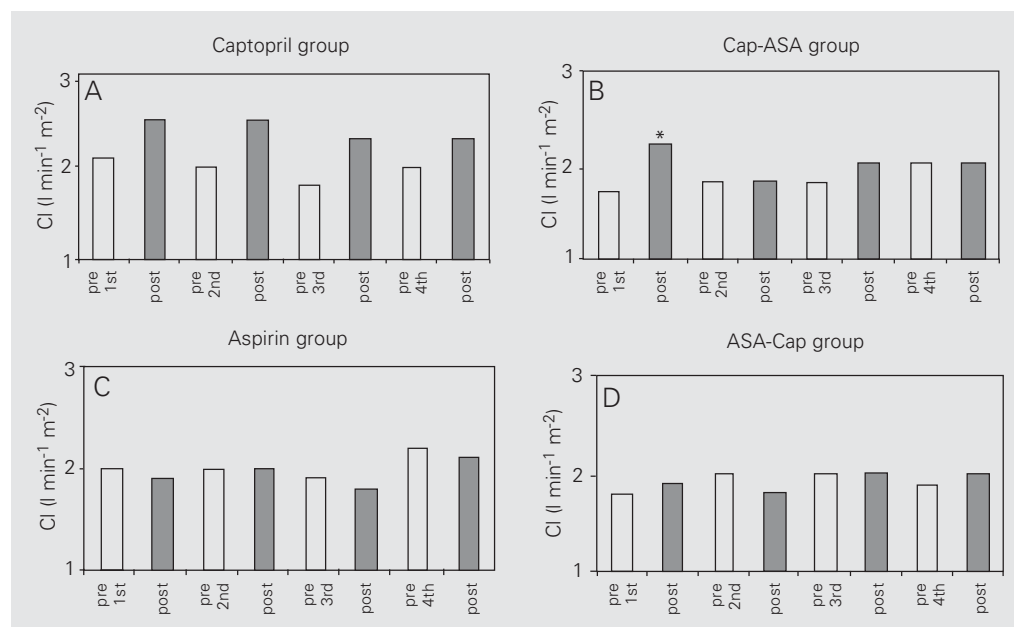
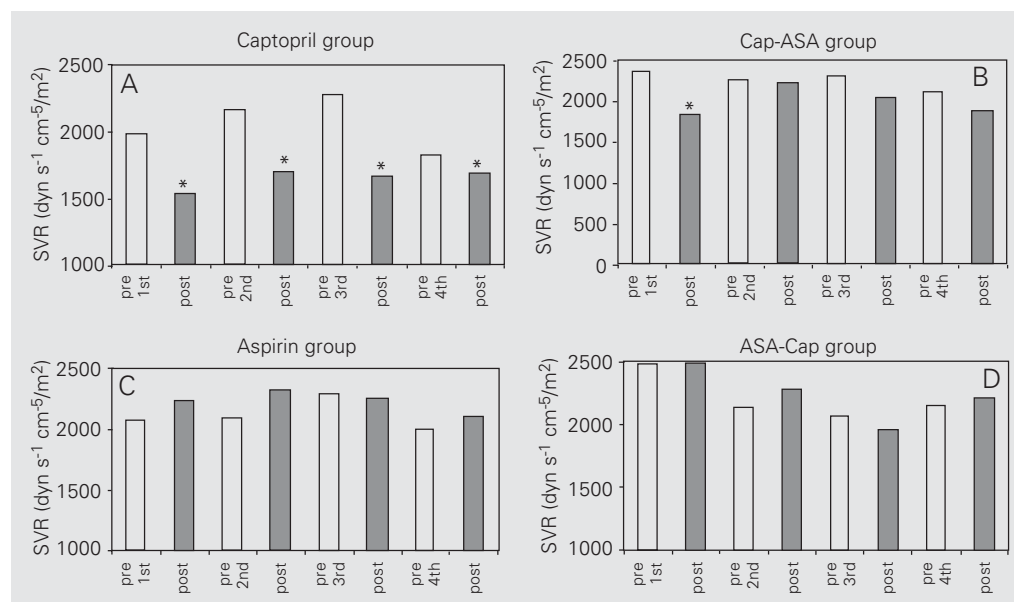


Figure 2. Changes in systemic vascular resistance (SVR) before (open bar) and 1 h after (filled bar) administration of captopril (Cap), aspirin (ASA) or both. SVR decreased significantly in the captopril group (A) and on the first day of treatment in the Cap-ASA group (B) ( $P < 0.0001$ , repeated-measures ANOVA), but increased with the introduction of aspirin on the second day in this group. SVR remained unchanged in the ASA (C) and ASA-Cap groups (D).



captopril reduced peripheral vascular resistance by 26% ( $1980 \pm 580$  to  $1545 \pm 506$  dyn  $s^{-1} cm^{-5}/m^2$ ,  $P < 0.0001$ ), and pulmonary wedge pressure by 28% ( $20 \pm 4$  to  $15 \pm 4$  mmHg,  $P < 0.0001$ ) (Figures 2A and 3A). There were no significant changes in heart rate, mean arterial, mean right atrial or mean pulmonary arterial pressure.

In contrast, ASA alone did not induce significant changes in cardiac index, peripheral vascular resistance or pulmonary wedge pressure (Figures 1C, 2C and 3C) or in heart rate, mean arterial, mean right atrial and mean pulmonary arterial pressures. On the other hand, patients who received captopril followed by ASA exhibited a dual response pattern: on the first day, the expected response to captopril was observed, namely, significant increases in cardiac index and reductions in peripheral vascular resistance and pulmonary wedge pressure, but no changes in heart rate, mean arterial, mean right atrial or mean pulmonary arterial pressure. However, when ASA was added the hemodynamic effect of captopril was completely abolished (Figures 1B, 2B and 3B).

Conversely, patients who received ASA first followed by captopril showed no initial hemodynamic alterations, just as in the pure

ASA group. Differently from the captopril group, when captopril was added, no hemodynamic responses were noted, thus indicating that previous ASA administration blocked the action of captopril (Figures 1D, 2D and 3D).

#### Neurohormonal effects

Mean NE values on the day of admission are shown in Table 2 and confirm the presence of a severe degree of cardiac decompensation when patients were hospitalized. After clinical stabilization, NE levels decreased significantly ( $P < 0.006$ ) compared to initial levels in all patients. During the study phase, patients in the captopril group showed a significant decrease in NE levels ( $533 \pm 233$  to  $408 \pm 235$  ng/dl;  $\Delta 30\%$ ;  $P < 0.02$ ); on the other hand, in the ASA, ASA-Cap and Cap-ASA groups NE levels were unchanged, although in the ASA group a trend towards an increase ( $620 \pm 250$  to  $806 \pm 595$  ng/dl;  $\Delta 23\%$ ;  $P < 0.07$ ) was noted. The percent variation of NE levels is illustrated in Figure 4.

The means of the three daily measurements of  $PGE_2$  and  $PGI_2$  (6-keto- $PGF_{1\alpha}$ ) were  $245 \pm 82$  and  $231 \pm 79$  ng/dl for the captopril group,  $270 \pm 150$  and  $265 \pm 146$  ng/dl for the

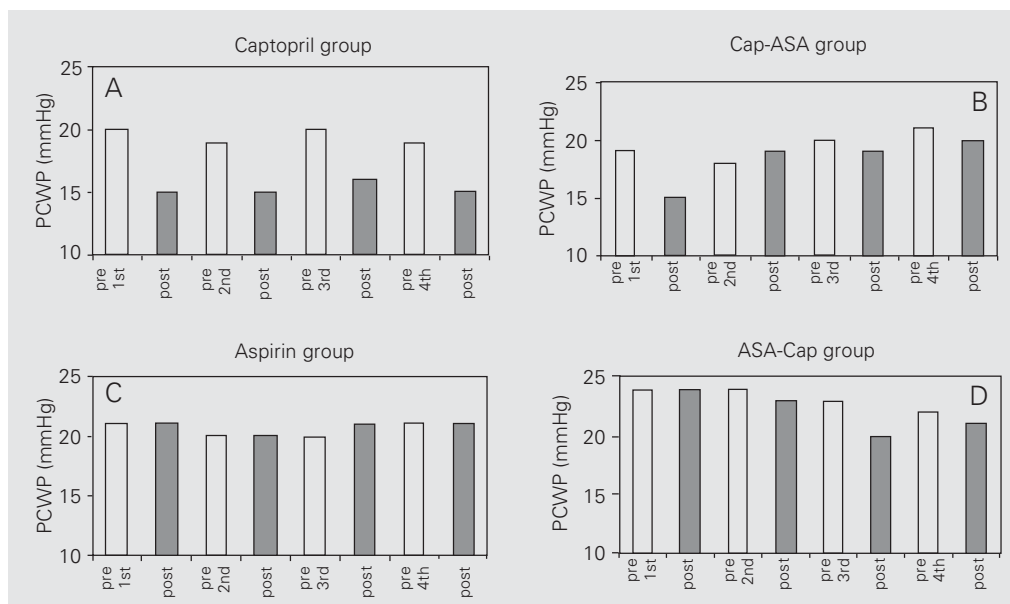
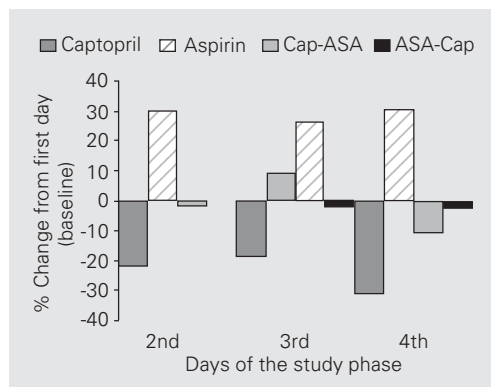


Figure 3. Changes in pulmonary capillary wedge pressure (PCWP) before (open bar) and 1 h after (closed bar) administration of captopril (Cap), aspirin (ASA) or both. PCWP was reduced significantly in the captopril group (A) and on the first day in the Cap-ASA group (B); this effect was abolished in the Cap-ASA group with introduction of aspirin. PCWP remained unchanged in the aspirin group (C). In the ASA-Cap group (D) no significant differences were noted with the addition of captopril.

Figure 4. Norepinephrine (NE) levels compared with mean levels on the first day of the study. Data are reported as means for 10 patients in each group. Blood for NE was collected before drug administration. There was a significant reduction ( $P < 0.02$ , repeated-measures ANOVA) in NE levels in the captopril group that persisted throughout the study period. There was a trend towards an increase in the aspirin group ( $P < 0.07$ , repeated-measures ANOVA); NE levels remained unchanged in the Cap-ASA (captopril plus aspirin) and ASA-Cap (aspirin plus captopril) groups.



ASA group,  $232 \pm 96$  and  $263 \pm 104$  ng/dl for the Cap-ASA group, and  $176 \pm 87$  and  $212 \pm 88$  ng/dl for the ASA-Cap group, respectively. There was no statistically significant difference among the groups during the study.

## Discussion

In this study we demonstrate an antagonism between acute ASA and captopril administration in patients with advanced stable heart failure. Thus, while captopril alone produced an increase in cardiac index and a decrease in systemic vascular resistance and pulmonary capillary wedge pressure, its combination with ASA completely eliminated these effects. ASA by itself did not cause any measurable hemodynamic effects. In addition, captopril reduced plasma NE levels, an effect that was not observed with ASA or with the combination of captopril and ASA. ASA antagonism was evident from the initial dose. In contrast, in patients already using ASA, the addition of captopril did not cause any variations in hemodynamic profile.

This is the first invasive hemodynamic study that used low doses of ASA. We used 300 mg ASA on the first day, which is sufficient to block cyclo-oxygenase within less than 24 h (1,3); this dose was followed by 100 mg/day, and this interaction persisted throughout the 4 days of the study. Thus, low doses of ASA had an antagonistic effect similar to that of higher doses used by other

researchers (6,11).

The mechanisms responsible for this interaction are not entirely clear, but interference with one or more components of the renin-angiotensin system is probably involved. ACE leads to formation of angiotensin II, but also inactivates BK because it also is kininase II, which degrades BK (7). BK has potent vasodilatory effects that can be attributed to two endothelium-related mechanisms: a direct effect and an indirect one due to the release of additional mediators, such as PG and nitric oxide. BK induces PG liberation by means of phospholipase A activation (7). Thus, arachidonic acid released from membrane phospholipids is converted, by cyclo-oxygenase, into PG ( $PGD_2$ ,  $PGE_2$ , PGF),  $PGI_2$  and thromboxane  $A_2$ .  $PGI_2$ , specifically, is also a potent vasodilator (7) and may thus contribute to the vasodilatory effect of ACE inhibitors. Consequently, ACE inhibitors decrease vasoconstriction due to reduced angiotensin II synthesis, and indirectly produce vasodilatation through the increase of BK, nitric oxide and PG (7). On the other hand, the negative interaction of ASA/ACE inhibitors can be explained by the blockade of cyclo-oxygenase by ASA (4). It is therefore suggested that ASA inhibits  $PGI_2$  synthesis to an extent sufficient to compromise the hemodynamic effects of captopril.

Several human studies have examined this pharmacological antagonism, but the results are conflicting. While six studies have suggested a negative interaction (6,11-15), six others did not find it (13,16-20) and still another (21) showed a positive interaction. Differences in hemodynamic methods, ASA doses, ACE inhibitor doses and types as well as in patient populations may account for these discrepancies. For instance, non-invasive hemodynamic methods were used in the six studies that did not show interaction (13,16-20). All studies except three (13,18,20) evaluated heart failure class II, III patients; in comparison, our patients had more advanced heart failure. Hence, our data not



only confirmed the antagonism, even with a very low ASA dose of 100 mg/day, but might suggest that invasive hemodynamic methods are more sensitive than non-invasive ones in detecting hemodynamic changes resulting from interaction between ASA and ACE inhibitors.

### Prostaglandin analysis

Prostaglandin analysis did not reveal antagonism with captopril in agreement with previous observations (4). Of the aforementioned studies, only three measured PG (16-18) and none found consistent variations. The absence of PG variations may be attributed to technical and/or methodological problems (22). Evidence suggests that PG have distinct behaviors in different biological systems: thus, blood from the microcirculation is more sensitive than blood from the systemic circulation (23). Our blood samples were taken from the main pulmonary artery and might not have represented peripheral endothelium PG levels.

### Norepinephrine levels

The high initial plasma NE levels indicated the severity of heart failure. As observed after a 48-h compensatory period, there was an important reduction of initial levels followed by clinical stabilization. As shown in Figure 4, a persistent and significant reduction of these levels occurred only in the captopril group. In contrast, patients of the ASA group showed a trend to increased NE levels, which did not reach statistical significance. In this case, standard treatment with digitalis, diuretics and water restriction was not sufficient to blunt this trend. This behavior may have been enhanced by ASA, i.e., via cyclo-oxygenase blockade of PGI<sub>2</sub> and its vasodilatory effects. No changes were observed when using ASA and captopril simultaneously. However, since ASA was the only drug added to conventional treatment, it may have been responsible for the

lack of reduction of NE levels, although a control group treated only by conventional therapy was not available.

Our data agree partly with those reported by Hall et al. (6), who observed a 20% drop in NE levels in patients taking enalapril, with or without ASA. The study by Baur et al. (17) did not show any changes, regardless of the drugs used.

### Long-term interaction

Because of the short duration of our study, the results cannot be extrapolated to long-term treatment observations. In this respect, a careful analysis of studies such AIRE, ISIS-4, SOLVD, Consensus II as well as a recent meta-analysis indicates that this issue remains unresolved (5,23-26).

### Implications

A recent survey of over 200,000 post-myocardial infarction patients showed that only 45% of those with important ventricular ischemic dysfunction took ACE inhibitors but 76% used ASA (10). Thus, ACE inhibitors are clearly underused. This fact could have implications in the morbidity and mortality rate in acute myocardial infarction complicated by ventricular dysfunction, since we would not know if the increased use of ACE inhibitors would interfere with survival because most patients would be using both drugs.

### Limitations of the study

It should be emphasized that the present study focused on acute effects; therefore, long-term results cannot be extrapolated from these data. Secondly, most patients were hypertensive and although the renin-angiotensin system and neurohormonal adaptation depend more on severity of heart failure than etiology, this fact should be considered. Third, the number of patients was somewhat

small. However, the consistency of the data suggests that the findings are reliable.

The results of the present study clearly showed that acute administration of low ASA doses compromised the acute hemodynamic

and neurohormonal effects of captopril on decompensated heart failure, mainly of hypertensive etiology. These observations deserve consideration in the management of acute decompensated heart failure.

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