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Acute Hemodynamic Effects of Amlodipine 15 Days After a Myocardial Infarction in Normotensive Patients Treated with Atenolol

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Summary. **The acute hemodynamic effects of 20 mg iv amlodipine were evaluated in a placebo-controlled study in 16 normotensive patients 15 ± 1 days after an acute myocardial infarction by covariance analysis. Atenolol was given orally for at least 1 week before the study to maintain the heart rate between 50 and 60 beats/min. All patients were given two doses of 10 mg of amlodipine, or 10 ml of a placebo twice, in iv infusion lasting 2 minutes each. Hemodynamic data were collected during the control period and 15 minutes after each of the two amlodipine or placebo infusions. At the time of the last measurements, 15 minutes after the second amlodipine or placebo infusion, the plasma amlodipine level was 31 ± 16 µg/l and the plasma atenolol level was 773 ± 564 µ/l in the amlodipine group versus 795 ± 916 µg/l in the placebo group. There were no chronotropic, dromotropic, or inotropic effects. The main hemodynamic effect was a fall in systemic vascular resistance (1548 ± 591 dynes.sec.cm^{-5} to 1176 ± 526 dynes.sec.cm^{-5}, p = 0.045) with decreases in aortic pressure and in the left ventricular stroke work index. The left ventricular ejection fraction was 51 ± 12% in the placebo group and 56 ± 15% in the amlodipine group (ns) during the control period, and did not change after infusion of placebo or amlodipine. Left ventricular compliance seemed to be enhanced by amlodipine, because the end-diastolic left ventricular volume index rose from 82 ± 11 ml/m^2 to 87 ± 11 ml/m^2 (p = 0.026) 15 minutes after the beginning of the second infusion of 10 mg of amlodipine, without any change in end-diastolic left ventricular pressure. Intravenous infusion of 20 mg of amlodipine is well tolerated 15 days after acute myocardial infarction in normotensive patients without deeply depressed left ventricular systolic function and chronically treated with atenolol. The main hemodynamic effects observed are potentially useful for such patients.**

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Key Words. **amlodipine, atenolol, hemodynamics, myocardial infarction**

The calcium antagonist amlodipine, which has a long elimination half-life and a large volume of distribution, is an antihypertensive drug with a predominantly vascular action and natriuretic effects [1]. Amlodipine is also an effective antianginal drug for chronically ischemic patients [2,3] and might, in addition, be useful in the treatment of normotensive patients after an acute myocardial infarction. However, these patients are often treated with beta-blockers, and the combination of a beta-blocker and a calcium antagonist, even when the latter is from the dihydropyridine group, might be harmful for systolic left ventricular function [4,5]. Nevertheless, these drug combinations, which have been studied by many authors [6], are most often well tolerated when systolic left ventricular function is not clearly impaired [6,7]. When the action of the combination of amlodipine beta-blocker was assessed in the acute phase of a myocardial infarction in animal studies, the authors did not observe harmful effect [8,9]. The purpose of the present study was evaluate the hemodynamic effects of amlodipine, 15 days after an acute myocardial infarction, in patients chronically treated with atenolol.

Methods

Patients

One woman and 15 men underwent routine postinfarction catheterization and agreed to participate in this study, which was approved by the regional ethics committee. They were given full oral and written information about the study, and their written consent to participate was obtained before inclusion. Hypertensive patients, patients with clinical signs of heart failure, with an echocardiographic left ventricular ejection fraction <40%, residual angina, contraindications for atenolol, or the usual causes of exclusion were not included in this study. Ingestion of a calcium antagonist

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other than amlodipine, or of vasodilators, was not allowed for 72 hours before catheterization.

The 16 patients were divided into two groups of 8 patients (Table 1). One group was given two iv infusions of 10 mg amlodipine and the other two iv placebo infusions. Inclusion in these groups was not randomized; patients were assigned to a group according to their initial clinical and hemodynamic features in order to make the groups comparable. There were no statistical differences between the two groups during the control period. The mean age was 54 ± 11 years (range, 39–68 years), and the locations of infarction and peaks of CPK were comparable in the two groups. Atenolol intake was adjusted to maintain the heart rate between 50 and 60 beats/min during the 3 days preceding the study, and initial plasma atenolol levels were similar in the two groups.

Protocol

The procedure was carried out in the morning, in the supine dorsal position, after fasting and without premedication. Control data were collected in 5–10 minutes after catheter insertion. They included right and left intracavitary pressures, cardiac output, left ventricular volumes measured by left ventriculography, and blood sample collection for plasma amlodipine and atenolol assays. Measurements were made at the control period, 15 minutes after the first iv infusion of 10 mg of amlodipine or placebo, and again 15 minutes after the second infusion of the 10 mg of amlodipine or placebo. The iv infusions of amlodipine or placebo were injected within 2 minutes. The study could be stopped at any time in case of any harmful event. For the three left ventriculographies (35 ml for each) the contrast medium was anionic, with an osmolarity of 450 mOsm. Coronary arteriography was performed during the 5 minutes after the control measurements to exclude from the study patients with life-threatening coronary lesions. The assays of plasma atenolol during the control period, and of plasma amlodipine during the control period and 15 and 30 minutes after the first injection, were done to ensure that the plasma levels of these drugs were in the therapeutic range.

Material

Right intracavitary pressures were measured via a Swan-Ganz 7F catheter with one lumen opening in the right atrium and another in the pulmonary artery. Car-

Table 1. Control hemodynamic data in the two groups

Parameters		Placebo group	p	Amlodipine group
Age (years)		52 ± 12	ns	56 ± 11
Body surface (m^2)		1.74 ± 0.16	ns	1.84 ± 0.14
Weight (kg)		68 ± 12	ns	74 ± 10
Myocardial infarction location:	Anterior	4		3
	Posterior	4		5
CPK peak (units)		1516 ± 833	ns	1673 ± 1149
Plasma atenolol level (μg/l)		795 ± 916	ns	773 ± 564
Intracardiac pressures (mmHg)				
Mean right atrium pressure (RAP)		4 ± 2	ns	3 ± 2
Mean pulmonary artery pressure (PAP)		17 ± 3	ns	18 ± 7
Pulmonary wedge pressure (PWP)		11 ± 3	ns	11 ± 7
End-diastolic left ventricular pressure (EDLVP)		17 ± 5	ns	16 ± 8
Systolic left ventricular pressure (SLVP)		114 ± 14	ns	123 ± 24
Mean aortic pressure (MAP)		82 ± 9	ns	89 ± 13
Other hemodynamic data				
PR interval (PR; sec)		0.17 ± 0.01	ns	0.18 ± 0.06
Heart rate (HR; beats/min)		58 ± 5	ns	60 ± 8
Cardiac index (CI; l/min/m^2)		2.52 ± 0.64	ns	2.66 ± 0.80
Stroke index (SI ml/beat/m^2)		44 ± 13	ns	45 ± 13
Pulmonary vascular resistance (PVR; dynes.s.cm^{-5})		129 ± 55	ns	129 ± 61
Systemic vascular resistance (SVR; dynes.s.cm^{-5})		1530 ± 454	ns	1548 ± 591
Left ventricular stroke work index (LVSWI; g/b.m^{-2})		54 ± 17	ns	61 ± 21
Left ventricular dp/dt (LVdp/dt; mmHg.sec^{-1})		879 ± 202	ns	1145 ± 313
Vmax (sec^{-1})		0.98 ± 0.19	ns	1.11 ± 0.23
Left ventricular (LV) angiographic data				
End-diastolic LV volume index (EDLVVI; ml.m^{-2})		80 ± 12	ns	82 ± 11
End systolic LV volume index (ESLVVI; ml.m^{-2})		40 ± 12	ns	36 ± 13
Stroke index (aSI; ml.m^{-2})		40 ± 8	ns	46 ± 15
Heart rate (aHR; beats/min)		56 ± 5	ns	58 ± 7
Cardiac index (aCI; l/min.m^{-2})		2.22 ± 0.37	ns	2.67 ± 0.93
Left ventricular ejection fraction (EF; %)		51 ± 12	ns	56 ± 15
LV circumferential fiber velocity (VCF; sec^{-1})		0.86 ± 0.27	ns	1.15 ± 0.49

diac output was measured by thermodilution. To ascertain left ventricular pressure, a high-fidelity micromanometer (Millard 6F model Pc 360) was inserted into a femoral artery through an introducing sheath (7F), which was larger than the micromanometer shaft, to allow the measurement of mean aortic pressure. Systolic aortic pressure was assumed to be equal to left ventricular systolic pressure.

The left ventricular pressure tracing was recorded and as also fed into a differential amplifier (Electronics for Medicine) to obtain the peak positive first derivative of left ventricular pressure, averaged over 15 cardiac cycles. The other catheters were connected to a Statham 23 ID transducer, and intracavitary pressures were transmitted via liquid columns. The signals were analyzed by an Electronics of Medicine electromanometer and recorded on a VR12 polygraph with four electrocardiographic leads. Left ventriculographies were performed in the 30° right anterior oblique position. Ventricular volumes were measured at end-diastole and end-systole, using to the method of Dodge [10], and were related to the body surface area. Mean circumferential fiber velocity was calculated as the angiographic end-diastolic left ventricular middle diameter minus the end-systolic left ventricular middle diameter divided by the ejection time and by the end-diastolic left ventricular middle diameter. The maximal shortening speed of myocardial fibers was assessed according to Grunk-Emeyer et al. [11]. Other hemodynamic data were calculated using standard formulas.

Statistical analysis

Data were entered in duplicate by two different observers, and the entries were compared by a third qualified observer. The amlodipine and atenolol assays were carried out using CEMAF SA, Poitiers, F-86000. The statistical analysis was conducted in two parts. The first consisted of a description of the study population, including, in particular, a comparison of the amlodipine and placebo groups. The second was an overall comparison of the values for the the parameters measured, using a time-wise comparison. The normality of the distributions was studied using the Shapiro and Wilk's test, including checking the conditions for the application of analysis of variance. Overall changes were assessed by an analysis of covariance for repeated measurements, with the pretreatment measurement being used as the covariate. Time-wise comparisons were analyzed using Mann-Whitney's nonparametric test. $p < 0.05$ was considered statistically significant. Values are expressed as means ± standard deviation (m ± SD).

Results

During the control period 5–10 minutes after catheterization, atenolol levels were 795 ± 916 µg/l in the placebo group and 773 ± 564 in µ/l in the amlodipine group. As regards the hemodynamic data for the two groups (Table 2), filling pressures increased slightly in both groups, and in the placebo group this increase was the only change observed (Fig. 1). Left ventricular ejection fraction was 51 ± 12% in the placebo group and 56 ± 15% in the amlodipine group (ns) in the control period and did not change after placebo or amlodipine infusion.

In the amlodipine group, heart rate and PR interval were unchanged. The main change was a drop in systemic vascular resistance (Fig. 2). Left ventricular stroke work index and aortic pressure decreased, and consequently the cardiac index tended to rise (Fig. 3). Amlodipine did not change any of the inotropic indices. After 20 mg of amlodipine the end-diastolic left ventricular volume index rose, but the simultaneous end-diastolic left ventricular pressure did not change compared with the placebo group (Fig. 4). Fifteen minutes after infusion of 10 mg of amlodipine, the mean plasma amlodipine level was 17 ± 9 µg/l, and 15 minutes after the second infusion of 10 mg of amlodipine it was 31 ± 16 µg/l.

Discussion

Initial group similarities

During the control period, clinical and hemodynamic data were comparable in the two nonrandomized groups. The small size required oriented selection for inclusion. As stated in the Methods, patients were assigned to a particular group according to their personal and clinical features, in order to make the two groups comparable. As a result, there were no statistical differences between the groups during the control period as regards either clinical or hemodynamic data.

Hemodynamic data during the control period

In both groups, cardiac output was slightly lower and systemic vascular resistance was higher than our normal patient standards. This might have been due to the action of atenolol [12] and/or to the myocardial infarction itself. The peak plasma CPK level of these 16 patients was consistent with a significant but not major myocardial infarction, and the overall left ventricular ejection fraction was close to normal levels (66 ± 10%) in our laboratory. Their end-diastolic left ventricular volume index, which was slightly higher than the usual index measured in normal patients in our laboratory, and their subnormal left ventricular ejection fraction both agreed with this assumption.

Plasma atenolol and amlodipine levels

Initially, plasma *atenolol* was at the therapeutic level [13]. Three days before the procedure, the oral dose of atenolol was adapted to the chronotropic response of each patient. However, in these patients, who were not given sedative premedication, heart rate had a ten-

Table 2. *Hemodynamic data at baseline and 15 minutes after each of two 10-mg amlodipine iv infusions*

			Amlodipine or Placebo		
		Control (before amlodipine)	10 mg	20 mg	p
Intracardiac pressures					
RAP	amlodipine	3 ± 2	3 ± 2	4 ± 2	ns
RAP	placebo	4 ± 2	4 ± 1	5 ± 1	
PAP	amlodipine	18 ± 7	18 ± 8	20 ± 6	ns
PAP	placebo	17 ± 3	18 ± 3	18 ± 3	
PWP	amlodipine	11 ± 7	11 ± 6	13 ± 6	ns
PWP	placebo	11 ± 3	11 ± 4	12 ± 3	
EDLVP	amlodipine	16 ± 8	17 ± 6	17 ± 6	ns
EDLVP	placebo	17 ± 5	18 ± 6	20 ± 6	
SLVP	amlodipine	123 ± 24	112 ± 25	103 ± 19	0.008
SLVP	placebo	114 ± 14	119 ± 17	124 ± 19	
MAP	amlodipine	89 ± 13	79 ± 11	76 ± 10	0.028
MAP	placebo	82 ± 9	85 ± 10	87 ± 11	
Other hemodynamic data					
PR	amlodipine	0.18 ± 0.06	0.18 ± 0.06	0.18 ± 0.06	ns
PR	placebo	0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	
HR	amlodipine	60 ± 8	61 ± 8	63 ± 10	ns
HR	placebo	58 ± 5	58 ± 3	58 ± 5	
CI	amlodipine	2.66 ± 0.80	2.84 ± 0.95	2.99 ± 0.95	ns
CI	placebo	2.52 ± 0.64	2.60 ± 0.73	2.58 ± 0.65	
SI	amlodipine	45 ± 13	46 ± 14	48 ± 15	ns
SI	placebo	44 ± 13	45 ± 11	45 ± 13	
PVR	amlodipine	129 ± 61	129 ± 111	113 ± 55	ns
PVR	placebo	129 ± 55	124 ± 54	115 ± 39	
SVR	amlodipine	1548 ± 591	1308 ± 561	1176 ± 526	0.045
SVR	placebo	1530 ± 454	1537 ± 451	1562 ± 485	
LVSWI	amlodipine	61 ± 21	55 ± 16	52 ± 15	0.027
LVSWI	placebo	54 ± 17	58 ± 19	60 ± 20	
LV dp/dt	amlodipine	1145 ± 313	1018 ± 201	1098 ± 206	ns
LV dp/dt	placebo	879 ± 202	887 ± 227	960 ± 252	
Vmax	amlodipine	1.11 ± 0.23	1.07 ± 0.19	1.21 ± 0.28	ns
Vmax	placebo	0.98 ± 0.19	1.03 ± 0.18	1.01 ± 0.18	
Left ventricular angiographic data					
EDLVVI	amlodipine	82 ± 11	80 ± 13	87 ± 11	0.026
EDLVVI	placebo	80 ± 12	77 ± 14	76 ± 10	
ESLVVI	amlodipine	36 ± 13	35 ± 11	36 ± 11	ns
ESLVVI	placebo	40 ± 12	40 ± 14	37 ± 10	
aSI	amlodipine	46 ± 15	45 ± 13	51 ± 14	ns
aSI	placebo	40 ± 8	37 ± 11	39 ± 6	
aHR	amlodipine	58 ± 7	58 ± 7	60 ± 9	ns
aHR	placebo	56 ± 5	57 ± 4	57 ± 3	
aCI	amlodipine	2.67 ± 0.93	2.65 ± 0.98	3.04 ± 0.99	ns
aCI	placebo	2.22 ± 0.37	2.14 ± 0.59	2.20 ± 0.36	
EF	amlodipine	56 ± 15	56 ± 13	58 ± 13	ns
EF	placebo	51 ± 12	49 ± 15	52 ± 10	
VCF	amlodipine	1.15 ± 0.49	1.18 ± 0.47	1.19 ± 0.57	ns
VCF	placebo	0.86 ± 0.27	0.83 ± 0.23	0.89 ± 0.22	
Plasma amlodipine (μg/l)		0	17 ± 9	31 ± 16	

Placebo group data are given in regular type below each amlodipine value, and amlodipine are in bold type.
Abbreviations as in Table 1.

dency to rise in the catheterization laboratory. For this reason, we chose an atenolol dose higher than usual, and all patients had an effective beta-blockade treatment on the day of the study.

The plasma *amlodipine* level observed in our study after the first intravenous dose of 10 mg of amlodipine was lower than that observed in healthy volunteers, but very close to the steady-state drug concentrations observed after repeated oral doses in such volunteers [14]. In elderly hypertensive patients, the pharmacokinetics of amlodipine change and its elimination half-life is longer than in young patients [15]. The recom-

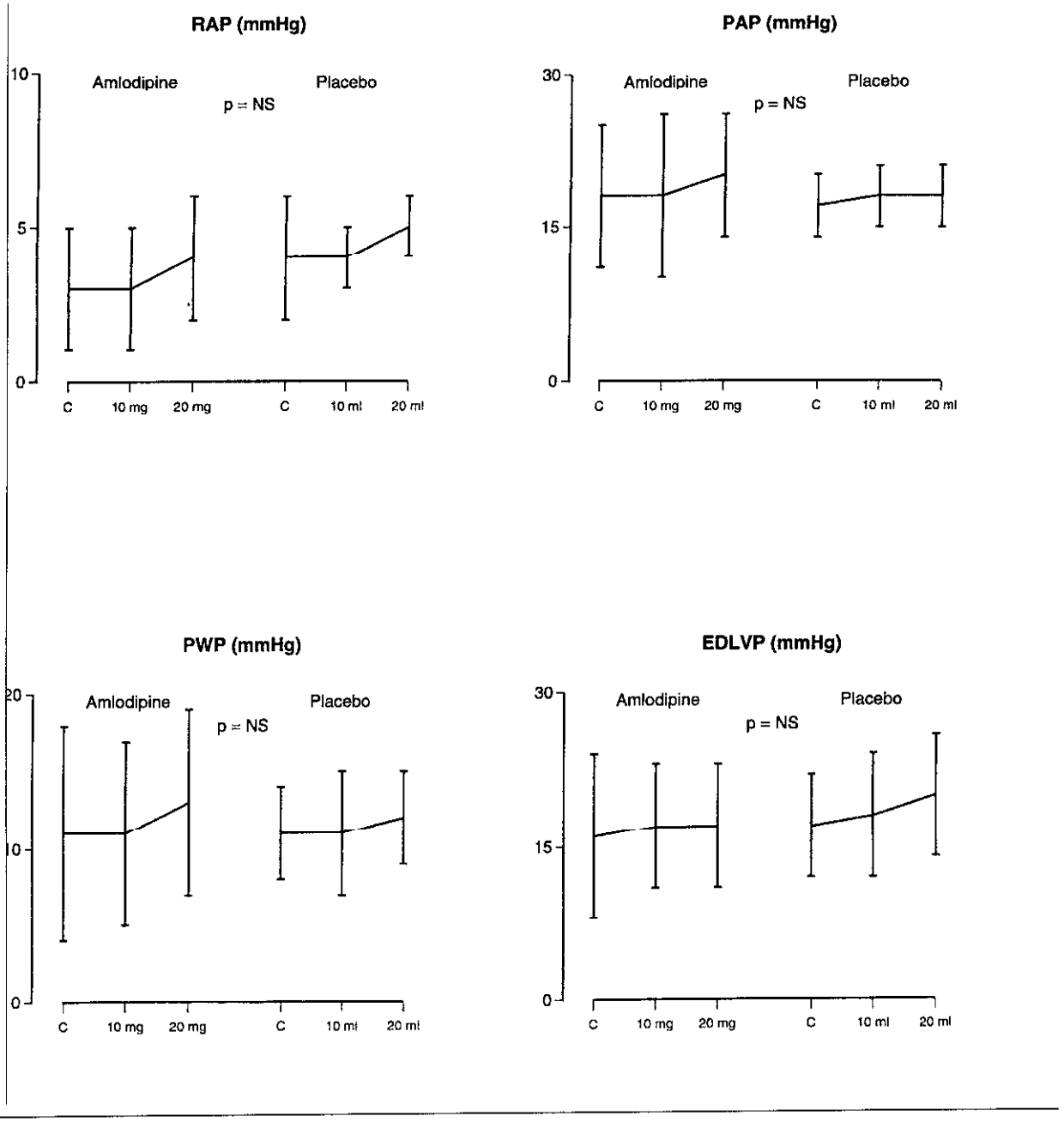

Fig. 1. *Filling pressures.*

mended daily oral dose of amlodipine for the treatment of hypertension and/or angina is 5–10 mg. The high plasma amlodipine levels observed were probably due to the incomplete distribution of the drug in the tissue, since its distribution is only complete 0.75–2 hours after an iv dose [14], and our measurements were made 15 minutes after each infusion. In addition, dihydropyridine clearance is reduced by beta-blockers, which reduce hepatic output [15] or disturb hepatic microsomal enzyme functions [16,17]. Clearance of amlodipine is also reduced in the case of hepatic dysfunction [1], and its plasma level can be modified by the direct decrease in hepatic flow observed with atenolol [18], as also observed with other combinations of a dihydropyridine drug and a beta-blocker [19].

Clinical tolerance of amlodipine

Intravenous infusion of 20 mg of amlodipine did not have any harmful clinical effects. The protocol of the present study included a provision for compulsory

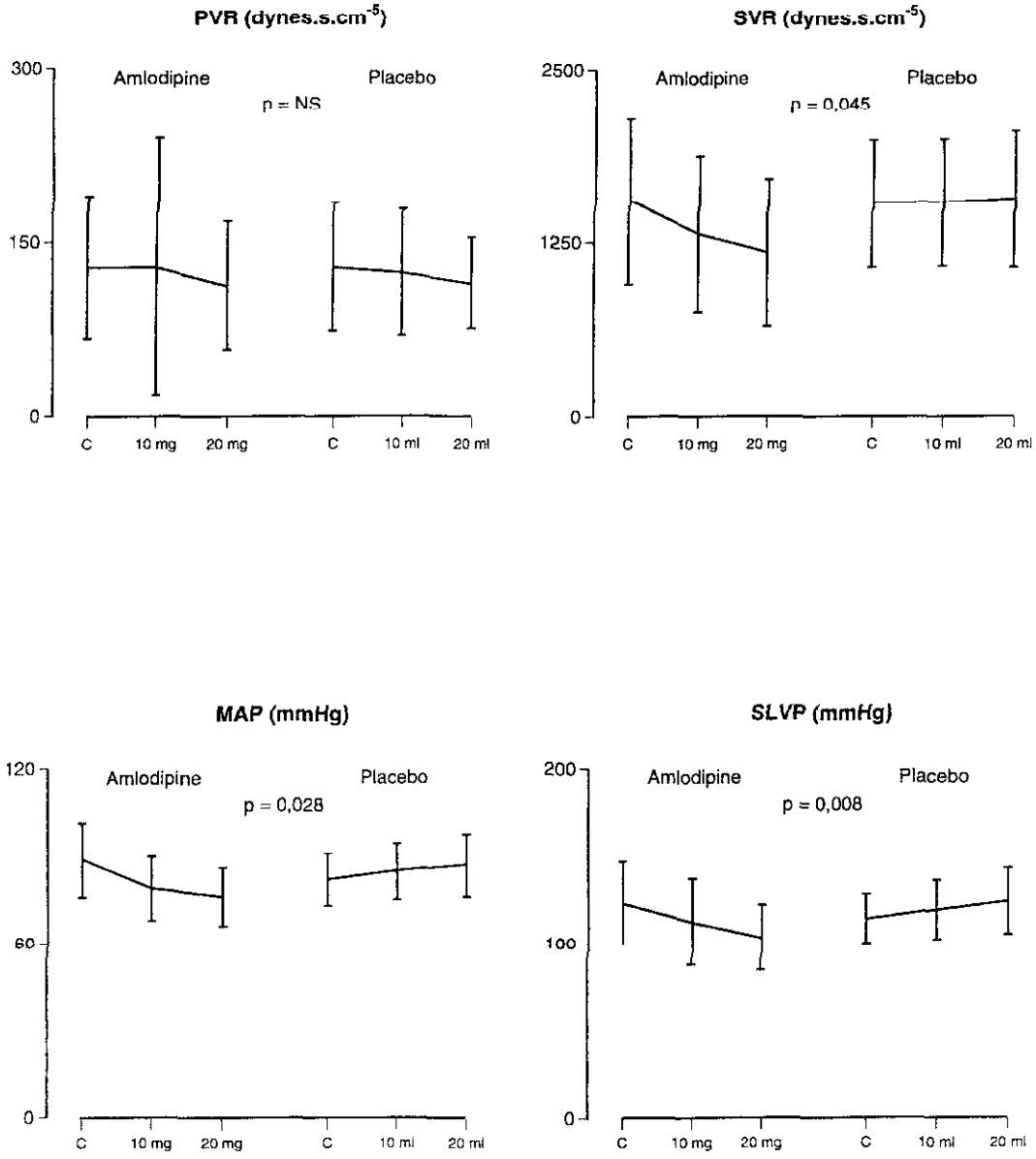

Fig. 2. Vascular resistances and aortic pressure.

shortening of the procedure in case of a threatened decrease in aortic pressure or a drop in mean aortic pressure of more than 20% after the first amlodipine infusion. However, all patients tolerated the two amlodipine infusions well. In fact, other authors observed that amlodipine reduces the aortic pressure more in hypertensive patients than in normotensive subjects [20].

Evolution of the hemodynamic data

A slight increase in filling pressures, particularly in the systemic circulation, was observed in the two groups 30 minutes after the control period (see Fig. 1). This was due to the choice of left ventriculography to assess left ventricular volumes, a technique chosen for its accuracy. However, left ventriculography increases the blood volume despite the small volume of x-ray contrast medium used and its low hyperosmolarity. In the placebo group, the increased blood volume simultaneously induced a trend towards an increase in aortic pressures and in the stroke work index. The few variations in hemodynamic data observed in this group confirm the stability of all the patients and the reproducibility of the measurements, in spite of the three left ventriculographies.

When amlodipine is administered shortly after a myocardial infarction to patients chronically treated

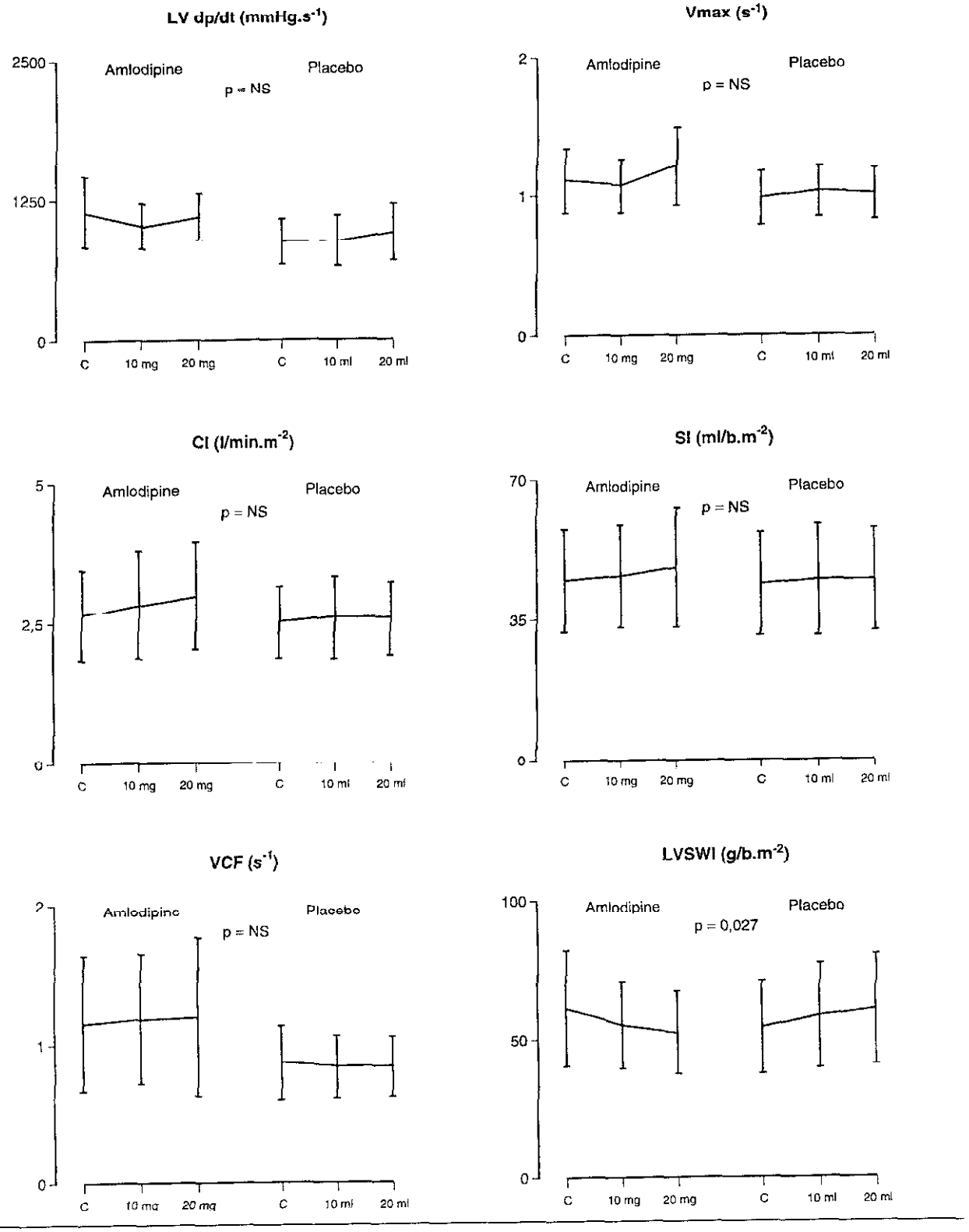

Fig. 3. *Left ventricular inotropic indices*

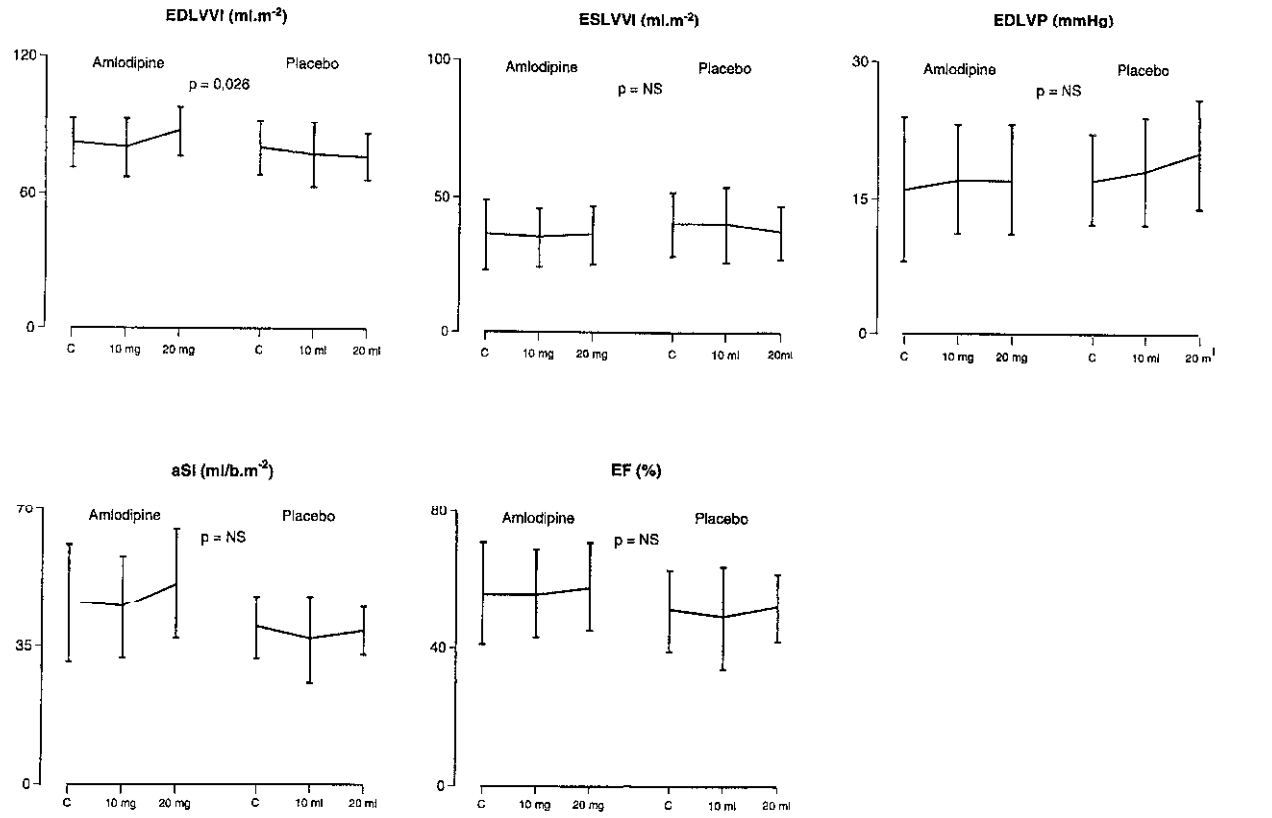

Fig. 4. Left ventricular angiographic data and end diastolic left ventricular pressure.

with atenolol, its hemodynamic effects are not well known. Arterial dilation is the major hemodynamic action of the dihydropyridines [1]. Usually, the mean drop in aortic pressure that occurs after iv infusion of a calcium antagonist is followed by a sympathetic response, with tachycardia, particularly when the calcium antagonist belongs to the dihydropyridine group. This tachycardia is generally followed by a rise in the cardiac index and sometimes an increase in contractility indices [7,21]. In theory, these sympathetic in-vivo responses to calcium antagonists are not desirable for hypertensive patients or for patients with critical coronary disease. However, these drugs were found to have a negative inotropic effect in isolated myocardial fibers, although this was only observed with higher doses than those given in this study [22].

In the present study, the fall in aortic pressures was not followed by a marked sympathetic response. Amlodipine seems to induce less sympathetic stimulation than other calcium antagonists from the dihydropyridine group [2,3,23], particularly if administered together with a beta-blocker [24]. In animal studies, amlodipine, with and without autonomic nervous systemic blockade, had hemodynamic and electrophysiological effects that were intermediate between those of dihydropyridines and those of calcium antagonists from other groups, such as diltiazem and verapamil (25). In the present study, heart rate and the PR interval remained stable and the inotropic indices did not change. The cardiac index exhibited a nonsignificant trend towards increase, probably due, at least in part, to the decrease in the left ventricular afterload (see Figs. 2 and 3). Other factors were certainly involved because if the decrease in the left ventricular afterload had been the only cause of the rise in the cardiac index, simultaneous end-systolic left ventricular volume should have decreased, and that was not the case (see Fig. 4). A rise in the cardiac index after amlodipine has been often reported [23,24], but it was smaller when amlodipine was given with a beta-blocker. The small number of patients in the present study explains why this increase did not attain statistical significance, although the rise in the cardiac index reached 12%.

The left ventricular stroke work index (a parameter closely related to myocardial oxygen consumption) decreased by about 20% (see Fig. 3), without any change in hemodynamic data, suggesting that amlodipine could have a harmful effect on systolic left ventricular function. In fact, the cardiac index, stroke index, and left ventricular ejection fraction did not decrease. This suggests that the hemodynamic balance induced by amlodipine allows the preservation of adequate left

ventricular systolic function, with a simultaneous fall in myocardial oxygen demand.

In addition, the end-diastolic left ventricular volume index increased, without a simultaneous increase in end-diastolic left ventricular pressure (Fig. 4), a strong indication that amlodipine enhances left ventricular compliance, as observed in reperfused dog hearts [26]. Nevertheless, the increase of 5 ml in the end-diastolic left ventricular volume index observed here was small and must be viewed with caution, in spite of its statistical significance. Moreover, this parameter did not increase after the first dose of 10 mg of amlodipine, contrary to what would have been expected, at the therapeutic [14] plasma amlodipine level of 17 ± 9 µg/l attained, at that time if amlodipine had clearly enhanced left ventricular compliance. Amlodipine probably does increase left ventricular compliance, but this requires confirmation by further studies.

Conclusion

Intravenous infusion of 20 mg amlodipine is well tolerated 15 days after an acute myocardial infarction in normotensive patients whose left ventricular systolic function was not highly depressed, and who have been treated with atenolol for at least 1 week. The main hemodynamic effects include decreases in systemic vascular resistance, aortic pressure, and the left ventricular stroke work index and a probable increase in left ventricular compliance. These effects are potentially useful for such patients.

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