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Effect of Cyclosporine on Left Ventricular Remodeling After Reperfused Myocardial Infarction

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Objectives This study examined the effect of a single dose of cyclosporine administered at the time of reperfusion on left ventricular (LV) remodeling and function by cardiac magnetic resonance 5 days and 6 months after myocardial infarction.

Background In a human study, administration of cyclosporine at the time of acute reperfusion was associated with a smaller infarct size.

Methods Twenty-eight patients of the original cyclosporine study had an acute (at 5 days) and a follow-up (at 6 months) cardiac magnetic resonance study to determine LV volumes, mass, ejection fraction, myocardial wall thickness in infarcted and remote noninfarcted myocardium, and infarct size.

Results There was a persistent reduction in infarct size at 6 months in the cyclosporine group compared with the control group of patients (29 ± 15 g vs. 38 ± 14 g; $p = 0.04$). There was a significant reduction of LV end-systolic volume (and a trend for LV end-diastolic volume; $p = 0.07$) in the cyclosporine group compared with the control group, both at 5 days and 6 months after infarction. There was no significant difference between the 2 groups in either global LV mass or regional wall thickness of the remote noninfarcted myocardium at 5 days or 6 months. Attenuation of LV dilation and improvement of LV ejection fraction by cyclosporine at 6 months were correlated with infarct size reduction.

Conclusions Cyclosporine used at the moment of acute myocardial infarction reperfusion persistently reduces infarct size and does not have a detrimental effect on LV remodeling. These results are preliminary and must be supported by further studies. (Ciclosporin A and Acute Myocardial Infarction; NCT00403728) (J Am Coll Cardiol 2010;55:1200–5) © 2010 by the American College of Cardiology Foundation

Recently, we showed that the administration of cyclosporine at the time of reperfusion in patients undergoing percutaneous coronary intervention for an acute myocardial infarction (AMI) was associated with a reduction in infarct size (1).

The rationale of this proof-of-concept study was that cyclosporine is a potent inhibitor of the opening of the mitochondrial permeability transition pore, which plays a crucial role in lethal myocardial reperfusion injury (2–5). Cyclosporine inhibits mitochondrial permeability transition pore opening via its binding to the peptidylprolyl isomerase cyclophilin D located in the mitochondrial matrix (6).

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However, cyclosporine is not specific for cyclophilin D and also forms a complex with cytosolic cyclophilin A that inhibits the calcium-activated protein phosphatase calcineurin. The calcineurin-dependent pathway seems to be crucial for the compensatory myocardial hypertrophy of the remote noninfarcted myocardium during the early post-AMI remodeling stage. Animal studies have found that long-term daily administration of cyclosporine can alter left ventricular (LV) remodeling after AMI and favor the

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development of heart failure (7,8). There are no published data showing a detrimental effect of a single dose of cyclosporine at the time of reperfusion on LV remodeling, although a single dose of cyclosporine is unlikely to exert any long-term detrimental effect on LV remodeling.

The aim of the present study was therefore to assess the safety and efficacy of a single dose of cyclosporine administered at the time of reperfusion using cardiac magnetic resonance (CMR) at 5 days and at 6 months after AMI in a subset of 28 patients of our original cyclosporine study (1).

Methods

All patients of this study were part of the original cyclosporine study, previously reported. The study protocol, setting, and inclusion and exclusion criteria were also previously reported (1).

The ethics committee of our institution approved the trial, and all subjects gave written informed consent before inclusion in the study.

Because of limited access to magnetic resonance imaging facilities, only a subgroup of patients underwent the acute and follow-up CMR studies.

Magnetic resonance imaging protocol and CMR analysis. CMR studies were performed on a 1.5-T whole-body scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). LV function, volumes, and mass at rest and infarct size were assessed as previously described (1) (Fig. 1).

Statistical analysis. Summary values are expressed as mean ± SD. Categorical data were compared by using the Fisher exact test and continuous variables were compared by using Student *t* test. Two-way analysis of variance was used to assess differences between the means of continuous variables at 5 days and 6 months between the 2 groups. When significant, differences within and between each group were tested by a post hoc analysis using the Bonferroni correction for multiple comparisons. We performed an analysis of covariance to test for equality of the slopes of the regression of infarct size defined by late gadolinium enhancement magnetic resonance imaging at 6 months on the area at risk in the cyclosporine and control groups. Simple linear regression analysis was used to assess the correlation between infarct size at 6 months and left ventricular ejection fraction (LVEF) and cavity volumes.

A computerized statistical program (SPSS for Windows, version 12.0, SPSS Inc., Chicago, Illinois) was used for all analyses. All tests were 2-sided. The p values <0.05 were considered statistically significant.

Abbreviations and Acronyms

AMI = acute myocardial infarction
CMR = cardiac magnetic resonance
LV = left ventricular/ventricle
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume

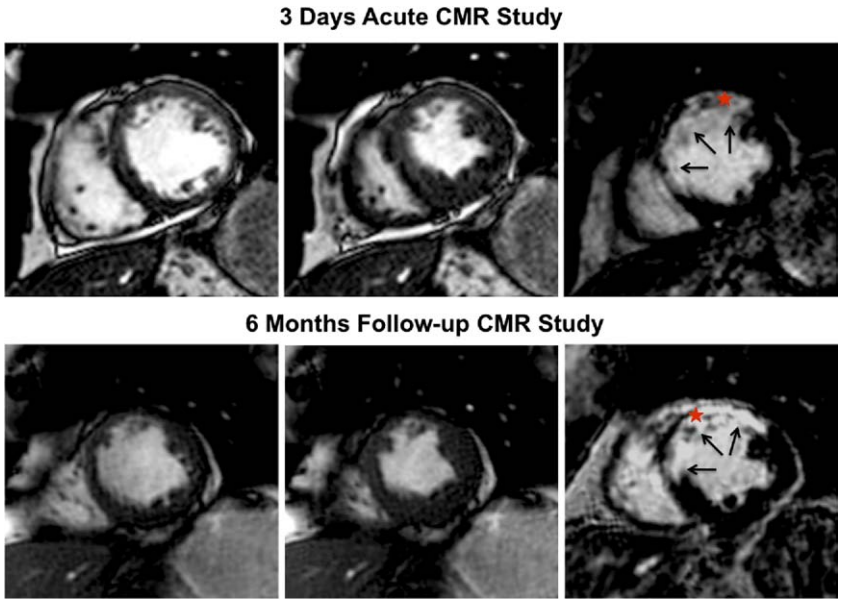

Figure 1 Extensive Anteroseptal Infarction in a 69-Year-Old Man (Control)

Acute **(top)** and 6-month follow-up **(bottom)** short-axis images using cine magnetic resonance at end diastole **(left panels)**, end systole **(middle panels)**, and their corresponding late gadolinium-enhanced images **(right panels)**. Contrast-enhanced magnetic resonance imaging shows complete transmural enhancement of the left ventricular anteroseptal wall **(arrows)** at both study times with small central hypointense spots of microvascular obstruction **(red asterisk)**. On cine magnetic resonance imaging, significant thinning of the left ventricular anteroseptal wall between baseline and 6 months can be observed.

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Table 1 Study Population Baseline Characteristics

	Cyclosporine (n = 15)	Control (n = 13)	p Value
Age, yrs	60 ± 10	63 ± 12	0.45
Sex, M/F	12/3	8/5	0.38
BMI, kg/m^2	27 ± 4	25 ± 4	0.44
Hypertension	4/15	4/13	1.0
Smokers	8/15	7/13	1.0
Dyslipidemia	6/15	4/13	0.41
Diabetes	4/15	3/13	0.67
LV and coronary angiography			
Infarct-related artery			0.46
LAD	6 (40%)	7 (54%)	
RCA	9 (60%)	6 (46%)	
LVEF, %	49 ± 9	53 ± 11	0.40
ACS, %	41 ± 15	39 ± 8	0.17
Ischemia time, min	379 ± 201	290 ± 129	0.31
Treatment at 6 months after AMI, %			
Aspirin	15/15	13/13	1.0
Clopidogrel	15/15	13/13	1.0
ACE inhibitors	13/15	10/13	0.64
Beta-blockers	13/15	11/13	1.0
Statins	14/15	12/13	1.0

Values are expressed as mean ± SD, n/N, or n (%).

ACE = angiotensin-converting enzyme; ACS = abnormally contracting segments; AMI = acute myocardial infarction; BMI = body mass index; LAD = left anterior descending coronary artery; LV = left ventricular; LVEF = left ventricular ejection fraction; RCA = right coronary artery.

Results

Study population. Characteristics of the whole study population at first admission were previously reported (1). Twenty-eight (13 in the control and 15 in the cyclosporine group) of 58 patients included in the initial study had a CMR study done at 5 days and 6 months. In the CMR subpopulation of patients, there was no significant difference between the 2 groups for comorbidities, LV and coronary angiography characteristics at admission, or medical treatment at 6 months (Table 1).

CMR results. INFARCT SIZE. At 5 days, infarct size in the cyclosporine group averaged 34 ± 14 g versus 48 ± 24 g in the control group ($p = 0.03$). There was a significant 15% to 20% shrinkage of the infarcted tissue area in the 2 groups between the 2 CMR studies. The initial significant difference between the 2 groups was maintained at 6 months, with the infarct size averaging 29 ± 15 g in the cyclosporine group and 38 ± 14 g in the control group ($p = 0.04$), as shown in Table 2.

The infarct size at 6 months correlated with area at risk as measured by LV angiography at admission (Fig. 2). Importantly most data points for the cyclosporine group fell below the control regression line, confirming that infarct size reduction by cyclosporine was independent of the size of the area at risk.

LV volumes and function at 5 days and 6 months. At 5 days, there were significantly lower left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) in the cyclosporine compared with the control group (Table 2). There was no significant difference in LVEF between the 2 groups.

Table 2 Results for Measures of CMR After 5 Days and 6 Months

	Cyclosporine (n = 15)	Control (n = 13)	p Value
After 5 days			
LVEDV, ml	143 ± 32	167 ± 43	0.05
LVESV, ml	72 ± 20	91 ± 36	0.04
LVEF, %	50 ± 10	47 ± 11	0.19
Infarct size, g	34 ± 14	48 ± 24	0.03
After 6 months			
LVEDV, ml	133 ± 28	151 ± 35	0.07
LVESV, ml	67 ± 24	84 ± 29	0.05
LVEF, %	51 ± 9	46 ± 11	0.10
Infarct size, g	29 ± 15	38 ± 14	0.04

Values are expressed as mean ± SD.

CMR = cardiac magnetic resonance; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

At 6 months, we observed a lower LVESV in the cyclosporine group compared with the control group. Regarding the LVEDV, there was a nonsignificant ($p = 0.07$) trend toward lower value in the cyclosporine group.

In each group, we noticed a nonsignificant decrease in LVEDV and LVESV between 5 days and 6 months.

There was a significant correlation between infarct size and both LVEDV ($r^2 = 0.40$; $p < 0.05$), LVESV ($r^2 = 0.66$; $p < 0.05$), and LVEF ($r^2 = -0.72$; $p < 0.05$) at 6 months in the whole group of patients (Figs. 3 to 5).

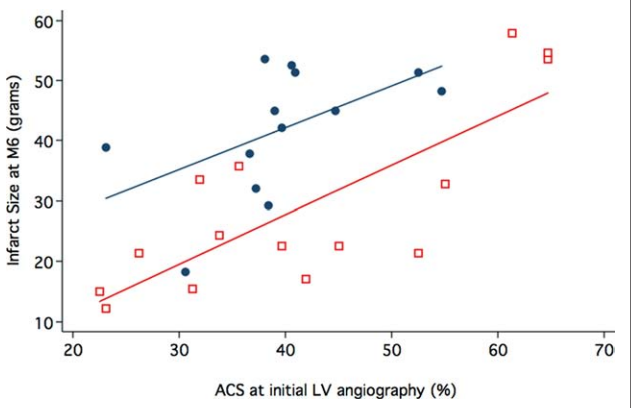

Figure 2 Infarct Size (CMR 6 Months After Acute Myocardial Infarction) as a Function of the Size of the Area at Risk (LV Angiography at Admission)

There was a significant correlation between the 2 variables in the control group ($r^2 = 0.84$). Data points for the cyclosporine group **(red squares)** ($r^2 = 0.67$) lie below the regression line for the control group **(blue circles)**. These data indicate that, for any given area at risk, cyclosporine administration was associated with a reduction in the resulting infarct size as measured by delayed enhancement cardiac magnetic resonance (CMR). This difference was significant by analysis of covariance ($p = 0.007$). ACS = acute coronary syndrome; LV = left ventricular; M6 = 6 months.

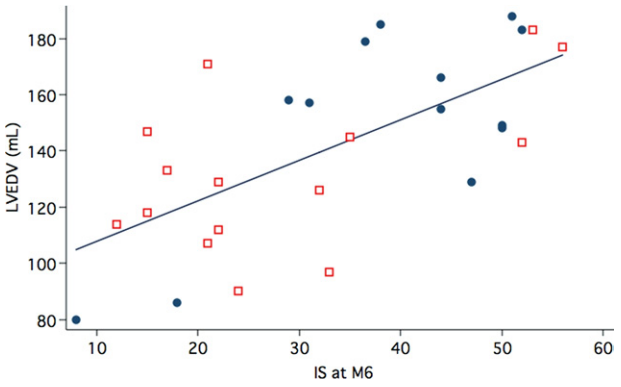

Figure 3 LVEDV as a Function of IS at 6 Months

There was a significant correlation between left ventricular end-diastolic volume (LVEDV) and infarct size (IS) at 6 months ($r^2 = 0.40$; $p < 0.05$) in the whole group of patients. **Blue circles** = control group; **red squares** = cyclosporine. Abbreviations as in Figure 2.

LV regional wall thickness at 5 days and 6 months. We found no significant difference in global LV mass between the 2 groups of patients at 5 days and 6 months (Table 3).

In the noninfarcted remote myocardium, there was no significant effect of cyclosporine on end-diastolic or -systolic wall thickness at either 5 days or 6 months after infarction. In both groups, there was a trend toward a moderate increase in end-diastolic and -systolic wall thickness between 5 days and 6 months.

In the infarcted myocardium, there was no significant effect of cyclosporine on end-diastolic or -systolic wall thickness at either 5 days or 6 months after infarction. In both groups, there was a trend toward a slight decrease in end-diastolic and -systolic wall thickness between 5 days and 6 months.

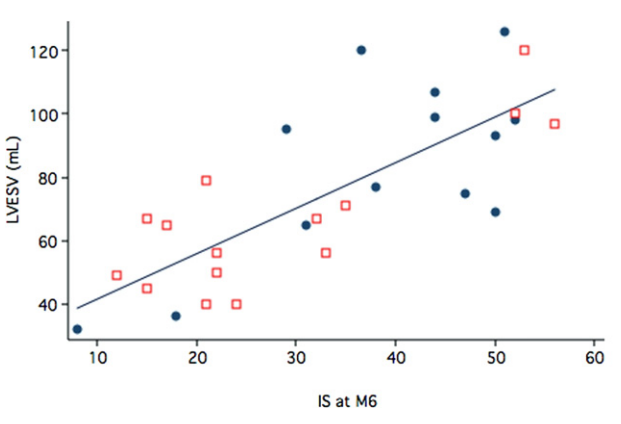

Figure 4 LVESV as a Function of IS at 6 Months

There was a significant correlation between left ventricular end-systolic volume (LVESV) and infarct size (IS) at 6 months ($r^2 = 0.66$; $p < 0.05$) in the whole group of patients. **Blue circles** = control group; **red squares** = cyclosporine.

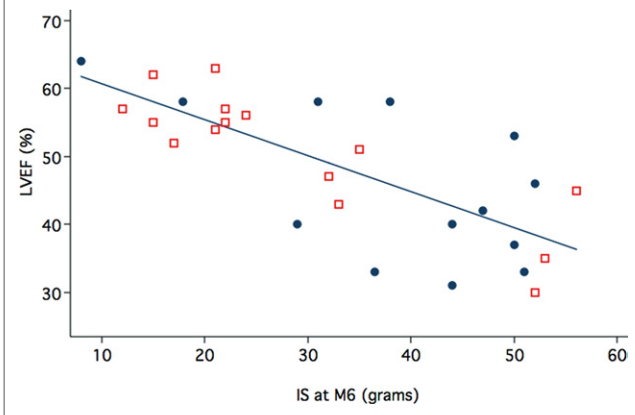

Figure 5 LVEF as a Function of IS 6 Months After Myocardial Infarction

There was a significant correlation between left ventricular ejection fraction (LVEF) and infarct size at 6 months ($r^2 = -0.72$; $p < 0.05$) in both groups. **Blue circles** = control group; **red squares** = cyclosporine. Abbreviations as in Figures 2 and 3.

Discussion

The present study suggests that cyclosporine administered in the acute phase of ST-segment elevation myocardial infarction before reperfusion does not have any detrimental effect on LV remodeling.

Absence of a detrimental effect of cyclosporine on LV remodeling. AMI induces scar formation and global changes in the surviving myocardium, designated as post-AMI ventricular remodeling. The early hypertrophic remodeling of the remote noninfarcted myocardium is considered an adaptive response to preserve cardiac performance. One signaling pathway that links extracellular stimuli to a hypertrophic transcrip-

Table 3 Left Ventricular Wall Thickness in the Infarcted Myocardium and in the Remote Nonischemic Myocardium at 5 Days and 6 Months

	Cyclosporine (n = 15)	Control (n = 13)
Infarcted myocardium, mm		
After 5 days		
EDWT	7.9 ± 2.0	7.5 ± 2.0
ESWT	8.7 ± 2.8	8.2 ± 2.9
After 6 months		
EDWT	6.7 ± 0.8	6.9 ± 0.8
ESWT	7.3 ± 0.6	8.1 ± 0.8
Remote myocardium, mm		
After 5 days		
EDWT	8.0 ± 1.4	8.4 ± 1.9
ESWT	12.7 ± 2.9	12.6 ± 2.6
After 6 months		
EDWT	8.8 ± 0.5	9.3 ± 0.6
ESWT	13.7 ± 0.5	15.0 ± 1.5

Values are expressed as mean ± SD. There were no statistical differences between groups as assessed by 2-way analysis of variance (p = NS).
EDWT = end-diastolic wall thickness; ESWT = end-systolic wall thickness.

tional response of the myocyte uses the Ca^{2+}/calmodulin-dependent phosphatase calcineurin and its downstream transcriptional effector nuclear factor of activated T cells. Cyclosporine binds to the mitochondrial cyclophilin D and thereby inhibits lethal reperfusion injury and reduces infarct size (2,3,9). However, cyclosporine also binds to the cytosolic cyclophilin A and inhibits the calcium-activated protein phosphatase calcineurin; it may therefore influence cardiac hypertrophic response and LV remodeling after AMI. The effects of cyclosporine on immediate and long-term post–myocardial infarction LV remodeling in animal experimental models have been equivocal. In some studies, cyclosporine was shown to impede the compensatory hypertrophy of the remote noninfarcted myocardium, increase LV dilation, and decrease the myocardial systolic performance (7,8).

We showed that cyclosporine had no detrimental effect on LV remodeling at 6 months. The regional modifications of infarcted and noninfarcted myocardium were not different between cyclosporine and control patients. This tends to suggest that a single dose of cyclosporine was enough to reduce infarct size, but not sufficient to modify the calcineurin-mediated hypertrophic response.

This apparent discordance between several experimental studies and the present clinical study may be associated with different factors. First, all experimental studies that found a detrimental effect of cyclosporine used repeated doses of this drug. In contrast, we used a single intravenous injection of cyclosporine. Second, we used a 2.5-mg/kg dose, which was 4 to 10 times lower than that used in the previously mentioned studies. Third, the timing of administration of cyclosporine differed greatly among all studies. Opening of the mitochondrial permeability transition pore has been shown to occur in the early minutes of reperfusion and represents a "point of no return" to cell death (10,11). Experimental studies using ischemic post-conditioning have shown that the time window to prevent lethal reperfusion injury is very narrow after reflow (12,13). This is the reason why cyclosporine was injected before angioplasty of the culprit coronary artery in this clinical trial.

Relationship between LV remodeling and persistent infarct size limitation by cyclosporine. At 6 months, cyclosporine–treated patients exhibited a 29% reduction of irreversible myocardial damage, very similar to that observed at 5 days (1). In previous studies, infarct size has been shown to be a major prognostic factor, predictive of increased LV remodeling, congestive heart failure, and clinical adverse outcome. In recent studies, when assessed at 4 months and up to 4 years, infarct size in multivariate analysis was one of the strongest independent predictors of ejection fraction and LV volumes independently of scar localization and transmurality (14). Other studies assessing LV remodeling at 6-month follow-up after AMI with echocardiography showed that peak troponin T and peak creatine phosphokinase levels, which are directly correlated with infarct size, were strong independent predictors of LV functional recovery (15,16). Thus, reducing the infarct size is an important target for the treatment of patients with ongoing acute myocardial infarction. Together with a persistent reduction of infarct size, we found that cyclosporine-treated patients displayed a significant attenuation of LVESV with a trend toward a diminution of LVEDV enlargement. The small number of patients likely explains the nonsignificant improvement of LVEF in the cyclosporine-treated patients compared with the control patients.

In the whole study population, the LV volumes and LVEF modifications followed patterns similar to those of previously published data in post-AMI LV remodeling CMR studies (14). Furthermore, we found comparable correlations between infarct size and LVEF, LVEDV, and LVESV with previously published data (17). The fact that the cyclosporine and the control groups share the same regression lines indicates that there was no specific effect of cyclosporine on LV remodeling and tells us that the observed trend toward improvement might be entirely due to infarct size reduction (Figs. 3 to 5).

Conclusions

This study shows that cyclosporine administered at the time of AMI reperfusion does not have a detrimental effect on LV remodeling. On the contrary, cyclosporine seems to have a sustained beneficial effect on infarct size reduction, which might improve the post-infarction remodeling process. These results are preliminary and must be supported by further studies.

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