Additional beneficial effects of canrenoate in patients with anterior myocardial infarction on ACE-inhibitor treatment. A pilot study

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Acute myocardial infarction; Aldosterone; Canrenoate; E/A ratio.

Background. **Recent evidence suggests that, via the mineralocorticoid receptors present in cardiovascular tissues, aldosterone exerts profibrotic effects, and that partial aldosterone escape occurs during ACE-inhibitor treatment.**

Methods. **A double-blind, randomized study was performed in order to evaluate the feasibility, tolerability, and the effects of the administration of 25 mg/day of canrenoate plus captopril versus captopril alone to patients with anterior acute myocardial infarction (AMI) unsuitable for or not receiving thrombolytic treatment and to patients in whom such treatment resulted or did not result in reperfusion. One hundred eighty-seven patients with anterior AMI were included in the present study. In all cases serum creatinine concentrations and serum K concentrations were < 2.0 mg/dl and < 5.5 mmol/l respectively. The patients were randomized in two groups: the canrenoate group included 94 patients who received captopril and 25 mg i.v. of canrenoate (1 mg/hour for the first 72 hours and then orally 25 mg/day) whereas the placebo group (93 patients) received captopril and placebo. On admission and on days 10, 90 and 180 all patients underwent echocardiography in order to determine the end-systolic volume (ESV), the ejection fraction (EF), the end-diastolic diameter, the E/A ratio, the E deceleration time as well as the isovolumetric relaxation time (IVRT) and the E and A peak velocities.**

Results. **Unreperfused patients did not show patency of the infarct-related artery whereas in reperfused patients this vessel was patent (7-10 days after AMI). The two groups were similar in age, sex, incidence of diabetes, smoking habits, hypertension, creatine kinase enzymatic peak, adjuvant therapy, baseline EF, ESV, and incidence of coronary artery bypass grafting/coronary angioplasty. Following 10 days of treatment (canrenoate group), only 9 patients presented with serum K and creatinine concentrations respectively > 5.5 mmol/l and > 2.0 mg/dl. Among those patients receiving canrenoate, the mitral E/A ratio was higher compared to the placebo group (p = 0.001) whereas the ESV was significantly reduced (p < 0.05). The deceleration time for reperfused patients receiving canrenoate was higher than that observed for reperfused patients in the placebo group. The intragroup EF was significantly increased (p = 0.042). Compared to the placebo group, the IVRT was significantly higher for unreperfused patients receiving canrenoate than in the placebo group (p = 0.001). Serum creatinine, blood urea and K levels as well as the incidence and extent of vessel disease were similar for both groups. No side effects were observed during the study period.**

Conclusions. **Our data suggest that the combination of captopril plus canrenoate is feasible for the initial treatment of patients presenting with AMI. Besides, compared to captopril alone it is more efficacious in improving the E/A ratio, the ESV, the EF, and the IVRT.**

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Introduction

In view of their effects on remodeling[1-3], angiotensin-converting enzyme (ACE) inhibitors have recently been employed for the treatment of early post-acute myocardial infarction (AMI). Activation of the renin-angiotensin-aldosterone system during the acute and subacute phases of myocardial infarction engenders an increase in circulating levels of norepinephrine and of angiotensin II. These effector hormones may exert more direct effects on the heart such as abnormal accumulation of collagen that surrounds and encases myocytes[4]. Such a structural remodeling of the myocardium can

lead to deterioration in diastolic and systolic ventricular function[5,6]. According to Van Belle et al.[7] administration of aldosterone following balloon-induced vascular injury in the rabbit model enhanced subsequent thickening whereas spironolactone inhibited the fibrointimal hyperplasia responsible for this thickening[7]. Thus, the profibrotic effects of aldosterone, presumably acting via the mineralocorticoid receptors (MR) present in cardiovascular tissue, were established. The MR antagonist spironolactone may exert antifibrotic effects by inhibiting fibroblast collagen turnover and angiogenesis[8]. Compared with that by the adrenals, aldosterone synthesis by cardiac tissue is minimal and probably does not contribute to circulating levels of this hormone. However, the concentration of myocardial aldosterone is approximately 17-fold higher than plasma levels[9] and it is likely that cardiac aldosterone, while not contributing to the circulation, plays autocrine and/or paracrine roles within the heart. Such roles may relate to local modulation of vessel tonicity and structure with consequent effects on blood pressure, and repair of damaged tissue possibly by up-regulation of collagen deposition and by promotion of angiogenesis at sites of injury[10]. The importance of MR as mediators of vascular injury was additionally underscored by the observation that the tissue-protective response to ACE-inhibitors in spontaneously hypertensive rats stroke prone was abrogated by the concomitant administration of either aldosterone or deoxycorticosterone[11]. The recent RALES trial revealed a significant reduction in mortality, nonfatal hospitalization and sudden death[10,12]. The fact that the patients were receiving an ACE-inhibitor, and that consequently circulating aldosterone levels were presumably reduced, raises the intriguing possibility that spironolactone blocks autocrine and paracrine effects of locally generated aldosterone[10]. It has been shown that ramipril and spironolactone (25 mg tid) have similar effects on ventricular remodeling following AMI[13]. A previous report showed that plasma renin activity and aldosterone levels were increased at admission and during the first 24 hours of hospitalization. Plasma renin activity did not change substantially, whereas aldosterone levels decreased[14]. Other reports showed partial aldosterone escape in patients treated with ACE-inhibitors[15,16]. Increasing evidence suggests that ACE-inhibitors only transiently suppress aldosterone production[17,18]. A recent study has shown that the addition of canrenoate is feasible and tolerable for the treatment of the early phases of AMI[19]. The study was aimed at verifying whether the therapeutic regimen including canrenoate and ACE-inhibitors administered during the early phases of AMI determines long-term benefits. Since the main cause of heart failure is usually anterior AMI, and since this disease is followed by the most important reparative processes, we performed a double-blind, randomized study comparing the combination of 25 mg/day of canrenoate plus captopril vs captopril plus placebo in anterior AMI patients suitable for thrombolysis and reperfused and in patients unsuitable for and/or not receiving thrombolysis, and unreperfused after thrombolysis. Endpoints were any changes in echocardiographic data and in laboratory parameters during 180 days of treatment.

Methods

Inclusion criteria. From March 1999 to March 2000, 388 consecutive patients with suspected AMI were hospitalized. The inclusion criteria were: a first episode of anterior AMI, Killip class I-II, an acceptable echocardiographic window and hospital admission within 4 hours of the onset of symptoms (pain). Patients unsuitable for and/or not receiving thrombolysis and those receiving thrombolysis who showed unsuccessful reperfusion were also enrolled. On ECG there had to be an ST segment elevation > 1 mm in the peripheral leads and/or 2 mm in the precordial leads. Involvement of more than one lead was required as was the presence of concomitant alterations of the segmentary wall motion observed during echocardiography performed at admission. Before thrombolysis basal creatine kinase (CK, CK-MB) levels had to be within normal limits. All the patients with successful reperfusion and admitted to the study had to meet the reperfusion criteria, whereas in those in whom reperfusion was unsuccessful none of these criteria was met. Successful reperfusion was defined as patency of the infarct-related artery as observed at late coronarography (7-10 days). On the other hand reperfusion was considered as unsuccessful when late coronarography revealed that the infarct-related artery was not patent in those patients who were unsuitable for thrombolysis and/or did not receive thrombolytic treatment or in those patients in whom such therapy was ineffective. There was no age limit. Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committees of the hospital.

Exclusion criteria. The presence of left bundle branch block as diagnosed at ECG performed at admission, a history of cardiomyopathy or of heart failure as well as therapy using ACE-inhibitors, beta-blockers, angiotensin II receptor antagonists and MR antagonists were all considered as exclusion criteria. Patients who showed no enzymatic alterations after thrombolysis were classified as having unstable angina and were excluded from the study. Serum creatinine and K levels > 2.0 mg/dl and > 5.5 mmol/l respectively (at admission) were also considered as exclusion criteria.

Classification and treatment of acute myocardial infarction. AMI was classified as anterior on the basis of the localization of the alterations in segmental contractility as revealed by echocardiography and on the basis of the localization of the ST segment alterations observed at standard 12 lead + V3R-V4R lead ECG performed at

admission before starting treatment. All patients received our standard treatment including glucose, insulin, potassium (GIK), nitrates (20-100 μ/min), heparin (25 000 IU/day), aspirin (160 mg/day) and ACE-inhibitors. When possible, three 5 mg doses of intravenous metoprolol followed by oral administration were also employed. The thrombolytic drug used was the accelerated recombinant tissue plasminogen activator (100 mg).

Reperfusion criteria. Criteria for the diagnosis of reperfusion of the infarct-related artery included the occurrence, within 12 hours of thrombolysis, of a peak in CK serum levels (considered mandatory) associated with one of the following: typical behavior of the ST segment (50% reduction), rapid pain regression, early ventricular arrhythmias occurring within 2 hours following initiation of thrombolytic treatment.

Study protocol. Patients suitable for thrombolysis received captopril 6.25 mg orally, as first dose between 2-4 hours after starting thrombolysis and also those unsuitable for thrombolysis and/or not receiving thrombolysis, and those showing unsuccessful reperfusion (2-4 hours after thrombolysis), received captopril 6.25 mg 2-4 hours after admission. Patient blood pressure (first 12 hours), heart rate, and ECG were monitored continuously, recorded on tape (first 6 hours), and then analyzed to check for the presence of any rhythm disturbance. Particular attention was paid to the time of pain cessation and of regression of the ST segment alterations. The presence of ventricular tachycardia or of ventricular fibrillation was also recorded. Blood CK concentrations were measured at 3 hour intervals during the first 24 hours and then every 6 hours until normal values were achieved. The enzymatic peak was determined. Providing blood pressure was > 100 mmHg, captopril doses were subsequently increased up to 25 mg every 8 hours. Following initial evaluation, patients were randomized in a double-blind fashion in two groups: the first group (canrenoate) included 94 patients to whom 25 mg/day of canrenoate (1 mg/hour) were administered intravenously for the first 72 hours and then orally (25 mg once daily); the second group (placebo) included 93 patients to whom matching doses of placebo were administered. All patients underwent echocardiography in order to evaluate baseline end-systolic volume (ESV), ejection fraction (EF), transmitral flow velocity, E wave and A wave peak velocities, E/A ratio, E wave deceleration time, and isovolumetric deceleration time (IVRT). Canrenoate or placebo was administered 4-6 hours following initiation of thrombolytic treatment. Laboratory analysis, including serum K and serum creatinine were performed daily during the study period (8-12 days), and then on days 90 and 180 to evaluate treatment safety and tolerability. Therapy was interrupted in case of hyperkalemia (> 5.5 mmol/l) or serum creatinine levels > 2.0 mg/dl.

Before discharge, all patients underwent a symptom limiting exercise test and to 24 hour Holter monitoring in order to check for the presence of late ventricular arrhythmias. Only arrhythmias Lown class > 2 were considered.

In all cases hemodynamic evaluation was performed 7-10 days following enrolment by physicians who were unaware of the patients' clinical data. Percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) were performed according to angiographic findings and to left ventricular function. Patients enrolled in the study continued treatment after discharge. Follow-up was performed regularly in an outpatients' setting.

Follow-up. On day 1 (just after randomization), and on days 10, 90 and 180 following enrolment, echocardiography was performed according to standard procedure. Patients were told to lay in the left lateral position; echocardiographic recordings were obtained at the end of a normal expiratory phase. Apical 4 chamber and 2 chamber views were employed. The ESV was measured at the end of the T wave. The modified Simpson's rule which uses two cross-section views (4 and 2 chamber apical views) was followed[20]. The transmitral flow velocity was measured using pulsed-wave Doppler with the sample volume positioned between the mitral leaflet tips during diastole[21]. The E wave and A wave peak velocities, the E/A ratio, the E wave deceleration time, and the IVRT were measured on three separate beats and the mean was then calculated. All members of the study team had completed at least 5 years of internal cardiology residency and training in two-dimensional echocardiography. Two observers, unaware of clinical and ECG data, evaluated the two-dimensional echocardiographic images. In case of discrepancy, the images were again reviewed, and a decision was made by consensus. The interobserver and intraobserver coefficients of variation were 4 and 3%, respectively.

Statistical analysis. Results are expressed as mean ± SD. Data were analyzed by the two tailed Student's t test to identify differences between the groups and analysis of variance (ANOVA) for repeated measures with Bonferroni correction for intragroup data. Nominal data were analyzed by the χ^2 test; a p value of < 0.05 was considered statistically significant.

Results

Of the 388 hospitalized patients, 201 did not meet the inclusion criteria: 137 presented with inferior AMI, 16 were in Killip class III-IV, 28 were admitted 12 hours after symptom onset and were classified as having late AMI and 20 presented with no enzymatic variations and were classified as having unstable angina. Thus only 187 patients were enrolled into the study: among

these, 117 were submitted to thrombolytic treatment. Reperfusion was unsuccessful in 26 of these patients. Seventy patients were not suitable for thrombolysis and/or were not receiving thrombolysis. Hence, the study group included 96 unreperfused and 91 reperfused patients. All patients were randomized in accordance with the study protocol (Table I). In patients not submitted to thrombolysis and in thrombolysed, unreperfused anterior AMI the infarct-related artery was not patent. Patients who had proved reperfused anterior AMI at late coronarography had an infarct-related artery patency corresponding to the classification of reperfusion based on non-invasive diagnosis. The groups were similar with regard to age, sex, history of diabetes, smoking habits, hypertension, CK enzymatic peak, adjuvant therapy, EF, ESV, and incidence of CABG/PTCA. Tables I and II show the clinical data of all patients according to reperfusion status (reperfused and unreperfused) and treatment received (canrenoate and placebo). The CK peak was significantly higher in unreperfused patients ($p < 0.0001$) (Table I). The enrolled patients were divided into two subgroups: 1) thrombolysed and reperfused, and 2) not thrombolysed and/or not reperfused. There were no significant differences between the two groups in serum sodium, blood pressure or heart rate during the study (data not shown). Creatinine, blood urea and serum K did not differ significantly between the two groups. Intragroup values of serum K and blood urea were significantly increased in both groups (Table III).

Table I. Clinical data and results of all the patients enrolled according to the reperfusion and non-reperfusion status.

	Reperfused (n=91)	Unreperfused (n=96)	p
Sex (F/M)	29/62	35/61	
Mean age (years)	61.5 ± 16	64.5 ± 17	NS
CK peak (IU/l)	2015 ± 1081	2675 ± 1118	< 0.0001
VT	78	36	
CVG	85	87	
3 vessels	34	35	
2 vessels	22	24	
1 vessel	28	27	
No critical stenosis	1	1	
PTCA/CABG	30/18	32/19	
Lown class > 2	8	15	
Beta-blockers	48	22	< 0.001
ACE-inhibitors (mg/day)	64.5 ± 15	66.2 ± 16	NS
Hypertension	40	43	
Diabetes	35	38	
Hypercholesterolemia	46	51	
Smokers	28	25	

CABG = coronary artery bypass grafting; CK = creatine kinase; CVG = coronarography; PTCA = percutaneous transluminal coronary angioplasty; VT = ventricular tachycardia.

Table II. Clinical data and results of all the patients enrolled according to the treatment received.

	Canrenoate (n=94)	Placebo (n=93)	p
Sex (F/M)	32/62	32/61	
Mean age (years)	63.6 ± 15	62.8 ± 16	NS
Suitable for thrombolysis	59	58	
Unreperfused	13	13	
Unsuitable for thrombolysis	34	36	
CK peak (IU/l)	2525 ± 1158	2495 ± 1095	NS
CVG	85	87	
3 vessels	34	35	
2 vessels	22	24	
1 vessel	28	27	
No critical stenosis	1	1	
CABG/PTCA	30/20	30/19	
VT	58	59	
Lown class > 2	9	14	NS
Beta-blockers	36	34	NS
ACE-inhibitors (mg/day)	64.44 ± 16	66.3 ± 15	NS
Hypertension	42	41	
Diabetes	36	37	
Hypercholesterolemia	47	50	
Smokers	27	26	

Abbreviations as in table I.

With regard to the 96 unreperfused patients (49 from the canrenoate group, 47 from the placebo group), there was no inter or intragroup reduction in systolic and diastolic blood pressure. Following 10 days of treatment, serum K levels > 5.5 mmol/l and serum creatinine levels > 2.0 mg/dl were observed in only 5 cases included in the canrenoate group. In both groups the mitral E/A ratio at 10, 90 and 180 days significantly differed from that at the start of the study ($p < 0.011$, $p < 0.0001$). The E/A ratios at 10, 90 and 180 days for the canrenoate group were significantly different from those of the placebo group ($p < 0.005$, $p < 0.0001$) (Table IV). In the canrenoate group the IVRT on day 180 was significantly different from that at the time of enrolment ($p < 0.008$) and from that of the placebo group on day 180 ($p < 0.001$). The ESV was significantly reduced in the canrenoate group ($p < 0.032$). The E wave deceleration time did not show any significant difference between the two groups (Table IV).

No inter or intragroup decrease in systolic or diastolic blood pressure was observed among the 91 reperfused patients (45 from the canrenoate group, 46 from the placebo group). Following 10 days of treatment, serum K levels > 5.5 mmol/l and serum creatinine levels > 2.0 mg/dl were observed in 4 cases included in the canrenoate group. The mitral E/A ratio showed a significant intragroup difference in both groups ($p < 0.0001$). The E/A ratio at 90 and 180 days for the canrenoate group was significantly higher than that for

Table III. Laboratory measurements on days 1, 10, 90 and 180.

	Canrenoate					Placebo				
	Entry	Day 10	Day 90	Day 180	p	Entry	Day 10	Day 90	Day 180	p
Unreperfused anterior AMI										
Serum K (mmol/l)	3.6 ± 0.4	4.67 ± 0.38	4.8 ± 0.2	4.61 ± 0.3	<0.0001	3.7 ± 0.5	4.59 ± 0.47	4.62 ± 0.4	4.54 ± 0.3	<0.0001
Creatinine (mg/dl)	1.11 ± 0.16	1.37 ± 0.18	1.36 ± 0.2	1.27 ± 0.2	<0.001	1.09 ± 0.18	1.34 ± 0.17	1.33 ± 0.12	1.25 ± 0.2	<0.0001
Urea (mg/dl)	35.8 ± 10.3	42.7 ± 9.5	43.6 ± 9	39.5 ± 8	<0.001	38.7 ± 13.5	41.18 ± 12	41.5 ± 8.2	37.5 ± 7.5	NS
Reperfused anterior AMI										
Serum K (mmol/l)	3.7 ± 0.5	4.75 ± 0.47	4.8 ± 0.35	4.5 ± 0.3	<0.001	3.6 ± 0.4	4.57 ± 0.28	4.68 ± 0.54	45 ± 0.4	<0.0001
Creatinine (mg/dl)	1.09 ± 0.2	1.34 ± 0.17	1.35 ± 0.16	1.21 ± 0.2	<0.001	1.11 ± 0.16	1.33 ± 0.15	1.31 ± 0.2	1.19 ± 0.11	<0.01
Urea (mg/dl)	36.9 ± 10	43.37 ± 9.5	41.5 ± 11	38.5 ± 10	<0.017	38.7 ± 13.5	42.2 ± 12.5	40.2 ± 9.5	35.2 ± 8.4	NS

AMI = acute myocardial infarction.

Table IV. Unreperfused anterior AMI: echocardiographic data on days 1, 10, 90 and 180.

	Canrenoate					Placebo				
	Day 1 (n=49)	Day 10 (n=44)	Day 90 (n=36)	Day 180 (n=36)	p	Day 1 (n=47)	Day 10 (n=43)	Day 90 (n=37)	Day 180 (n=37)	p
EF (%)	40.11 ± 12	42.9 ± 9.7	43 ± 10	45.3 ± 9.5	NS	39.82 ± 13	40.86 ± 9.9	40.5 ± 11	41.2 ± 10	NS
EDD (mm)	53.8 ± 13	54.7 ± 9.5	55 ± 7.5	55 ± 10	NS	54.6 ± 11	56.1 ± 4.5	56.8 ± 5.5	57.3 ± 7	NS
ESV (ml/m^2)	55.1 ± 16	53.7 ± 13	54 ± 12	53.5 ± 7.5*	NS	55.2 ± 14	55.6 ± 13	57.3 ± 14	57.9 ± 10*	NS
E/A ratio	0.63 ± 0.14	0.85 ± 0.18§	0.88 ± 0.16§§	0.89 ± 0.15§	<0.0001	0.67 ± 0.12	0.75 ± 0.14§	0.71 ± 0.11§§	0.70 ± 0.12§§	<0.011
IVRT (m/s)	95 ± 27	87 ± 21	81 ± 15	76 ± 11**	<0.008	97 ± 25	89 ± 22	88 ± 21	86 ± 14**	NS
DT (ms)	175 ± 30	197 ± 31	206 ± 39	209 ± 32	<0.0001	186 ± 47	205 ± 35	215 ± 42	211 ± 37	<0.006

AMI = acute myocardial infarction; DT = deceleration time; EDD = end-diastolic diameter; EF = ejection fraction; ESV = end-systolic volume; IVRT = isovolumetric relaxation time. * p = 0.032; ** p = 0.001; § p <0.005; §§ p <0.0001 (Student's t test).

the placebo group (p = 0.001) (Table V). In the canrenoate group the E wave deceleration time showed a significant intragroup and intergroup difference (p = 0.0001, p = 0.049). With regard to the IVRT, there was a significant intragroup but no intergroup difference (Table V). There was no significant intragroup difference in the ESV, but following 180 days of treatment values were significantly decreased in the canrenoate group compared to the placebo group (p = 0.034). The EF was significantly increased in the canrenoate group (p < 0.042).

Hemodynamic evaluation was performed 7-10 days following AMI in 172 patients (85 from the canrenoate group and 87 from the placebo group). The remaining patients were not submitted to this procedure: 4 refused, 9 were over 75 years old, and 2 for other reasons. The incidence and extent of vessel disease was similar in both groups (Table II). In 99 patients either PTCA or CABG was performed. During the follow-up period lasting from March 1999 to July 2000 (range 4-17 months) 6 patients died in the canrenoate group as a result of reinfarction (n = 3) and heart failure (n = 3), and

Table V. Reperfused anterior AMI: echocardiographic data on days 1, 10, 90 and 180.

	Canrenoate					Placebo				
	Day 1 (n=45)	Day 10 (n=41)	Day 90 (n=38)	Day 180 (n=38)	p	Day 1 (n=46)	Day 10 (n=40)	Day 90 (n=37)	Day 180 (n=37)	p
EF (%)	46.3 ± 12	49.2 ± 8	50.8 ± 9	52.1 ± 10	<0.042	47.3 ± 11	47.9 ± 8	48.4 ± 9	49.5 ± 10	NS
EDD (mm)	54.6 ± 11	54.6 ± 5.5	55.2 ± 9	55.3 ± 6	NS	53.8 ± 13	56.7 ± 8.3	57.5 ± 11	57.7 ± 9	NS
ESV (ml/m^2)	45.8 ± 14	44.6 ± 10	41.4 ± 11	40.5 ± 8*	NS	45.1 ± 14	43.5 ± 12	44.8 ± 9	45.3 ± 11*	NS
E/A ratio	0.61 ± 0.13	0.84 ± 0.18	0.95 ± 0.16§	0.98 ± 0.12§	<0.0001	0.63 ± 0.14	0.77 ± 0.14	0.81 ± 0.15§	0.83 ± 0.1§	<0.001
IVRT (ms)	97 ± 25	89 ± 22	75 ± 18	76 ± 15	<0.0001	95 ± 27	87 ± 21	81 ± 20	82 ± 16	<0.014
DT (m/s)	169 ± 45	189 ± 35	190 ± 28	202 ± 25§§	<0.0001	175 ± 30	187 ± 32	183 ± 36	190 ± 27§§	NS

Abbreviations as in table IV. * p = 0.034; § p = 0.001; §§ p = 0.049 (Student's t test).

9 in the placebo group (3 reinfarction and 6 heart failure). One hundred forty-eight patients completed the study period of 90 and 180 days (75 from the canrenoate group and 73 from the placebo group) and underwent echocardiographic evaluation (Tables IV and V). Ten ischemic events were observed during follow-up (4 in the canrenoate group and 6 in the placebo group).

With regard to drop-outs, some patients who were referred to CABG developed AMI intraoperatively and were excluded from the study. In addition, 9 patients discontinued treatment after 10 days and 15 patients died during the first 3 months. Beta-blocker treatment was similar in all subgroups. Compared to reperfused patients, the EF in unreperfused patients was lower. For this reason, the doses of beta-blockers employed in these patients were inferior.

Tables VI and VII show results of the study for all groups. These groups were followed for 3 months only. Data analysis revealed a statistically significant difference in ESV and in the E/A ratio between the two groups.

Discussion

Inhibition of the renin-angiotensin-aldosterone system by ACE-inhibitors suppresses aldosterone production. On the other hand, the combination of aldosterone receptor blockers and ACE-inhibitors has been considered to be relatively contraindicated owing to potential hyperkalemia. Recent studies suggest that ACE-inhibitors only transiently suppress aldosterone production[15,18,22-24]. It has recently been shown that low doses of spironolactone (12.5-25 mg), an effective and well tolerated loop diuretic, associated with standard ACE-inhibitor treatment, decrease atrial natriuretic peptide and do not determine hyperkalemia[12,25]. The recent RALES study demonstrated that an aldosterone receptor antagonist used in combination with an ACE-inhibitor reduces the risk of death due to progressive heart failure and of sudden death related to other cardiac causes. This study suggests that such a combination could be useful in hypertensive patients who have had a myocardial infarction[12]. Moreover, a limitation of the excessive extracellular matrix turnover has been shown to be one of the extrarenal mechanisms contributing to the beneficial effects of spironolactone in heart failure patients[26]. Aldosterone was originally thought to be important in the pathophysiology of heart failure because of its ability to increase sodium retention and K loss. However, it has been shown that aldosterone also causes myocardial and vascular fibrosis[4,27], direct vascular damage[17], baroreceptor dysfunction[28] and prevents the uptake of norepinephrine by the myocardium[12,28]. The presence of a steroidogenic system within cardiac tissue has also been proposed[29]. Moreover, gene expression of the terminal enzymes, 11-beta-hydroxylase and aldosterone synthase, involved in corticosterone and aldosterone synthesis respectively, as well as the production of both these steroids have recently been demonstrated in the rat heart[9]. This confirms the potential for steroid metabolism in cardiac tissue. These reports emphasize the potential role of cardiac aldosterone in the regulation of tissue function. Accumulating evidence indicates that the

Table VI. Changes in ESV and EF after 90 days of treatment in patients receiving canrenoate or placebo.

	Canrenoate				Placebo			
	Day 1 (n=94)	Day 10 (n=85)	Day 90 (n=74)	p	Day 1 (n=93)	Day 10 (n=83)	Day 90 (n=74)	p
EF (%)	44.3 ± 11	47.1 ± 8.5	46.2 ± 8	NS	44.3 ± 12	44.7 ± 8.2	43.7 ± 10	NS
EDV (ml/m^2)	90.6 ± 22	91.1 ± 21	87.2 ± 19	NS	89.8 ± 23	92.7 ± 28	92.5 ± 21	NS
ESV (ml/m^2)	50.7 ± 12	49.3 ± 10	46.5 ± 12*	<0.059	49.5 ± 12	49.8 ± 8.5	50.9 ± 11*	NS
E/A ratio	0.62 ± 0.11	0.84 ± 0.12	0.91 ± 0.13§	<0.0001	0.65 ± 0.12	0.76 ± 0.10	0.76 ± 0.14§	<0.0001
IVRT (ms)	96.5 ± 22	88.7 ± 20	79.1 ± 16	<0.0001	96.2 ± 23	88.1 ± 19	84 ± 18	<0.0001
DT (m/s)	173 ± 36	193 ± 27	197 ± 31	<0.0001	175 ± 21	196 ± 29	192 ± 32	<0.0001

EDV = end-diastolic volume. Other abbreviations as in table IV. * p = 0.021; § p = 0.001.

Table VII. Laboratory measurements on days 1, 10 and 90 in all patients receiving canrenoate or placebo.

	Canrenoate				Placebo			
	Entry	Day 10	Day 90	p	Entry	Day 10	Day 90	p
Serum K (mmol/l)	3.6 ± 0.4	4.68 ± 0.39	4.8 ± 0.3	<0.0001	3.6 ± 0.3	4.58 ± 0.3	4.24 ± 0.4	<0.0001
Creatinine (mg/dl)	1.10 ± 0.18	1.36 ± 0.16	1.35 ± 0.18	<0.0001	1.10 ± 0.15	1.33 ± 0.14	1.31 ± 0.1	<0.0001
Urea (mg/dl)	36.1 ± 10	43.8 ± 8.5	42.3 ± 9.1	<0.011	38.7 ± 10.5	41.7 ± 11	40.5 ± 8.5	NS

myocardial angiotensin II generating pathway is also activated in AMI. Indeed, increased cardiac expression of angiotensinogen, ACE and AT_1 receptor proteins as well as ACE activity and angiotensin II content have been previously described in infarcted hearts[30-35]. In fact, ACE-inhibitors, angiotensin II and AT_1 receptor antagonists, alone or combined, reduce post-AMI cardiac remodeling[32,36-38]. Angiotensin II is an important regulator of aldosterone biosynthesis and secretion in the adrenal cortex as well as in the heart[9,39]. Such a role of tissue angiotensin II in local aldosterone synthesis has been previously demonstrated in the adrenals[40]. Since, in AMI, cardiac angiotensin II levels are increased, it is probable that this increase triggers a rise in cardiac aldosterone production and a decrease in cardiac corticosterone synthesis. The tissue aldosterone system may also be activated in AMI and may contribute to the pathophysiology of this disease state. Furthermore, the increase in myocardial aldosterone production (3.7 fold) may be implied in post-infarction ventricular fibrosis and in the regulation of tissue norepinephrine concentrations[41]. The suppression of circulating aldosterone by ACE-inhibitors is transient, as exemplified by the term "escape" used to describe this phenomenon[16,42]. The brevity of the suppression may be accounted for in several ways. Standard doses of ACE-inhibitors do not fully suppress angiotensin-regulated aldosterone production by the adrenals. Potent renin releasing stimuli may counter the effects of ACE-inhibitors. Aldosterone secretion also proceeds independently of angiotensin concentrations[5,28,43-45]. Although the mechanism of aldosterone-induced cardiac fibrosis remains unclear[46], some reports suggest that the increase in myocardial aldosterone levels may be involved in post-AMI ventricular fibrosis. Cardiac aldosterone does not contribute to circulating levels of this hormone. Its concentration within the heart, however, greatly exceeds circulating levels, suggesting that cardiac aldosterone generation has autocrine or paracrine properties[47,48]. Therefore, it is conceivable that the effects of treatment strategies including aldosterone antagonists may be 2-fold: prevention of fibrosis in vascular and myocardial tissues, and enhancement of the effects of ACE-inhibitors.

Bearing the above in mind, we considered that it would be interesting to test the association between ACE-inhibitors and canrenoate administered during the early phases of post-AMI in a selected group of patients. After 180 days patients treated using both captopril as well as canrenoate presented with improvements in E/A ratio, ESV, EF and IVRT which were significantly better than those observed in patients treated using captopril alone regardless of reperfusion or otherwise of the infarct-related artery. These data suggest that the combination captopril and canrenoate may determine a more significant decrease in aldosterone-mediated collagen production during the early phases of anterior AMI. These benefits may persist in the short and long term. We hypothesized that ACE-inhibitors could decrease the detrimental effects of angiotensin II and canrenoate those of aldosterone. It is difficult to reach definitive conclusions regarding the value of the data observed in patients treated with captopril and canrenoate. In view of the fact that, in case of AMI, tissue remodeling starts early and that the hormone increase is more significant during the early phases of this disease we thought that this combined therapeutic regimen, administered during the initial phases of AMI could prevent and/or reduce myocardial fibrosis. The improvement in the E/A ratio observed in the canrenoate group suggests that captopril plus canrenoate could reduce myocardial fibrosis and consequently improve myocardial compliance. Patients with anterior AMI were selected since this disease constitutes the first step towards heart failure. Patients with unreperfused anterior AMI were also selected, because they are at greater risk, they present with more extensive necrosis and myocardial reparation and collagen deposition (accumulation) and since they are the candidates who would most likely benefit from canrenoate therapy. In fact, compared to the placebo group these patients showed an improvement in the E/A ratio just 10 days after initiating therapy.

Reperfused patients usually present with lesser damage and consequently less extensive reparation processes and collagen accumulation. In fact, canrenoate benefits were observed 90 and 180 days after admission. For this reason, we divided the patients according to the success or otherwise of reperfusion. The two groups were different with regard to the extent of necrosis and to myocardial function. The most striking results of the study were the safety and tolerability of the captopril plus canrenoate combination even in the long term and the significant improvement in the E/A ratio, IVRT, EF and ESV after 90 and 180 days of treatment. In fact, only 9 patients showed an increase in serum creatinine concentration of > 2.0 mg/dl and in serum K concentration of > 5.5 mmol/l during hospitalization and they discontinued the canrenoate treatment. No side effects (creatinine and serum K increase) were observed in the remaining patients after 180 days of treatment.

Owing to the small number of patients recruited, these results should be interpreted with caution. However, strict selection criteria were employed. To our knowledge, this is the first study evaluating the effects of combined captopril and canrenoate treatment in patients with AMI. The data in the present study suggest a beneficial effect of this combined therapeutic regimen on remodeling. However, they must be interpreted with caution since ACE-inhibitors were employed in both groups. It is very difficult to determine the effects of ACE-inhibition and MR antagonism, but it is very important to observe that patients receiving canrenoate presented with an improvement in both diastolic (E/A ratio, deceleration time, IVRT) and systolic data (ESV and EF). We are not able to explain these effects on systolic function. Because of the small number of patients the effects of such therapy in terms of morbidity and mor-

tality could not be evaluated. In addition, our data raise a question: is it correct to wait for symptomatic heart failure before administering MR inhibitors or should an attempt at preventing the development of heart failure be made? Further investigations are required. Our data are very preliminary. In fact, this is the first time that the combination of ACE-inhibitors and MR antagonists was administered to patients with AMI.

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