Synthetic High-Density Lipoproteins Exert Cardioprotective Effects in Myocardial Ischemia/Reperfusion Injury

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ABSTRACT

Human high-density lipoproteins (HDLs) protect the heart against ischemia/reperfusion injury. In the present study, the cardioprotective effects of synthetic high-density lipoproteins (sHDLs) made of phosphatidylcholine and apolipoprotein A-I were investigated in isolated rat hearts, which underwent a 20-min low-flow ischemia followed by a 30-min reperfusion. The administration of sHDL during the 10 min immediately before ischemia caused a rapid, dose-dependent improvement of postischemic cardiac function: at the maximum dose (2.0 mg of sHDL protein/ml), left ventricular developed pressure (LVDP) recovered to 71.0 ± 3.2 versus 40.5 ± 3.8 mm Hg in saline-treated hearts, and coronary perfusion pressure (CPP) increased to 100.3 ± 6.2 versus 132.0 ± 9.0 mm Hg. The preservation of postischemic cardiac function was associated with a dose-dependent reduction of creatine kinase release into the coronary effluent. sHDLs administered in the first 10 min postischemia also exerted a significant, dose-dependent improvement of postischemic LVDP, CPP, and creatine kinase release, but the cardioprotective effect was less than when sHDLs were given preischemia. The preservation of postischemic cardiac function by sHDL was mediated through a reduction of cardiac tumor necrosis factor-α content and an enhanced cardiac production of prostaglandin E2 and I2. The present experimental data indicate that sHDLs may provide a novel therapeutic approach to clinical conditions in which myocardial ischemia/reperfusion occurs, such as acute coronary syndromes, cardiac surgery, or revascularization procedures.

Cardiovascular diseases that are initiated by tissue ischemia remain the chief cause of death in the industrialized world. The high morbidity and mortality of these diseases have focused the attention of physicians on restoring coronary blood flow to resuscitate the ischemic or hypoxic myocardium. Timely reperfusion indeed facilitates cardiomyocyte salvage and decreases cardiac morbidity and mortality. Reperfusion of an ischemic area may result, however, in paradoxical cardiomyocyte damage, thereby limiting the recovery of function (Carden and Granger, 2000). Cardiac dysfunction induced by ischemia/reperfusion (I/R) is now recognized as a potentially serious problem that is encountered during an acute coronary syndrome, or a variety of standard medical and surgical procedures, such as thrombolytic therapy, coronary angioplasty, organ transplantation, and cardiopulmonary bypass (Carden and Granger, 2000).

A low plasma high-density lipoprotein (HDL) cholesterol level has been associated with a high risk of ischemic heart disease in many case-control and prospective studies (Gordon and Rifkind, 1989). The mechanism(s) behind this inverse correlation has been the object of intense investigation. There is a general agreement that HDL may protect the arterial wall against the development of atherosclerotic lesions by removing lipids (Yancey et al., 2003) and limiting endothelial dysfunction (Calabresi et al., 2003a). A low plasma HDL cholesterol has been also associated with unfavorable prognosis after an acute ischemic event (Berge et al., 1982; Miller et al., 1992). This association may reflect either accelerated atherogenesis or a direct detrimental effect of a low HDL level on postischemic cardiac function. We recently showed a direct cardioprotective effect of plasma-derived human HDL against I/R injury, which is mediated through a reduced cardiac tumor necrosis factor-α (TNF-α) content and an enhanced cardiac prostaglandin release (Calabresi et al., 2003b). Human plasma HDLs are heterogeneous in size, lipid, and protein composition (Skinner, 1994). Most of their functions

ABBREVIATIONS: I/R, ischemia/reperfusion; HDL, high-density lipoprotein; TNF-α, tumor necrosis factor-α; sHDL, synthetic high-density lipoprotein; EPC, egg phosphatidylcholine; CPP, coronary perfusion pressure; LVDP, left ventricular developed pressure; PBS, phosphate-buffered saline; ELISA, enzyme-linked immunosorbent assay; ROS, reactive oxygen species; CAM, cell adhesion molecule.
can be mimicked by well defined, apolipoprotein-specific synthetic HDLs (sHDLs) made of phosphatidylcholine and apolipoprotein A-I, the major lipid and protein constituents of plasma HDL (Calabresi et al., 1997a,b, 1999; Deakin et al., 2002). These sHDLs have been proposed as novel therapeutic tools for a variety of cardiovascular diseases (Sirtori et al., 1999). The purposes of the present study were to 1) examine the effect of sHDL, given either before or after ischemia, on cardiac function in isolated rat hearts subjected to I/R injury; 2) establish the dose-response relationship of sHDL in this setting; and 3) investigate the mechanism of the cardioprotective effect of sHDL.

Materials and Methods

Preparation of sHDL. Apolipoprotein A-I was purified from human blood plasma (Calabresi et al., 1997b); sHDLs were prepared by mixing apolipoprotein A-I and egg phosphatidylcholine (EPC; Sigma-Aldrich Chemie GmbH, Steinheim, Germany) at a weight ratio of 1:2.5, as described previously (Calabresi et al., 1997b). Preparations were dialyzed against sterilized saline immediately before use. Protein and EPC contents were measured as described previously (Calabresi et al., 1997b).

Isolated Rat Heart Preparation. Male Sprague-Dawley rats weighing 200 to 250 g were anesthetized with sodium pentobarbital (50 mg/kg i.p.). The hearts were rapidly excised, placed in ice-cold Krebs-Henseleit buffer (118 mM NaCl, 2.8 mM KCl, 1.2 mM KH2PO4, 2.5 mM CaCl2, 1.2 mM MgSO4, 25 mM NaHCO3, and 5.5 mM glucose), and mounted for retrograde perfusion at 37°C through the aorta, as described previously (Rossoni et al., 1998). A saline-filled latex balloon, connected to a pressure transducer, was inserted into the left ventricular cavity. A latex balloon, connected to a pressure transducer, was inserted into the left ventricular cavity. Left ventricular pressure, coronary perfusion pressure (CPP), and left ventricular developed pressure (LVDP) were monitored as described previously (Calabresi et al., 1997b).

Treatments. sHDLs diluted into Krebs-Henseleit buffer at a flow rate of 15 ml/min for 30 min. I/R was carried out as described previously (Calabresi et al., 1997b). The hearts were equilibrated with Krebs-Henseleit buffer at a flow rate of 15 ml/min for 30 min. A moderate ischemia was induced by reducing the perfusion flow rate to 1 ml/min for 20 min; the normal flow rate (15 ml/min) was then restored, and reperfusion continued for 30 min. Immediately at the end of the experiment, hearts were snap-frozen in liquid nitrogen and stored at −80°C. Cardiac homogenates were prepared by grinding tissue under liquid nitrogen with Micro Dismembrator 2. The investigation conformed with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health, National Institutes of Health Publication 85-23, (revised 1986).

Cardiac TNF-α Content. The myocardial homogenate was suspended in PBS containing 31 nmol/ml aprotinin, 1 mM phenylmethylsulfonyl fluoride, and 1% Triton X-100. After 1-h incubation at 4°C, the homogenate was centrifuged for 20 min at 20,000g at 4°C. The supernatant was dialyzed overnight against PBS to eliminate Triton X-100, which interferes with the following analyses. Protein and TNF-α contents were measured by the method of Lowry et al. (1951) and by a sandwich ELISA specific for rat TNF-α (Endogen Inc., Woburn, MA), respectively.

Statistical Analysis. Results are reported as means ± S.E.M. Group differences in continuous variables were determined by variance analysis. Pearson correlation coefficients were computed to assess the association between parameters. A stepwise regression analysis was performed by entering the independent variable with the highest partial correlation coefficient at each step, until no variable remained with an F value of 4 or more. Group differences or correlations with p < 0.05 were considered as statistically significant.

Results

Effect of sHDLs on Cardiac Dysfunction in I/R Hearts. Baseline (initial) LVDP and CPP values were similar in all saline-perfused hearts (90.2 ± 7.3 and 70.1 ± 5.0 mm Hg, respectively) (Fig. 1). Twenty minutes of low-flow ischemia followed by reperfusion caused a severe cardiac dysfunction, manifested by decreased LVDP and enhanced CPP (Fig. 1). LVDP recovered only partially on reperfusion (40.5 ± 3.8 mm Hg, 30 min after reperfusion); CPP rapidly increased, reaching a maximum (132.0 ± 9.0 mm Hg) 3 min after reperfusion, slightly declining thereafter (to 124.0 ± 7.5 mm Hg, 30 min after reperfusion) (Fig. 1). These functional changes were accompanied by a remarkable release of creatine kinase into the coronary effluent during reperfusion, indicative of a disruption of the cardiac myocyte membrane. During equilibration and ischemia, creatine kinase activity in the coronary effluent did not change, ranging between 38 and 48 mU/min/g wet tissue; it increased immediately after ischemia, reaching a maximum (367 ± 35 mU/min/g wet tissue) 10 min after reperfusion.

Baseline LVDP and CPP values in sHDL-treated I/R hearts (89.8 ± 6.6 and 68.5 ± 6.2 mm Hg, respectively) did not differ from those of saline-perfused I/R hearts. sHDL given preischemia remarkably attenuated the I/R-induced myocardial dysfunction, as indicated by relative preservation of LVDP and minimization of increase in CPP (Fig. 1); at the maximum dose (2.0 mg of protein/ml), LVDP recovered to 71.0 ± 4.5 mm Hg (30 min after reperfusion) and CPP increased to a maximum of 100.3 ± 6.2 mm Hg (3 min after reperfusion), and then declined to 80.2 ± 3.8 mm Hg (30 min after reperfusion). The cardioprotection by sHDL was dose-dependent (LVDP: F = 18.5; CPP: F = 55.6; both p values < 0.001) (Table 1), with a minimal effective dose of 0.5 mg/ml (LVDP and CPP of 44.3 ± 2.8 mm Hg and 122.0 ± 5.2 mm Hg, 30 and 5 min after reperfusion, respectively) (Fig. 1). The
Cardioprotective Effects of Synthetic HDL

Postischemic cardiac function and creatine kinase release in I/R hearts

**TABLE 1**

Postischemic cardiac function and creatine kinase release in I/R hearts

Concentrations are reported as milligrams of protein per milliliter of buffer. Results are expressed as area under the curve estimated accordingly to the trapezoid method (LVDP and CPP: in ordinate, mm Hg; in abscissa, time; creatine kinase: in ordinate, μU/min/g wet tissue; in abscissa, time) from data recorded during the 30 min of reperfusion (mean ± S.E.M., n = 5 for each treatment group).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LVDP (μU/min/g)</th>
<th>CPP (μU/min/g)</th>
<th>Creatine Kinase Release (μU/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>898 ± 51</td>
<td>1616 ± 94</td>
<td>5554 ± 361</td>
</tr>
<tr>
<td>shHDL (0.5 mg/ml) preischemia</td>
<td>1055 ± 132*</td>
<td>1305 ± 63*</td>
<td>4390 ± 305*</td>
</tr>
<tr>
<td>shHDL (1.0 mg/ml) preischemia</td>
<td>1467 ± 93**</td>
<td>947 ± 66**</td>
<td>3155 ± 183**</td>
</tr>
<tr>
<td>shHDL (2.0 mg/ml) preischemia</td>
<td>1777 ± 75**</td>
<td>447 ± 31**</td>
<td>2060 ± 138**</td>
</tr>
<tr>
<td>shHDL (1.0 mg/ml) postischemia</td>
<td>1106 ± 65*</td>
<td>1292 ± 80*</td>
<td>3974 ± 110*</td>
</tr>
<tr>
<td>shHDL (2.0 mg/ml) postischemia</td>
<td>1548 ± 62**</td>
<td>765 ± 41**</td>
<td>2741 ± 148**</td>
</tr>
</tbody>
</table>

Creatine kinase, creatinephosphokinase.

*p < 0.05; **p < 0.001 versus saline.

**Fig. 1.** Changes in cardiac function during I/R in isolated rat hearts perfused with saline (circles) or sHDLs at 0.5 mg/ml (triangles), 1.0 mg/ml (inverted triangles), and 2.0 mg/ml (squares) during the 10 min immediately before ischemia. Results are means ± S.E.M., n = 5 for each treatment group.

Preservation of postischemic cardiac function in sHDL-treated I/R hearts was associated with a dose-dependent reduction of postischemic creatine kinase release into the coronary effluent (F = 33.3; p < 0.001) (Table 1); with the maximum dose, the highest creatine kinase activity in the coronary effluent was limited to 220 ± 19 μU/min/g wet tissue.

sHDLs administered postischemia also exerted a significant, dose-dependent improvement of postischemic LVDP (F = 31.0; p < 0.001) and CPP (F = 32.7; p < 0.001), but the cardioprotective effect was less than when sHDLs were given preischemia (Table 1). At the maximum dose, LVDP recovered to 61.0 ± 3.2 mm Hg (30 min after reperfusion), and CPP increased to a maximum of 116.6 ± 11.0 mm Hg (5 min after reperfusion) and then declined to 90.8 ± 6.8 mm Hg (30 min after reperfusion). A parallel, dose-dependent reduction of creatine kinase release into the coronary effluent was observed (F = 36.3; p < 0.001) (Table 1).

**Cardiac TNF-α Content and Prostaglandin Release.** TNF-α release is one of the earliest deleterious events in response to a variety of forms of I/R injury (Frangogiannis et al., 2002), and plasma-derived HDL are able to remove TNF-α from the ischemic myocardium, thus limiting its damaging effects (Calabresi et al., 2003b). Tissue homogenates of control and I/R hearts were thus assayed for TNF-α content.

As expected, saline-perfused I/R hearts had a 50% higher cardiac TNF-α content than control hearts (Fig. 2). sHDL given preischemia caused a dose-dependent reduction of cardiac TNF-α content compared with saline-perfused I/R hearts (F = 13.6; p < 0.001) (Fig. 2); at the maximum dose, sHDL completely blunted the rise of cardiac TNF-α. sHDLs administered postischemia also reduced, in a dose-dependent manner, cardiac TNF-α content (F = 6.6; p = 0.012), but less effectively than when given preischemia; at the maximum dose, the cardiac TNF-α content was still 13% higher than in control, non-I/R hearts (Fig. 2). The reduction of cardiac TNF-α in sHDL-treated I/R hearts was paralleled by an increase in TNF-α release into the coronary effluent (Fig. 2); when data from control, saline-perfused, and sHDL-treated I/R hearts were analyzed together, a significant inverse correlation was found between cardiac and coronary effluent TNF-α contents (r = −0.793; p < 0.001). The sHDL-mediated removal of TNF-α from the hearts was highly significantly correlated with the improved postischemic cardiac function and with the limited cardiomyocyte damage. When data from all experiments were analyzed together, cardiac TNF-α correlated negatively with postischemic LVDP (r = −0.795; p < 0.001) and positively with postischemic CPP (r = 0.735; p < 0.001) and creatine kinase release (r = 0.784; p < 0.001).

Another mechanism by which plasma-derived HDLs limit postischemic cardiac dysfunction is to amplify the defensive response elicited by the myocardium through enhanced prostaglandin production (Calabresi et al., 2003b). To verify whether this is true also for sHDL, aliquots of the coronary effluent collected immediately before or after ischemia were assayed for prostaglandin I2 and E2 content. sHDLs given preischemia caused a dose-dependent increase of baseline cardiac prostaglandin I2 and E2 content compared with saline-perfused I/R hearts (F = 8.9 and 11.8, respectively, both p values < 0.001) (Table 2). No changes were found when sHDLs were given postischemia. As expected, ischemia caused a 4-fold increase in the release of cardiac prostaglandins into the coronary effluent of saline-perfused I/R hearts.
respectively, both p values p = 0.001 and 0.025, respectively; together, they explained 69.6% of the variation in postischemic LVDP. Cardiac TNF-α and postischemic prostaglandin E₂ release independently predicted creatine kinase release at reperfusion (F = 17.1, 6.4, and 4.4; p < 0.001, p = 0.18, and p = 0.046, respectively); the three parameters together explained 78.3% of the variation in creatine kinase release.

A stepwise regression analysis was performed on all data to identify the independent predictors of improved cardiac function and limited cardiomyocyte damage in sHDL-treated hearts. Both the reduction of cardiac TNF-α and the increase of postischemic prostaglandin E₂ release independently predicted postischemic LVDP recovery (F = 28.6 and 5.6; p < 0.001 and p = 0.025, respectively); together, they explained 69.6% of the variation in postischemic LVDP. Cardiac TNF-α and postischemic prostaglandin E₂ and I₂ release independently predicted cardiac TNF-α and enhancing protection by prostaglandins, i.e., in a way that reproduces the effects of plasma-derived HDLs (Calabresi et al., 2003b). Indeed, both plasma-derived and synthetic HDLs bind and neutralize TNF-α in the heart, down-regulate cardiac TNF-α expression, and enhance cardiac prostacyclin production, by providing the arachidonate substrate for prostanooid synthesis (Pomerantz et al., 1985) and by inducing the cyclooxygenase-2 enzyme (Vinals et al., 1999). Moreover, HDLs may act as antioxidants (Banka, 1996), thus preventing the damaging effects of reactive oxygen species (ROS) on the heart (Carden and Granger, 2000). This multiple mode of action seems unique to HDLs, because other agents that have shown cardioprotective effects in this same ischemia/reper-

Discussion

The present study in an isolated heart model demonstrates that sHDLs provide marked protection against I/R-induced cardiac dysfunction. sHDLs are cardioprotective when given either before or after ischemia, but cardioprotection is higher when sHDLs are given preischemia. The cardioprotective effect is dose-dependent and is mediated through a reduction of cardiac TNF-α content and an increase of cardiac prostaglandin release. These findings suggest that sHDLs may provide a novel therapeutic approach directed to the reduction of myocardial I/R injury.

In the present study, the isolated hearts were buffer-perfused according to the Langendorff technique, thus excluding the influence of hemodynamic factors, blood cells, and constituents. Therefore, in this particular experimental setting, the I/R-induced cardiac dysfunction is the result of a balance between the effects of damaging and protective responses generated within the heart. sHDLs preserve myocardial function by both limiting the damaging effects of TNF-α and enhancing protection by prostaglandins, i.e., in a way that reproduces the effects of plasma-derived HDLs (Calabresi et al., 2003b). Indeed, both plasma-derived and synthetic HDLs bind and neutralize TNF-α in the heart, down-regulate cardiac TNF-α expression, and enhance cardiac prostacyclin production, by providing the arachidonate substrate for prostanooid synthesis (Pomerantz et al., 1985) and by inducing the cyclooxygenase-2 enzyme (Vinals et al., 1999). Moreover, HDLs may act as antioxidants (Banka, 1996), thus preventing the damaging effects of reactive oxygen species (ROS) on the heart (Carden and Granger, 2000). This multiple mode of action seems unique to HDLs, because other agents that have shown cardioprotective effects in this same ischemia/reper-

![Graph](image_url)

**Fig. 2.** TNF-α content of cardiac homogenate (top) and coronary effluent (bottom) from nonischemic rat hearts (control), I/R hearts perfused with saline, and I/R hearts treated with sHDL either pre- or postischemia. Results are means ± S.E.M., n = 5 for each treatment group.

A further dose-dependent enhancement of postischemic prostaglandin I₂ and E₂ release was observed when sHDLs were given either preischemia (F = 20.0 and 12.4, respectively, both p values < 0.001) or postischemia (F = 6.9 and 5.4; p = 0.01 and 0.021, respectively) (Table 2). When data from all experiments were analyzed together, a significant correlation was found between postischemic cardiac function, assessed as LVDP, and postischemic prostaglandin I₂ and E₂ release (r = 0.637 and 0.611, respectively; both p values < 0.001).

**Table 2**

Prostaglandin release in the coronary effluent of I/R hearts.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Postischemia</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prostaglandin I₂ (ng/min)</td>
<td>Prostaglandin E₂ (ng/min)</td>
<td>Prostaglandin I₂ (ng/min)</td>
</tr>
<tr>
<td>Saline</td>
<td>2.02 ± 0.11</td>
<td>3.53 ± 0.17</td>
<td>9.10 ± 0.61</td>
</tr>
<tr>
<td>sHDL (0.5 mg/ml) preischemia</td>
<td>2.41 ± 0.25</td>
<td>3.98 ± 0.33</td>
<td>10.32 ± 0.67</td>
</tr>
<tr>
<td>sHDL (1.0 mg/ml) preischemia</td>
<td>2.80 ± 0.15*</td>
<td>4.75 ± 0.12*</td>
<td>12.88 ± 0.47*</td>
</tr>
<tr>
<td>sHDL (2.0 mg/ml) preischemia</td>
<td>3.17 ± 0.14**</td>
<td>5.21 ± 0.20**</td>
<td>14.45 ± 0.36**</td>
</tr>
<tr>
<td>sHDL (1.0 mg/ml) postischemia</td>
<td>2.06 ± 0.20</td>
<td>3.58 ± 0.23</td>
<td>10.52 ± 0.91</td>
</tr>
<tr>
<td>sHDL (2.0 mg/ml) postischemia</td>
<td>2.24 ± 0.12</td>
<td>3.62 ± 0.13</td>
<td>12.62 ± 0.40*</td>
</tr>
</tbody>
</table>

*p < 0.01; **p < 0.001 versus saline.
fusion model either neutralize TNF-α (Calabresi et al., 2003b), enhance prostacyclin production (Rossoni et al., 1999), or act as prostacyclin analogs (Berti et al., 1993).

sHDLs seem to be less effective than plasma HDLs, suggesting that some components of plasma HDL, not included into sHDL, may participate in the cardioprotective action. Plasma HDLs carry substantial amounts of arachidonate, which was shown to be used as a substrate for prostanooid production by cultured rabbit arterial smooth muscle cells (Pomerantz et al., 1984) and by Langendorff-perfused rabbit heart (Van Sickle et al., 1986a,b). The sHDLs used in the present experiments are made with EPC, which contains very little arachidonate, and less prostaglandins are indeed found in the coronary effluent of sHDL-treated I/R hearts (the present study) compared with I/R hearts treated with the same dose of plasma HDLs (Calabresi et al., 2003b).

sHDLs remove less TNF-α from the ischemic myocardium than plasma HDLs, suggesting a lower TNF-α binding capacity (Calabresi et al., 2003b). Finally, various antioxidant enzymes, as paraoxonase, platelet activating factor-acetylhydrolase, and lecithin:cholesterol acyltransferase are bound to plasma HDLs and can contribute to cardioprotection by limiting the damaging effects of oxygen radicals to the myocardium (Lefer and Granger, 2000). Whether the addition of these enzymes, which can be produced through recombinant DNA technology (Tjoelker et al., 1995; Jin et al., 1997; Brushia et al., 2001), to sHDLs may improve their cardioprotective activity remains to be established.

sHDLs are cardioprotective when given either before ischemia or at the onset of reperfusion. Although the cardioprotective effect is higher when sHDLs are administered before or soon after the onset of ischemia and continued through late reperfusion, is required to eliciting maximum benefit. Although the experimental setting used in the present study limits the observation to the earliest events in I/R injury, there is compelling in vitro and in vivo evidence that sHDLs may also affect later events in I/R injury. The development of cardiac dysfunction after I/R injury involves up-regulation of cell adhesion molecules (CAMs) on the endothelial surface, which triggers the adhesion, activation, and transmigration of leukocytes into myocardial tissue, and the subsequent release of ROS. These ROS sustain leukocyte adhesion by activating genes that encode adhesion molecules (Collins et al., 1995) and directly cause cardiac dysfunction and tissue necrosis, via lipid peroxidation, protein oxidation, and DNA damage (Lefer and Granger, 2000). sHDLs may inhibit the up-regulation of CAM expression (Calabresi et al., 1997b) through a reduction of cardiac TNF-α content (as shown here) and a perturbation of TNF-α signaling pathways at postreceptor sites (Calabresi et al., 2003a), thus limiting leukocyte adhesion (Cockerill et al., 2001) and subsequent tissue infiltration (Shah et al., 1998, 2001). Moreover, apolipoprotein A-I, the protein component of sHDLs, may inhibit the production of ROS by activated leukocytes (Blackburn et al., 1991) and inactivate lipid peroxides (Garner et al., 1998).

sHDLs can be produced on a large scale and can be safely administered, even at high doses, to human subjects (Sirtori et al., 1999). Such sHDLs proved effective in animal models of human atherosclerosis (Shah et al., 1998, 2001; Chiesa et al., 2002), postangioplasty restenosis, and in-stent stenosis (Ameli et al., 1994; Kaul et al., 2003), arterial thrombosis (Li et al., 1999), and hemorrhagic and septic shock (Quezado et al., 1995; Cockerill et al., 2001). The present experimental data indicate that sHDLs may become a clinically useful form of treatment in situations in which myocardial I/R occurs, such as acute coronary syndromes, cardiac surgery and transplantation, or revascularization with angioplasty, thrombolysis, or bypass surgery. Patients with diagnosed coronary artery disease who are at risk for further ischemic events might also be candidates for repeated sHDL treatments. Finally, I/R has been described in a number of different organs, and it has been implicated in the pathogenesis of a variety of disease states. Although the quality and quantity of tissue damage after I/R can vary among tissues, there are key components of this pathological process, such as endothelial dysfunction, leukocyte infiltration, and enhanced ROS production, that are shared by all organs. Therefore, the protective effects of sHDL may be relevant to organs other than the heart, such as kidney (Thiemermann et al., 2003), liver, brain, and lung.

References


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