The myocardial response to ischemic heart injury has two distinct phases. The first phase is infarction, namely cell death in the region of ischemia, which occurs within hours and reaches a maximal extent well within 2 days (24). The second phase is a reactive phase over weeks called remodeling during which a scar replaces the nonviable myocardium and other reactive changes occur globally in distal myocardium that originally was never ischemic (53). The extent of remodeling is proportional to infarct size (5, 37). After larger infarcts, remodeling can lead to apoptosis in distal myocardium, ventricular dilation, cardiac failure, and late cardiac death. An increase in cells undergoing apoptosis, as occurs in myocardium remote from the myocardial infarction (MI) region, is considered to be a factor that contributes to late adverse remodeling leading to left ventricular (LV) dilation and post-MI heart failure. Recent studies suggest that apoptotic cell death can be caused by mitochondrial inner membrane permeabilization and the onset of mitochondrial permeability transition (MPT) (12, 26, 28). Conversely, prevention of MPT onset can prevent apoptosis (1, 7, 41).

In various models of acute ischemia-reperfusion, in vitro and in vivo administration cyclosporin A (CsA), a blocker of the MPT, decreases cell death and infarct size associated with the early phase of ischemic heart injury (16, 18, 25, 38). However, the role of MPT specifically in the second late phase of remodeling after MI is unknown. Accordingly, the overall goal of this project was to determine whether and to what degree inhibition of the MPT by CsA can also attenuate the late phase of adverse LV remodeling after MI.

MATERIALS AND METHODS

Experimental design. C57BL/6 mice were subjected to coronary artery ligation and then randomized to vehicle (n = 15) and CsA (n = 15) treatment groups (Fig. 1). Beginning 48 h after surgery, mice were gavaged with CsA (2 mg/kg) or vehicle once daily. LV end-diastolic volume and LV ejection fraction were assessed by echocardiography before MI induction and terminal at either 7 days (n = 7) or 28 days (n = 8) post-MI. LV end-diastolic volume increased and LV ejection fraction decreased in all MI groups with no difference between the CsA-treated and untreated groups. After vehicle and CsA, areas of necrosis were present at 7 and 28 days post-MI with no difference between treatment groups. Caspase-3 activity and terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling in distal nonnecrotic LV both increased after MI but were lower in CsA-treated mice compared with vehicle (P < 0.05). In conclusion, CsA decreased apoptosis occurring late after MI, confirming involvement of a CsA-sensitive MPT in the cell death. However, CsA-mediated reduction in apoptosis in non-MI myocardium was not beneficial against late pump dysfunction occurring during post-MI remodeling.

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mediated nick-end labeling (TUNEL), and caspase activity measurement.

By tissue harvest for histology, terminal deoxynucleotidyl transferase dUTP-infarction (MI), at which time final echocardiography was performed followed by 14–28 days after MI for analysis of creatinine in serum by using a commercial kit (Pointe Scientific, Canton, MI). Histology. Hearts were fixed by immersion in 4% buffered paraformaldehyde for 24 h and embedded in paraffin. Sections (4 μm) were stained with hematoxylin and eosin. Necrosis was evaluated blindly by cell drop out, loss of architecture, karyolysis, increased basophilia, fibrosis, and presence of granulation tissue.

**Immunohistochemistry.** TUNEL was performed on paraffin sections by using an in situ cell death detection kit (Roche Diagnostics, Penzberg, Germany) according to the manufacturer’s directions. TUNEL-positive cells were counted blindly by light microscopy in 10 random high-power fields (HPF) of myocardium of remote nonnefarct, not-at-risk regions of the posterior wall of LV. Border zones were excluded, since border zones as relatively small transition regions are difficult to characterize unambiguously and reproducibly by techniques like TUNEL.

**Caspase-3 activity.** Heart tissue from remote noninfarcted regions of the posterior LV wall (~100 mg) was homogenized (Polytron PT-MR2100; Kinematica, Luzern, Switzerland) in 1 ml of lysis buffer containing 0.1% 3-[(3-Cholamidopropyl)-dimethylammonio]-1-propane sulfonate, 2 mM EDTA, 5 mM DTT, 1 mM pefabloc, 10 ng/ml pepstatin A, 10 ng/ml aprotinin, 20 μg/ml leupeptin, and 10 mM HEPES buffer (pH 7.4). The lysate were centrifuged at 15,000 rpm for 30 min. Activity of caspase-3 in the supernatant was determined using a caspase-3 colorimetric assay kit (R&D Systems, Minneapolis, MN) according to the manufacturer’s instructions. Activity was normalized to protein concentration of each sample and expressed as fold increase compared with heart tissue from control mice.

**Statistical analysis.** Data are presented as means ± SE. Statistical analysis of was performed by ANOVA and Student-Newman-Keuls test, as appropriate, using P < 0.05 as the criterion of significance. Statistical analysis for survival was assessed by Kaplan-Meier test for 28-day post-MI survival. All statistical procedures were performed using the Sigma Plot statistical software package (Systat Software, San Jose, CA). Final sample sizes for each experiment are indicated in the figure legends.

**RESULTS**

**CsA nephrotoxicity.** Although kidney histology after MI in all groups was indistinguishable (data not shown), CsA at a dose of 10 mg/kg increased serum creatinine on day 7 (Fig. 2), indicating nephrotoxicity, and this dosage was therefore discontinued. By contrast, serum creatinine in mice receiving 2 mg/kg of CsA was similar to that of non-CsA-treated mice (Fig. 2).

**Survival in the presence or absence of CsA.** Survival through 28 days after MI was 75% with vehicle treatment and 87.5% after CsA treatment. The difference in survival between CsA and vehicle-treated groups was not significant. Operative mortality within 12 h of LAD ligation was about 15% in all groups.
Operative and long-term mortality was similar to previous findings in this model (21, 31).

Heart histology. Heart injury was assessed histologically at day 7 and day 28 postoperatively by hematoxylin and eosin staining in whole transverse heart sections. Heart histology was normal in unoperated control (non-MI) mice, and no signs of necrosis (vacuolization, loss of architecture, etc.) were present. After vehicle or CsA treatment, large areas of necrosis (30–35%) were present at day 7 and day 28 post-MI. Percentage of necrosis was calculated in transverse sections going through the center of the anterior wall infarct by the ratio of the area of necrosis to the total area of the heart. There was no difference in the amount of necrosis between MI groups with and without CsA treatment (Fig. 3).

LV geometry, ejection fraction, and lung weight. LV end-diastolic volume (LVEDV) and LV ejection fraction were used to assess LV geometry and pump function. On day 7 and day 28 post-MI, LVEDV increased in both MI groups compared with baseline values (Fig. 4A and Table 1). However, LVEDV was not different between the vehicle and CsA groups. LV ejection fraction decreased in all MI groups compared with baseline values. CsA treatment did not show any beneficial effect on LV pump function post-MI (Fig. 4B).

The ratio of lung weight to tibia length at 7 days post-MI (8.24 ± 0.31 mg/mm) after vehicle treatment was not different from control mice (8.65 ± 0.09 mg/mm; P = 0.6). At 28 days post-MI, however, the ratio of lung weight to tibia length increased (10.69 ± 0.30 mg/mm) compared with that of control mice (P < 0.05), suggesting pulmonary edema that was likely due to developing heart failure (Table 1). When compared to vehicle treatment, CsA treatment did not alter the increase of lung weight-to-tibia length ratio at 28 days post-MI (Table 1).

Heart apoptosis after CsA. TUNEL was performed on remote noninfarcted myocardium of posterior LV areas that excluded border zones near infarct regions to assess double-stranded DNA breaks that are characteristic of apoptosis. TUNEL-positive cells were rare in control mice, averaging less than 1 cell/HPF (Fig. 5A). On day 7 post-MI, TUNEL increased to 3.0 cells/HPF in the vehicle group, which decreased with CsA treatment (2.15 cells/HPF; Fig. 5A). On day 28 post-MI, TUNEL again decreased significantly from 2.94 cells/HPF after vehicle to 1.98 cells/HPF after CsA (Fig. 5A). By histological criteria, TUNEL-labeled cells were predominantly myocardial muscle fibers (data not shown).

Caspase-3 activity. To investigate further the extent of apoptosis after CsA treatment, caspase-3 activity was measured in homogenates of regions remote to the infarcted LV on days 7 and 28 post-MI (Fig. 5B). On day 7 after vehicle treatment, post-MI caspase-3 increased 2.26-fold compared with untreated, non-MI mice, which was decreased to 1.93-fold by CsA treatment (P < 0.05). On day 28 post-MI, caspase-3 activity also decreased from 2.13-fold after vehicle to 1.54-fold after CsA (Fig. 5B; P < 0.05). Thus, CsA treatment significantly decreased caspase-3 activity at both day 7 and day 28 post-MI. There was no correlation between LV mass and TUNEL or between LV mass and caspase-3 activity (data not shown).

Fig. 3. Heart histology post-MI. Mice were subjected to LAD occlusion, as described in Fig. 1. A–C, E, and F: necrosis was assessed by hematoxylin-eosin staining in control, vehicle, and CsA (2 mg/kg) treatment groups on days (d) 7 and 28. D: percentage infarction area is plotted as combined from data for 7 and 28 days for the indicated treatment groups. n = 5–7 per group. ND, none detected.
and 28 days after myocardial infarction. Table 1. Tibia length, body weight, LV mass, and LV end-diastolic and end-systolic posterior wall thicknesses before (baseline) 7 and 28 days after myocardial infarction.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (7 Days)</th>
<th>Vehicle (7 Days)</th>
<th>Cyclosporin A (7 Days)</th>
<th>Vehicle (28 Days)</th>
<th>Cyclosporin A (28 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia length, mm</td>
<td>17.83 ± 0.16</td>
<td>18.44 ± 0.22</td>
<td>18.26 ± 0.38</td>
<td>18.14 ± 0.21</td>
<td>18.27 ± 0.22</td>
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<tr>
<td>Body weight, g</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Terminal</td>
<td>29.13 ± 0.89</td>
<td>27.26 ± 1.72</td>
<td>27.62 ± 0.96</td>
<td>28.25 ± 1.19</td>
<td>27.03 ± 0.85</td>
</tr>
<tr>
<td>LV mass, mg</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>82.29 ± 1.85</td>
<td>100.15 ± 8.29</td>
<td>106.90 ± 9.91</td>
<td>110.28 ± 8.62</td>
<td>105.22 ± 4.22</td>
</tr>
<tr>
<td>Terminal</td>
<td></td>
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<tr>
<td>LV wall thickness, mm</td>
<td></td>
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<tr>
<td>Baseline</td>
<td></td>
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<tr>
<td>Terminal (myocardial infarction)</td>
<td>0.76 ± 0.010</td>
<td>0.63 ± 0.045</td>
<td>0.61 ± 0.042</td>
<td>0.58 ± 0.035*</td>
<td>0.59 ± 0.025*</td>
</tr>
<tr>
<td>Lung weight-to-tibia length ratio</td>
<td>8.65 ± 0.09</td>
<td>8.24 ± 0.31</td>
<td>8.34 ± 0.46</td>
<td>10.69 ± 0.30*</td>
<td>11.04 ± 1.00*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LV, left ventricular. *P < 0.05 vs. control.
for CsA is cyclophilin D (CypD). CypD deficient (CypD−/−) dogs with heart failure (45). CsA also protects mitochondria. In vitro, CsA attenuates the MPT and improves mitochondrial respiratory function in cardiomyocytes isolated from mitochondria into the cytosol, which triggers caspase-dependent apoptosis, and release of cytochrome c from the intermembrane space into the cytosol, which triggers caspase-dependent apoptosis. In vitro, CsA attenuates the MPT and improves mitochondrial respiratory function in cardiomyocytes isolated from dogs with heart failure (45). CsA also protects mitochondria from calcium overload (18). The mitochondrial binding partner for CsA is cyclophilin D (CypD). CypD deficient (CypD−/−) mice are resistant to infarction and detrimental LV remodeling after MI (2). Moreover, CsA has been reported to preserve mitochondrial morphology in the heart after ischemia-reperfusion (29).

The myocardial response to ischemic injury to the heart has two phases. The early phase leads to ischemic infarction and is complete within 2 days, whereas the late phase of remodeling involves the left ventricle globally and evolves over weeks. Previous studies showed that inhibition of the MPT during the early phase of ischemic injury decreases infarct size (16, 38). However, the possible role of the MPT in late LV remodeling has not been determined. Therefore, our overall goal was to evaluate the therapeutic efficacy of CsA in an in vivo model of LV remodeling after acute MI and, specifically, to determine whether CsA decreases apoptosis and improves myocardial function occurring late after an MI. After an MI, the workload on the remnant viable myocardium increases with a concomitant increase of intracellular free Ca2+ and respiration-dependent reactive oxygen species formation; this may then predispose to MPT pore opening (27). Because the MPT causes mitochondrial dysfunction and cell death, a vicious cycle may then develop of fewer and fewer cells doing progressively more work and being exposed to even more Ca2+ and reactive oxygen species. The consequence is a downward spiral to cell death and heart failure (27). Accordingly, we evaluated this hypothetical scenario that the MPT plays a major role in adverse LV remodeling post-MI. Remote noninfarcted, not-at-risk regions of myocardium were chosen for our analysis over border zones, since our goal was to determine whether a CsA-sensitive MPT contributes to post-MI apoptosis and remodeling in myocardium never actually subjected to ischemic stress.

In post-MI mice treated with CsA, myocardial apoptosis and caspase-3 activation in the viable, remote myocardium decreased in comparison with vehicle treatment (Fig. 5). Necrosis was unlikely to account for changes of measures of apoptosis, because 1) TUNEL and caspase-3 activity were measured in remote, noninfarcted myocardium; 2) although necrosis can cause some DNA strand breaks, TUNEL distinguishes the much greater number of DNA strand breaks in apoptotic cells and differentiates apoptotic from necrotic cells (15, 17, 22); and 3) caspase-3 activation is very specific for apoptosis (23, 39). CsA is a specific MPT blocker, which binds and inhibits CypD, a peptidyl prolyl isomerase that regulates MPT pore conductance (11, 18). CsA is also an immunosuppressant working via inhibition of cyclophilin A. Overall, these findings are consistent with the conclusion that the CsA-sensitive MPT occurs in the remaining viable myocardium after MI, as implied previously (29, 30).

Lymphocytes also influence LV remodeling. Different lymphocyte populations have different effects on LV remodeling, namely natural killer T cells ameliorate LV remodeling post-MI, whereas γδT cells contribute to adverse LV remodeling (47, 50). CsA inhibits immune cell-activating cyclophilin A comparably with CypD in mitochondria (8). The main conclusion of the present study is that decreased apoptosis by CsA administered 2 days after coronary artery ligation did not translate into protection against adverse LV remodeling over longer post-MI periods. However, the effects of CsA on lymphocytes—or inflammatory cytokines—in the post-MI setting were not examined here. Future studies will be needed to determine the effects of CsA on lymphocytes during remodeling.

CsA is protective at lower concentrations (0.5 to 2 μM), but protection is lost at higher concentrations (≥5 μM), giving the drug a rather narrow therapeutic window (33). Because CsA at a dose 2 mg/kg decreased apoptosis as assessed by TUNEL and caspase-3 but at a higher dose of 10 mg/kg caused nephrotoxicity (Fig. 2), which is characteristic of excessive CsA dosage (34), we continued our study only with the lower dosage. Infarct size is a major determinant of the extent and severity of post-MI remodeling (5, 37). Because myocardial death may continue for up to 40 h post-MI (24), mice began to receive CsA at 48 h after coronary artery ligation to preclude the possibility that CsA treatment was decreasing infarct size and...
hence attenuating adverse remodeling. Indeed, infarct size in CsA- and vehicle-treated mice was not different (Fig. 3).

Although CsA decreased post-MI apoptosis in remote myocardium, this attenuation of apoptosis did not translate into improvement of LV pump function at 7 or 28 days post-MI (Fig. 4B). By contrast, in CypD−/− mice, LV pump function is improved versus wild-type mice on days 2 and 28 post-MI (30). However, infarct size in CypD−/− mice is smaller than in wild-type, which likely explains improved myocardial function post-MI (30). By contrast in the present study, CsA was added 48 h after MI induction, and infarct size was the same in the CsA- and vehicle-treated groups (Fig. 3). Thus the favorable effect on LV pump function in CypD−/− mice is likely due to suppression of the CypD-dependent MPT at the time of ischemia (16, 38). In the present study, the effects of CsA on LV remodeling were examined only through 28 days post-MI. Whether longer administration of CsA might improve LV geometry and function will require further investigation.

In conclusion, CsA decreased apoptosis occurring in remote, viable myocardium after MI, confirming involvement of the MPT. However, CsA-mediated reduction in apoptosis in non-MI myocardium was not beneficial in preventing or attenuating late LV dilation and heart failure post-MI. Because the CsA-mediated decrease of apoptosis in non-MI myocardium was not beneficial to decrease in LV volume or improve in LV pump function post-MI, we suggest that the CsA-sensitive MPT, although decreasing infarct size in the early phase of ischemic injury, likely does not play an important role in late-phase adverse LV remodeling for at least 28 days post-MI.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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