Cyclosporine Impairs Release of Endothelium-Derived Relaxing Factors in Epicardial and Resistance Coronary Arteries

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Background  Cyclosporin A is reported to impair endothelium-mediated vasorelaxation and induce endothelin release in some noncoronary vascular beds. We wished to determine whether acute cyclosporine administration induces endothelial dysfunction in coronary conductance or resistance arteries.

Methods and Results  We examined the effect of intracoronary acetylcholine, \(N^\text{a}-\text{nitro-L-arginine methyl ester (L-NAME)}\), l-arginine, nitroglycerin, and adenosine before and after acute cyclosporine administration (3 mg/kg IV over 30 minutes) in anesthetized dogs. Flow velocity was measured with a 0.014-in Doppler wire to assess resistance vessel responses, and epicardial coronary lumen area was simultaneously measured with a 4.3F, 30-MHz imaging catheter inserted over the Doppler wire. In 6 dogs, acetylcholine-induced increase in flow velocity was attenuated by cyclosporine in vehicle (137% to 55% at \(10^{-4}\) mol/L, \(P<.01\)), as was acetycholine-induced epicardial vasodilation (14.1% to 6.7% at \(10^{-4}\) mol/L, \(P<.01\)). Vasodilation in response to intracoronary nitroglycerin (200 \(\mu\)g) and adenosine (6 mg) were unchanged by cyclosporine. Epicardial vasoconstriction with L-NAME (\(10^{-4}\) mol/L) was reduced by cyclosporine (Pre, 7.4±0.9%; Post, 2.6±1.2%; \(P=.04\)), but l-arginine (\(10^{-4}\) mol/L) had no effect after cyclosporine. In another 5 dogs, pure cyclosporine impaired acetylcholine-induced vasodilatation to the same degree as cyclosporine in vehicle (Cremophor); vehicle infusion did not impair endothelial function. In 5 more dogs, cyclosporine did not increase either arterial or coronary sinus concentrations of endothelin-1.

Conclusions  The present study shows that cyclosporine acutely impairs release of endothelium-derived relaxing factor in canine conductance and resistance coronary arteries and provides evidence for decreased epicardial nitric oxide release after cyclosporine. The potential contribution of acute cyclosporine-induced coronary endothelial dysfunction to post-transplant vasculopathy needs further study. (Circulation. 1994;90:3018-3023.)

Key Words  • acetylcholine • \(N^\text{a}-\text{nitro-L-arginine methyl ester}•\) endothelin • transplantation

Endothelial dysfunction observed in the coronary arteries of orthotopic cardiac transplant recipients is said to be due to the interaction of several factors such as hypercholesterolemia, hyper tension, and immune-mediated vascular disease. The role of the immunosuppressive agent cyclosporin A, widely used after cardiac transplantation, has not been examined as a potential cause of coronary endothelial dysfunction. In noncoronary beds such as the rat renal artery, the isolated rat aorta, and human subcutaneous resistance vessels, cyclosporine has been shown to impair endothelium-mediated vasorelaxation. In addition, cyclosporine is reported to induce release of endothelin, which may mediate its renal vasoconstrictor effect. Further, a direct toxic effect of cyclosporine has been shown in cultured rat microvascular endothelial cells.

In the present study, we hypothesized that cyclosporine might induce endothelial dysfunction in the coronary circulation. We examined the effect of acute cyclosporine administration in vivo in the canine coronary epicardial and microcirculation using simultaneous two-dimensional (2D) and Doppler ultrasound. Specifically, we studied vasorelaxation responses to endothelium-dependent and endothelium-independent vasodilators to determine the influence of cyclosporine on endothelial function. We also examined the effect of acute cyclosporine administration on endothelin release in the peripheral circulation and across the coronary vascular bed.

Methods  Sixteen dogs (mean body weight, 27±0.9 kg) were anesthetized with Innovar (0.04 mg/kg SC) and sodium pentobarbital (15 mg/kg IV), with additional doses as needed to maintain the level of anesthesia. The dogs were mechanically ventilated with room air, blood pressure was continuously monitored from a cannula placed in the left internal carotid artery, and heart rate was monitored from the ECG. All studies conformed to the “Position of the American Heart Association on Research Animal Use” (November 11, 1984).

Catheterization Procedures  In the first 11 dogs, the left main coronary artery was cannulated via the transfemoral approach under fluoroscopic guidance by use of an 8F canine guiding catheter (Advanced Cardiovascular Systems). A 0.014-in Doppler wire (FloWire, Cardiometrics Inc) was first introduced through the 8F guiding catheter, after which the 2D ultrasound imaging catheter (Cardiovascular Imaging Systems, CVIS) was introduced di-
rectly over the Doppler wire into the mid segment of the circumflex coronary artery. As previously described, the Doppler transducer was positioned approximately 2 cm distal to the tip of the imaging catheter. In the next 5 dogs, the coronary sinus was cannulated via the right internal jugular vein with an 8F multipurpose guiding catheter. This catheter was used to sample coronary venous blood for endothelin levels.

2D Ultrasound System Description and Image Analysis

2D ultrasound images were obtained with a commercially available imaging system (CVIS). The ultrasound catheter (4.3F) has a fixed 30-MHz transducer and a rotating mirror assembly. Images were displayed on a video monitor; axial resolution was \( \pm 150 \) μm and lateral resolution \( \approx 250 \) μm. Gain, contrast, and reject settings were adjusted by the operator to yield a well-balanced gray-scale appearance on the video display. Real-time images were stored on higher resolution VHS videotape for subsequent off-line analysis. As previously described, selected portions of the videotape were digitized (12 bits, Rasterops 324) in real time (30 frames per second) and transferred to a computer disk for off-line determination of luminal area.

Doppler Ultrasound System Description

Coronary blood flow velocities were measured by use of a steerable Doppler guide wire. This guide wire system has a miniature ultrasound crystal that transmits signals at a carrier frequency of 12 MHz and receives pulsed-wave Doppler ultrasound signals. The ultrasound beam has an angular width of approximately 25°, and the sample volume is located at a distance of 5 mm from the guide wire tip. The Doppler signals are analyzed by a FloMap instrument (Cardiometrics Inc) that uses dedicated digital signal processing chips to perform the fast Fourier transformation required for the spectral display. The signals were then transformed into a gray scale, and the resultant spectrum was displayed on a monitor screen. The ECG, the arterial pressure wave tracing, and quantitative measurements of average peak velocity (APV) were also displayed. The monitor display was continuously recorded on a VHS videotape.

Vasoactive Agents

Dimensions and flow in the coronary arteries are influenced by perfusion pressure, which varies with systemic arterial blood pressure. To minimize effects on the systemic vasculature that would alter blood pressure and thus affect interpretation of results, all drugs (with the exception of cyclosporine and Cremophor) were infused directly into the coronary circulation through the guiding catheter in the left main coronary artery. Previous studies with saline infusions of similar volume have shown that the "bolus" effect had little influence on flow beyond 20 seconds. Measurements of coronary artery cross-sectional area (CSA) were therefore made at 30 seconds, and every 30 seconds thereafter with each administration. Measurements of flow velocity were made continuously on-line. Observations reported indicate peak effects of the administered drugs. Sufficient "washout" periods of 15 minutes were allowed between administration of different drugs, with documentation that coronary artery dimensions and flow velocity returned to the baseline state. Cyclosporine and Cremophor were obtained from Sandoz Pharmaceutical Corp and administered in the doses described below after dilution in 20 mL of autologous blood. Adenosine was obtained from Fujisawa Pharmaceuticals. All other drugs were obtained from Sigma Chemical Co.

Protocol 1

In 6 dogs, by use of an approach similar to that previously described and assuming a coronary blood flow of 80 mL/min, increasing concentrations of intracoronary acetylcholine were administered over 1-minute periods to achieve concentrations from \( 10^{-7} \) to \( 10^{-5} \) mol/L. Intracoronary N-nitro-L-arginine methyl ester (L-NAME) was administered similarly to achieve increasing concentrations from \( 10^{-8} \) to \( 10^{-5} \) mol/L. Intracoronary L-arginine (L-Arg) was administered immediately after L-NAME (with no "washout" period between them) over a 1-minute period to obtain a final concentration of \( 10^{-4} \) mol/L. Intracoronary adenosine (6 mg) and nitroglycerin (200 μg) were given as boluses as previously described. Next, cyclosporine in Cremophor (3 mg/kg body wtIV) was infused over a period of 30 minutes. Intracoronary acetylcholine, L-NAME, L-Arg, adenosine, and nitroglycerin infusions were then repeated to assess the influence of cyclosporine on endothelium-dependent and endothelium-independent coronary vasomotion. A peripheral venous blood sample was drawn 15 minutes after the termination of the cyclosporine infusion for measurement of cyclosporine levels.

Protocol 2

In the next 5 dogs, acetylcholine-induced vasodilation was measured before and after a 30-minute infusion of the vehicle, Cremophor, 2 mL. Next, cyclosporine (3 mg/kg body wt) was administered as pure powder dissolved in 20 mL of autologous blood over a period of 30 minutes, and the effect of acetylcholine-induced vasodilation was measured once again.

Protocol 3

In a separate series of 5 dogs, arterial and coronary sinus blood was collected in 5 mmol/L EDTA containing 1 μg/mL aprotinin for determination of endothelin levels before and after a 30-minute infusion of pure cyclosporine powder (3 mg/kg body wt) dissolved in autologous blood.

Endothelin Assays

Endothelin-1 was measured in extracted plasma by a specific radioimmunoassay that recognizes the mature 1-21 peptide (RPA 555) according to the following protocol: C18 Amprep columns (Amersham) were equilibrated by washing with 3 mL methanol, 2 mL water, and 2 mL 10% acetic acid, and 0.5 to 1.0 mL plasma with an equal volume of 20% acetic acid was applied. The columns were washed with 2 mL of 10% acetic acid, followed by 3 mL of ethyl acetate, and eluted with a mixture of 80% methanol and 20% 50 mmol/L ammonium bicarbonate. The eluates were evaporated under nitrogen gas, reconstituted in assay buffer, and assayed by a double-antibody radioimmunoassay according to the manufacturer's recommendations. Cross-reactivities of the radioimmunoassay were 52% for endothelin-3 and 0.4% for big endothelin. The assay was linear for endothelin-1 in dog plasma over a range of plasma volumes of 0.25 to 2 mL and over a concentration range of 2 to 400 pg/mL. The assay sensitivity was 1.2 pg/mL, with interassay and intra-assay coefficients of variation of 15% and 7%, respectively.

Calculations and Statistical Analysis

Luminal CSA at baseline and after administration of drugs was determined by computer-assisted planimetry. Measurements were gated to end-systolic and end-diastolic dimensions, respectively. As previously described, a mean CSA value was obtained by correcting for the fractional diastolic time interval (fDTI, the duration of diastole as a fraction of the cardiac cycle length) and the fractional systolic time interval (fSTI, the duration of systole as a fraction of the cardiac cycle length) as follows: mean CSA = (fDTI × end-diastolic CSA) + (fSTI × end-systolic CSA). Volumetric coronary blood flow (CBF) was calculated from the relation CBF = mean CSA × APV × 0.5, as previously described and validated in a dog model. Concentration-response curves for CSA and Doppler-derived APV were analyzed by one-way ANOVA for repeated measures followed by a post hoc Student-Newman-Keuls test. The
Changes in Mean Arterial Pressure and Heart Rate Induced by the Various Pharmacological Agents Infused Before and After Cyclosporine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Before Cyclosporine</th>
<th>After Cyclosporine</th>
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<tbody>
<tr>
<td></td>
<td>MAP, mm Hg</td>
<td>HR, bpm</td>
</tr>
<tr>
<td>Baseline</td>
<td>90±5</td>
<td>140±5</td>
</tr>
<tr>
<td>Acetylcholine 10⁻⁷</td>
<td>90±6</td>
<td>136±6</td>
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<tr>
<td>Acetylcholine 10⁻⁶</td>
<td>92±4</td>
<td>142±7</td>
</tr>
<tr>
<td>Acetylcholine 10⁻⁵</td>
<td>94±5</td>
<td>135±6</td>
</tr>
<tr>
<td>L-NAME 10⁻⁵</td>
<td>94±3</td>
<td>144±6</td>
</tr>
<tr>
<td>L-NAME 10⁻⁴</td>
<td>97±7</td>
<td>141±8</td>
</tr>
<tr>
<td>L-NAME 10⁻³</td>
<td>99±4</td>
<td>133±7</td>
</tr>
<tr>
<td>L-Arg 10⁻³</td>
<td>92±5</td>
<td>145±9</td>
</tr>
<tr>
<td>Adenosine</td>
<td>83±11</td>
<td>147±8</td>
</tr>
<tr>
<td>Nitroglycerin 200 µg</td>
<td>84±10</td>
<td>150±14</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; HR, heart rate; bpm, beats per minute; L-NAME, N°-nitro-L-arginine methyl ester; and L-Arg, L-arginine.

dose-response relations to acetylcholine and L-NAME before and after cyclosporine were compared by two-way repeated-measures ANOVA. The effects of adenosine and nitroglycerin before and after cyclosporine were compared by Student’s paired t test, as were endothelin levels. Values are expressed as mean±SEM.

Results

In all 16 dogs, interpretable 2D images and Doppler flow spectra were obtained. There were no instances of arrhythmias, spasm, or thrombosis during catheter/Doppler wire placement.

Resting Coronary Dimensions and Flow and Cyclosporine Levels

Mean resting heart rate and mean arterial pressure at baseline are shown in the Table. Mean resting coronary CSA was 9.2±0.6 mm², and the mean value for APV was 27±6 cm/s. Mean volumetric coronary blood flow at baseline was 75.5±15.2 mL/min. Peak cyclosporine levels achieved 15 minutes after the end of the infusion were 791±98 µg/L.

Effect of Cyclosporine on Acetylcholine-Induced Increases in Coronary CSA and Flow Velocity

Acetylcholine caused a dose-dependent increase in mean coronary CSA and APV, as shown in Fig 1. The mean increase in CSA at 10⁻⁷ mol/L was 14.1±2%, and the mean increase in APV was 137±45% at the 10⁻⁵ mol/L concentration of acetylcholine. As a result, volumetric coronary blood flow increased by 172±42% at the 10⁻⁵ mol/L concentration of acetylcholine. The peak effect on CSA was observed at 30 seconds, and flow velocity reached its peak at 40±5 seconds. Mean arterial pressure remained unchanged. A transient slowing of the heart rate was observed at the highest concentration (10⁻⁵ mol/L), lasting about 5 to 10 beats, with full recovery at 30 seconds. No other significant changes in heart rate were observed with any dose (Table).

After administration of cyclosporine, mean arterial pressure was unchanged, as was heart rate (Table). There was a 5±2% decrease in baseline CSA (P=.08) but no change in APV, and volumetric blood flow decreased to 61.9±6.5 mL/min (P=.09). There was a significant attenuation of the increase in CSA to 6.7±1.3% at 10⁻⁵ mol/L (F=12.83, P=.016 for precyclosporine versus postcyclosporine dose-response curves from two-way ANOVA) and APV to 55±22.1% at 10⁻⁵ mol/L (F=37.44, P<.01 for precyclosporine versus postcyclosporine dose-response curves from two-way ANOVA) in response to acetylcholine. The 10⁻⁵ mol/L concentration of acetylcholine, the increase in volumetric flow after cyclosporine was reduced to 65±18% (P<.01). With respect to both CSA and APV, the concentration-response curve to acetylcholine after administration of pure cyclosporine powder was identical to that after cyclosporine in Cremophor (Fig 1). Cremophor vehicle per se did not result in any shift in the acetylcholine concentration-response relation with respect to either CSA or APV (Fig 1). There was a small decrease in baseline CSA in response to Cremophor, which did not reach statistical significance (P=.15) (Fig 1).

Effect of Cyclosporine on L-NAME- and L-Arg-Induced Changes in Coronary CSA and Flow Velocity

Before cyclosporine administration, L-NAME caused a significant dose-dependent decrease in CSA, as shown in Fig 2, the peak effect occurring at 6±2 minutes.

![Graph showing effect of increasing concentrations of N°-nitro-L-arginine methyl ester (L-NAME) and L-arginine (L-Arg) on epicardial coronary cross-sectional area (CSA) measured by intravascular ultrasound imaging. CYA indicates cyclosporin A.](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.90.6.3020)
FIG 3. Bar graph showing coronary flow reserve measured as the ratio of peak to baseline flow velocity in response to adenosine, showing no change after administration of cyclosporine. CyA indicates cyclosporin A.

There was no significant change in APV (31±6, 30±4, and 28±4 cm/s at concentrations of 10⁻⁶, 10⁻⁵, and 10⁻⁴ mol/L, respectively). There was a small decrease in volumetric coronary blood flow at the 10⁻⁴ mol/L concentration of L-NAME (12±6%, P=.04). No changes in systemic arterial pressure or heart rate were observed with L-NAME (Table).

After cyclosporine administration, there was again a 6±2% decrease in baseline CSA (P=.06) but not APV and a significantly attenuated vasoconstrictor response to L-NAME in the epicardial coronary arteries (Precylosporine, 7.4±0.9% decrease in CSA; postcyclosporine, 2.6±1.2% decrease in CSA at 10⁻⁴ mol/L; P=.04). The coronary flow velocity response to L-NAME after cyclosporine was not different from that before cyclosporine, with no change in APV at any dose of L-NAME (28±7, 24±6, and 27±8 cm/s at concentrations of 10⁻⁶, 10⁻⁵, and 10⁻⁴ mol/L, respectively). After cyclosporine, there was no significant change in the effect of L-NAME on volumetric coronary blood flow (10±3% at the 10⁻⁴ mol/L concentration of L-NAME).

L-Arg (10⁻⁴ mol/L), infused immediately after L-NAME, reversed the epicardial vasoconstriction induced by blockade of NO synthesis before cyclosporine (Fig 2), the reversal being completed in 4±1 minutes. After cyclosporine, L-Arg, infused after L-NAME, failed to increase CSA. There was, however, no increase in flow velocity in response to L-Arg either before (APV 29±7 cm/s) or after (APV 31±5 cm/s) cyclosporine. There was no change in blood pressure or heart rate with L-Arg either before or after cyclosporine (Table). After L-NAME (10⁻⁴ mol/L), L-Arg increased volumetric coronary blood flow before cyclosporine by 23±4% but did not change volumetric coronary blood flow after cyclosporine (−3±2%).

Effect of Cyclosporine on Coronary Flow Reserve

A transient decrease in heart rate (range, 18 to 40 beats per minute) was observed in response to adenosine, lasting a maximum of 15 seconds, with full recovery by 30 seconds. Blood pressure was not significantly reduced (Table). Adenosine did not change coronary CSA (baseline, 9.1±0.5 mm²; adenosine, 9.3±0.4 mm²; P=NS). The ratio of peak flow to baseline flow in response to intracoronary adenosine was 3.5±0.4 before cyclosporine and 3.3±0.1 after cyclosporine (P=NS) (Fig 3). The peak response to adenosine was observed between 45 seconds and 1 minute after administration.

Effect of Cyclosporine on the Coronary Vasodilator Response to Nitroglycerin

There was no significant change in either heart rate or blood pressure in response to intracoronary nitroglycerin 200 μg (Table). Nitroglycerin caused an increase in both CSA and APV before cyclosporine administration. After cyclosporine, nitroglycerin-induced increases in CSA and APV were not significantly different from those before cyclosporine (Fig 4). The magnitude of the increase in volumetric blood flow induced by nitroglycerin was also similar before and after cyclosporine (before cyclosporine, 76.3±13 to 115.4±11 mL/min; after cyclosporine, 65±4 to 107.9±9 mL/min). The peak response to nitroglycerin was observed 2 minutes after administration.

Effect of Cyclosporine on Endothelin Levels

Cyclosporine did not increase either arterial or coronary sinus endothelin (arterial: before cyclosporine, 26.6±5.1 pg/mL; after cyclosporine, 26.0±2.3 pg/mL; P=NS; coronary sinus: before cyclosporine, 29.8±1.5 pg/mL; after cyclosporine, 28.0±6.1 pg/mL; P=NS).

Discussion

The present study demonstrates that acute intravenous administration of cyclosporin A impairs acetylcholine-induced vasorelaxation in the coronary circulation. This impairment was seen in both conductance and resistance coronary arteries and was not restored acutely by L-Arg. In the epicardial coronary arteries, NO release is reduced after cyclosporine administration. Endothelium-independent relaxation in response to nitroglycerin and coronary flow reserve as assessed by intracoronary adenosine appeared to be preserved after cyclosporine administration. No significant increase in either peripheral or coronary venous endothelin levels was observed after cyclosporine.

In general, impaired endothelium-dependent vasorelaxation may be mediated by several potential mechanisms, such as decreased release of NO or a decreased sensitivity of vascular smooth muscle to NO. Our data showing a decrease in baseline CSA after cyclosporine and a significantly decreased vasoconstrictor response...
to L-NAME in epicardial coronary arteries suggest impaired production of NO in the conductance vessels after exposure to cyclosporine. Previous studies from our laboratory and others suggest that NO production may contribute less to acetylcholine-induced vasorelaxation in coronary resistance vessels compared with the conductance vessels, an observation that has now been reported in humans as well. In the present study, L-NAME did not have any significant influence on coronary flow, and cyclosporine did not influence this response in the resistance vessels. This would suggest that cyclosporine-induced impairment of acetylcholine-induced vasorelaxation in coronary resistance arteries may be mediated by endothelium-derived relaxing factors other than NO. Rather than interference with a specific endothelial pathway, a generalized toxic effect on the endothelium in both the large and small coronary vessels could account for the impairment in acetylcholine-induced increases in coronary CSA and blood flow as well as a decrease in basal epicardial arterial release of NO. Indeed, cyclosporine has been shown to directly cause abnormalities in the endothelial cytoplasm and nucleus and to inhibit endothelial cell replication. Toxic endothelial injury would also explain the lack of response to L-Arg; by contrast, competitive inhibition of NO synthase should have been reversed by increasing the concentration of its substrate, L-Arg.

Cyclosporine clearly did not impair endothelium-independent relaxation in our study, as demonstrated by preserved relaxation in response to nitroglycerin. Nitroglycerin acts via conversion to NO in vascular smooth muscle; hence, the responsiveness of vascular smooth muscle to NO is not influenced by cyclosporine. Previous studies with acute cyclosporine administration have shown similar preservation of endothelium-independent relaxation in noncoronary vessels; however, with more prolonged periods of cyclosporine administration, impaired vasorelaxation in response to sodium nitroprusside has been reported. While the predominant effect of nitroglycerin is on coronary conductance arteries, intracoronary adenosine mainly dilates coronary resistance arteries. In the present study, the ability of the microcirculation to maximally vasodilate was also preserved after cyclosporine administration, as shown by a preserved response to a dose of intracoronary adenosine in excess of that shown to cause maximal hyperemia. This finding lends further support to an endothelium-specific toxicity of cyclosporine.

Endothelin has been proposed as a potential mediator of cyclosporine-induced vascular toxicity. In endothelial cells in culture, in rat grafts, and in the dog renal circulation, and in an anecdotal report in a renal transplant patient, cyclosporine has been reported to cause release of endothelin. In our study, however, cyclosporine did not result in any elevation of peripheral endothelin levels. Further, there was no increase in coronary sinus concentrations of endothelin, suggesting no net release of endothelin across the heart in our model. Our data do not, however, rule out potential elevation of endothelin levels with more prolonged administration of cyclosporine. The decrease in baseline CSA after administration of cyclosporine would also appear to be mediated by mechanisms other than increased endothelin release. A decrease in basal release of endothelium-derived NO (see above) could account for this epicardial vasoconstriction. In human arteries, endothelium-derived relaxing factor (EDRF) inhibits endothelin-1–induced contractions, while endothelin-1 specifically attenuates the vasodilator effect of EDRF in veins, suggesting that vascular tone is maintained as a result of balance between these factors. Therefore, it is conceivable that in the presence of a deficiency of EDRF release after cyclosporine, endothelin may exert a greater vasoconstrictor effect even without an increase in its secretion.

Cyclosporine is markedly hydrophobic and is usually clinically administered in an oil-based vehicle, Cremophor. Cremophor has been shown to have marked hemodynamic effects; in particular, it can decrease renal blood flow. In the present study, however, apart from a small decrease in baseline CSA that did not reach statistical significance, Cremophor administration did not influence endothelium-dependent vasorelaxation in response to acetylcholine in either coronary conductance or resistance arteries. Further, administration of pure cyclosporine without vehicle yielded a similar attenuation of acetylcholine-induced coronary vasorelaxation as cyclosporine in Cremophor, suggesting that this impaired endothelium-dependent vasorelaxation was a direct result of cyclosporine administration and not its vehicle.

**Limitations of This Study**

We have made the assumption that in the normal canine coronary arteries studied, changes in vascular reactivity observed by intravascular ultrasound at one cross-sectional location are representative of the whole artery. This is an inherent limitation of the current technology; in the future, three-dimensional reconstructions from a series of cross-sectional “slices” may allow inferences to be made on vasomotion in longer vascular segments.

The present study investigated the effects of acute cyclosporine administration on coronary endothelial function in a canine model. The extent to which these findings relate to the clinical situation of chronic exposure to cyclosporine after cardiac transplantation is unclear. Hypertension, hypercholesterolemia, and immune-mediated vascular disease probably contribute to coronary endothelial damage in cardiac transplant recipients. We would suggest that the potential role of chronic cyclosporine therapy in the development of endothelial dysfunction and subsequent posttransplant vasculopathy requires further consideration.

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