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Vascular Remodeling 1 Year After Cardiac Transplantation

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Background: The belief that vascular remodeling and intimal hyperplasia are causes of luminal narrowing in cardiac allograft vasculopathy (CAV) is controversial. This study evaluated the relationship of vascular remodeling and intimal hyperplasia to luminal narrowing 1 year after orthotopic heart transplantation.

Methods: Intravascular ultrasound imaging was performed on 190 cardiac transplant recipients at baseline and again 1 year after transplantation as part of a randomized trial of mycophenolate mofetil (MMF) and azathioprine (Aza). Studies 1 year apart were matched at 625 sites. All sites were classified into positive, non-significant and negative remodeling patterns, depending on a change of $\pm 10\%$ in external elastic membrane area. Of the 190 patients, 99 were randomized to receive MMF, and 91 to receive Aza.

Results: A total of 625 sites were observed. Of these, 52% had no remodeling, 25% exhibited vessel dilation, and 23% had vessel shrinkage in the presence of variable intimal growth (Δ intimal area: 0.73 ± 1.70 mm^2, $p < 0.0001$; 1.23 ± 2.02 mm^2, $p < 0.0001$; and 0.20 ± 1.40 mm^2, $p = 0.09$, respectively). Sixty percent of the lumen loss was due to a decrease in external elastic membrane area and 40% to an increase in intimal area ($p = 0.005$). Compared with Aza-treated patients, the MMF-treated patients had a lower incidence of vessel shrinkage (17% vs 28%, $p = 0.001$), and a trend for smaller maximum intimal thickness (0.21 ± 0.25 mm vs 0.29 ± 0.31 mm, $p = 0.052$).

Conclusions: Positive remodeling is associated with intimal growth, but negative remodeling does not correlate with any specific change in intimal hyperplasia. Constrictive remodeling is more responsible than intimal hyperplasia for the luminal narrowing that occurs. MMF is more efficacious than azathioprine in preventing the development of CAV at 1 year, by reducing the degree and incidence of vessel shrinkage and the progression of intimal hyperplasia. J Heart Lung Transplant 2007;26:56–62. Copyright © 2007 by the International Society for Heart and Lung Transplantation.

Cardiac allograft vasculopathy (CAV) is characterized by diffuse and concentric intimal thickening that may involve all portions of the coronary arteries and veins, including the intramyocardial branches.[1] CAV is the major factor limiting long-term survival of heart transplant recipients.[2–4] After orthotopic heart transplantation (OHT), 83% of adult patients survive to 1 year and 75% to 3 years post-transplant.[5] In the first year after OHT, intravascular ultrasound (IVUS) detects abnormal intimal thickening in 50% of recipients.[6] Angiography

detects the presence of CAV in 10% to 20% of recipients at the first year post-transplant, rising 10% per year to 50% at 5 years.[7] There is no definitive treatment to prevent CAV, but current therapies may slow its progression. Repeat transplantation is the only alternative for patients with severe diffuse CAV.[4,8] Several IVUS studies have demonstrated that luminal narrowing is caused not only by intimal hyperplasia but also by the change in the vascular geometry after OHT.[9–15] Vascular remodeling is known to play an important role in influencing luminal narrowing for native coronary arteries and vascular grafts.[16–18] The objective of this study was to evaluate the relationship of vascular remodeling and intimal hyperplasia to luminal narrowing in the first year after OHT.

METHODS
Patient Population

A randomized, multicenter, double-blind, controlled trial of mycophenolate mofetil (MMF) in heart transplant recipients was initiated in 1994.[19] One hundred ninety patients with evaluable baseline and 1-year IVUS studies were analyzed. All patients received cyclosporine and prednisone and were randomized to receive

Table 1. Clinical Characteristics in MMF-treated and Aza-treated Patients

Characteristics	MMF (n = 99)	Aza (n = 91)	p-value
Baseline demographics			
Recipient age (years)	52.8 ± 8.6	50.6 ± 10.1	0.11
Recipient female gender	21 (21.2)	14 (15.4)	0.30
Donor age (years)	27.7 ± 12.2	29.4 ± 13.2	0.36
Cold ischemic time (hours)	3.1 ± 1.0	3.0 ± 0.9	0.60
HLA mismatch	4.64 ± 1.16	4.58 ± 1.13	0.76
Pre-transplant CAD	55 (55.6)	41 (45.1)	0.15
Risk factors			
Cholesterol, mean value during the first year (mg/dl)	212.2 ± 34.8	204.2 ± 34.0	0.11
Diabetes	49 (49.5)	54 (59.3)	0.17
Hypertension	98 (99.0)	88 (96.7)	0.35
Use of medications			
Statins	49 (49.5)	42 (46.2)	0.65
Calcium blockers	77 (77.8)	74 (81.3)	0.55
Rejection Grade ≥3A at Year 1	41 (41.4)	48 (52.7)	0.12

Values are n (%) or mean ± SD. Significance (p-value) assessed using independent t-test for continuous variables and Fisher's exact or chi-square tests for categoric data. CAD, coronary artery disease; HLA, human leukocyte antigen.

either MMF or azathioprine (Aza). The trial was approved by the institutional review board of each participating center, and signed informed consent was obtained from all patients.

IVUS Imaging Procedure

Quantitative angiography and IVUS imaging were performed at 1 to 8 weeks and 12 months post-transplantation. After full anti-coagulation with heparin 100 U/kg, an 8F guide catheter was advanced over a guide-wire into the selected coronary artery. Patients received 0.4 mg of sub-lingual nitroglycerin and/or 200 μg of intracoronary nitroglycerin before advancing the IVUS catheter. A 30-MHz ultrasound transducer (4.3 Fr, CVIS, Sunnyvale, CA; 3.5 Fr, Hewlett-Packard, Palo Alto, CA) was inserted into a distal position of the selected vessel where the luminal diameter exceeded 2 mm. A manual slow (>30-second) pullback was performed from the distal position to the proximal coronary artery. The catheter location was recorded with cine-angiography. IVUS images were recorded on s-VHS videotape with voice annotation.

IVUS Imaging Analysis

The IVUS tapes were sent to a core laboratory that was blinded to patient treatment. The IVUS images were digitized using ECHOPLAQUE software (version 2.5, Indec Systems, Inc., CA). IVUS landmarks, such as side branches, calcification, pericardium and cardiac veins, were used in matching the sites. Two to four matched sites from the same artery were chosen using side-by-side comparison of the baseline and follow-up images. These sites included the left main, proximal, middle and distal sites of each coronary artery. Frames obtained during the diastolic phase of the cardiac cycle were selected for measurement. The frame with the most severe intimal thickening from each site was identified in the first-year IVUS study after OHT. These selected frames were matched with sites from the baseline IVUS study. Only sites that had clear matching identifiers were chosen for analysis. Luminal and vessel contours were drawn with the planimetry software on each cross-sectional view by manually tracing the border

Table 2. Geometric Features in Three Vascular Remodeling Patterns

Parameter changes at Year 1	Expansive remodeling (n = 159 sites)	No remodeling (n = 325 sites)	Constrictive remodeling (n = 141 sites)
MIT (mm)	0.13 ± 0.25	0.09 ± 0.21	0.04 ± 0.23[d]
IA (mm²)	1.23 ± 2.03	0.73 ± 1.70[b]	0.20 ± 1.40[c,f]
EEM area (mm²)	2.91 ± 2.00	−0.06 ± 0.92[a]	−3.31 ± 2.36[c,e]
LA (mm²)	1.67 ± 2.54	−0.80 ± 1.91[a]	−3.51 ± 2.75[c,e]
IA/EEM area (%)	4.69 ± 9.88	3.71 ± 8.75	3.66 ± 9.65

Values are mean ± SD. Significance (p-value) assessed 1-way ANOVA followed by multiple comparisons with the Bonferroni post hoc test. MIT, maximum intimal thickness; IA, intimal area; EEM area, external elastic membrane area; LA, lumen area; IA/EEM area, cross-sectional area stenosis.
  [a]p < 0.001, [b]p = 0.009 for the comparison with expansive remodeling.
  [c]p < 0.001, [d]p < 0.05 for the comparison with expansive remodeling.
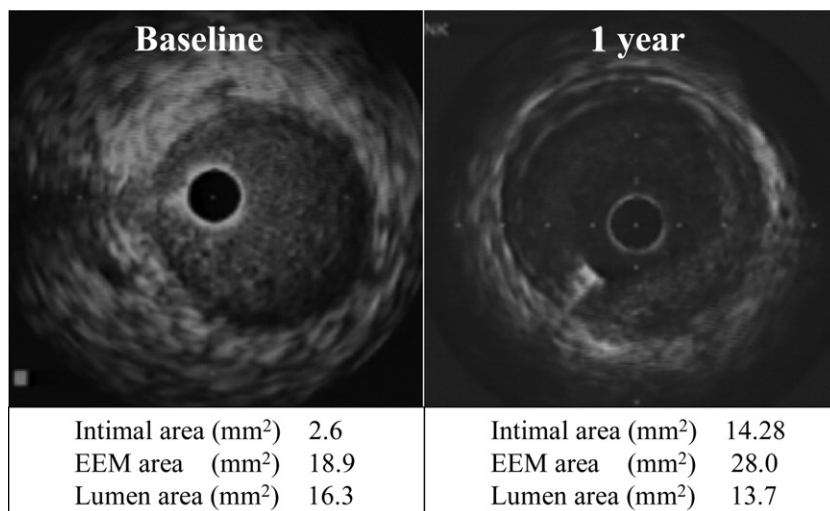 [e]p < 0.001, [f]p < 0.05 for the comparison with no remodeling.

Figure 1. An example of positive remodeling. EEM area: external elastic membrane area.

between the intima and the lumen, and the boundary between the media and adventitia. At each site, maximum intimal thickness (MIT), intimal area (IA), external elastic membrane area (EEM area) and lumen area (LA) were measured. Percent area stenosis was defined as (IA/EEM area) $\times$ 100%.

The reproducibility of measurement in terms of mean interobserver variability was $1.4 \pm 3.8\%$ for LA and $2.7 \pm 3.3\%$ for EEM area. Therefore, a change of $>10\%$ was chosen to represent a measurable difference of >2 standard deviations of interobserver variability. Based on the interobserver value, positive remodeling was defined as sites with an increase of $>10\%$ in EEM area from baseline to 12 months; negative remodeling was defined as sites with a decrease of $>10\%$ in EEM area; no significant remodeling was defined as an absolute change of $\leq10\%$ in EEM area.

Statistical Analysis

The mean $\pm$ standard deviation was calculated for all numeric data. Comparisons between baseline and follow-up were determined by paired t-test. The data from different groups were compared using an independent t-test and 1-way analysis of variance (ANOVA). Differences among categoric variables were assessed using the chi-square or Fisher's exact test. A linear regression was used to describe the correlation between measured variables. Two-sided $p < 0.05$ was considered statistically significant.

RESULTS
Patient Enrollment

A total of 190 de novo cardiac transplant recipients (155 men, 35 women, mean age 51.8 ± 9.4 years) were analyzed. IVUS imaging was performed on all recipients
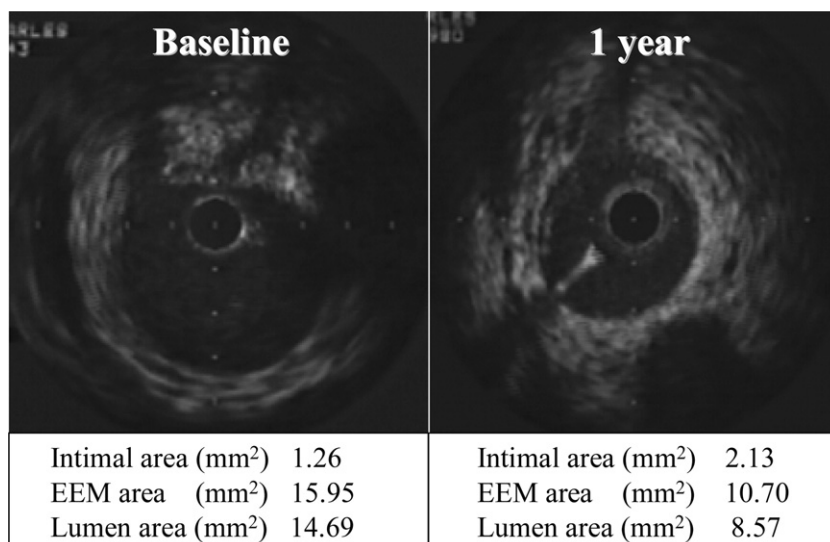

Figure 2. An example of negative remodeling. EEM area: external elastic membrane area.

at 1.4 ± 0.6 months and again at 12.1 ± 0.7 months after OHT. A total of 625 sites from 190 arteries (mean 3.3 sites per artery) were matched from baseline to 12 months. The mean donor age was 28.6 ± 12.7 years (range 11 to 61 years). IVUS studies were performed on 154 left anterior descending arteries, 29 left circumflex arteries and 7 right coronary arteries. Of the 190 patients, 99 were assigned to receive MMF, and 91 to receive Aza. The patients in the two groups had similar demographic characteristics (Table 1).

Serial Changes in IVUS Parameters

By the first year after OHT, the coronary artery lumen area decreased by 5.7% (from 13.59 ± 6.40 mm^2 at baseline to 12.81 ± 5.90 mm^2, $p < 0.0001$), but the average EEM area did not change significantly (from 15.47 ± 6.95 mm^2 at baseline to 15.43 ± 6.93 mm^2, $p = 0.7$). The intimal area increased by 39.6% compared with baseline (2.61 ± 2.63 mm^2 vs 1.87 ± 1.92 mm^2, $p < 0.0001$) and the maximum intimal thickness increased by 33.3% (from 0.27 ± 0.31 mm at baseline to 0.36 ± 0.37 mm, $p < 0.0001$).

Vascular Remodeling Patterns

The 625 sites were classified into three vascular remodeling patterns depending on the change of ±10% for EEM area (Table 2). Of the 625 sites, 325 (52.0%) had no significant remodeling, 159 (25.4%) had vessel enlargement (positive remodeling; Figure 1), and 141 (22.6%) had vessel shrinkage (negative remodeling; Figure 2) in the presence of variable intimal growth. The average EEM area at baseline was smaller at sites with positive remodeling than at sites with negative remodeling (14.10 ± 5.87 mm^2 vs 17.11 ± 7.38 mm^2, $p = 0.001$).

Intimal Hyperplasia and Vascular Remodeling

For the 625 sites, the change in EEM area correlated only mildly with the change in intimal area ($r = 0.21$, $p < 0.0001$). Of the 625 sites, 345 (55.2%) had intimal growth of >10% from baseline to 12 months. The average increase in intimal area was 1.62 ± 1.88 mm^2, an increase of 97.6% over baseline. Of the 345 sites with intimal growth, 180 (52.2%) did not show significant remodeling, 120 (34.8%) exhibited compensatory vessel enlargement, and 45 (13.0%) had vessel constriction.

Lumen Loss or Gain

For the 625 sites, the change in lumen area correlated most closely with the change in EEM area ($r = 0.81$, $p < 0.0001$; Figure 3A), and mildly with the change in intimal area ($r = -0.41$, $p < 0.0001$; Figure 3B). Of the 625 sites, 227 (36.3%) showed a decrease of >10% in lumen area (lumen loss), 125 (20.0%) had an increase of >10% in lumen area (lumen gain), and 273 (43.7%) had no significant change (absolute percent change in lumen
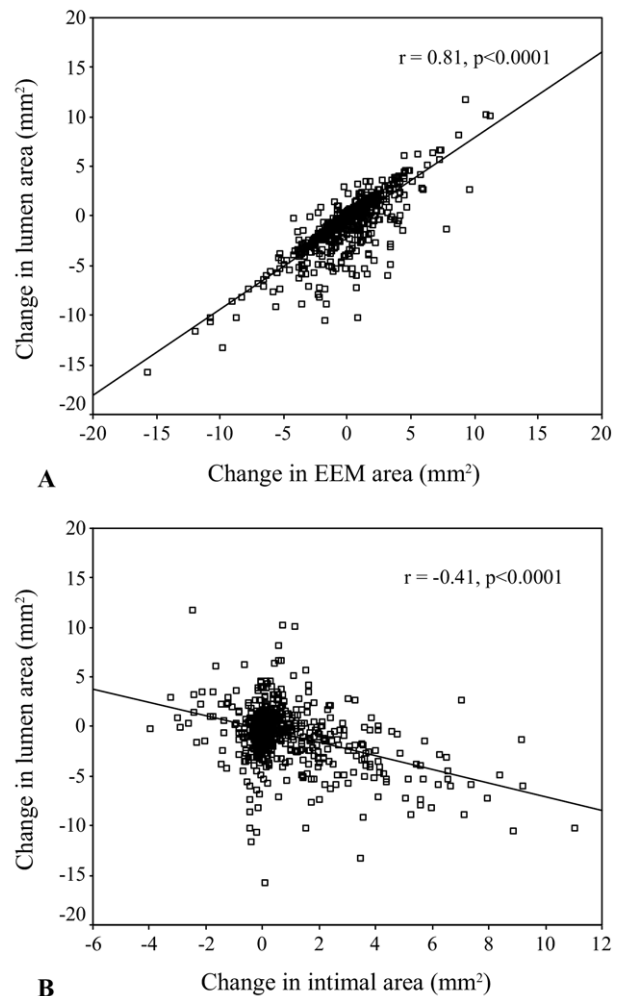

Figure 3. Relationship between the change in lumen area, the change in EEM area and the change in intimal area. EEM area: external elastic membrane area.

area ≤10%). In addition, 59.5% of lumen loss was due to a decrease in EEM area and 40.5% to an increase in intimal area ($p = 0.005$; Table 3). Lumen gain was caused primarily by an increase in EEM area, whereas intimal area did not change significantly.

Discordant Vascular Remodeling Patterns Within the Same Artery

Table 4 describes the relative incidence of remodeling patterns found within each artery. Only 24% (46 of 190) of the arteries had the same remodeling pattern at all sites measured (two to four sites per artery).

MMF and Aza

Of the 625 sites, 319 came from 99 MMF-treated patients and 306 came from 91 Aza-treated patients. At baseline IVUS study, there was no significant difference in MIT, intimal area, EEM area, lumen area or percent area stenosis between the MMF group and the Aza

Table 3. Determinants of Lumen Loss or Gain

Parameter changes at Year 1	Lumen loss ($n = 227$ sites)	Lumen gain ($n = 125$ sites)
LA (mm^2)	-3.51 ± 2.46[a]	2.61 ± 1.96[a]
EEM area (mm^2)	-2.09 ± 2.55[a]	2.75 ± 2.30[a]
IA (mm^2)	1.42 ± 2.27[a]	0.14 ± 1.20

IA, intimal area; EEM area, external elastic membrane area; LA, lumen area.
[a]$p < 0.001$: baseline compared with the first year after orthotopic heart transplantation, by paired t-test.

Table 5. Predictors for Lumen Loss by Multivariate Logistic Regression Analysis

Variable	Odds ratio	95% CI	p-value
Constrictive remodeling	195.74	25.04–1530.37	<0.001
Progression of intimal thickening	21.48	2.48–186.29	0.005

CI, confidence interval. Significance (p-value) assessed using the backward stepwise method (likelihood ratio).

group. At the first year after OHT, the average decrease in lumen area was 2.4 times greater in the Aza group than in the MMF group ($p = 0.005$; Table 5). The cumulative average percent area stenosis was higher in the Aza group than in the MMF group at 1 year ($p = 0.03$). Compared with Aza-treated patients, the MMF-treated patients had a trend for smaller maximal MIT per patient (0.21 ± 0.25 mm vs 0.29 ± 0.31 mm, $p = 0.052$).

The distribution in the two groups was different for the three vascular remodeling patterns, defined as a change of $\pm 10\%$ for EEM area. The incidence of negative remodeling was lower in the MMF group than in the Aza group (17% vs 28%, $p = 0.001$), and the incidence of no significant remodeling was higher in the MMF group than in the Aza group (57% vs 46%, $p = 0.006$). However, there was no difference in incidence of positive remodeling between the two groups (26% vs 25%). At those sites with positive remodeling, the degree of vessel enlargement was higher in the MMF

Table 4. Geometric Features in MMF-treated and Aza-treated Patients at Year 1

Parameters	MMF ($n = 99$ patients)	Aza ($n = 91$ patients)	p-value
Baseline			
MIT (mm)	0.26 ± 0.29	0.28 ± 0.32	0.60
IA (mm^2)	1.78 ± 1.79	1.97 ± 2.05	0.22
EEM area (mm^2)	15.40 ± 6.76	15.54 ± 7.15	0.80
LA (mm^2)	13.62 ± 6.20	13.57 ± 6.61	0.92
IA/EEM area (%)	11.70 ± 10.16	12.54 ± 11.11	0.33
Changes at Year 1			
MIT (mm)	0.08 ± 0.20[a]	0.11 ± 0.25[a]	0.09
IA (mm^2)	0.69 ± 1.60[a]	0.79 ± 1.91[a]	0.46
EEM area (mm^2)	0.23 ± 2.78	-0.32 ± 2.60[b]	0.01
LA (mm^2)	-0.46 ± 2.78[b]	-1.11 ± 3.00[a]	0.005
IA/EEM area (%)	3.27 ± 8.19[a]	4.65 ± 10.20[a]	0.06
At Year 1			
IA/EEM area (%)	14.97 ± 10.96	17.19 ± 14.68	0.03

Mean $\pm$ SD are the average value of all matched sites in each group. p-value for comparison between MMF-treated and AZA-treated patients by independent t-test. MIT, maximum intimal thickness; IA, intimal area; EEM area, external elastic membrane area; LA, lumen area; IA/EEM area, cross-sectional area stenosis.
[a]$p < 0.001$, [b]$p < 0.05$, baseline compared with one year by paired t-test.

group than in the Aza group (ΔEEM area: 3.36 ± 2.30 mm^2 vs 2.43 ± 1.47 mm^2, $p = 0.003$).

DISCUSSION

This study has shown that 52% of all sites had no significant remodeling, 25% exhibited vessel enlargement, and 23% had vessel shrinkage in the presence of variable intimal thickening in the first year after OHT. Vessel compensatory enlargement is associated with intimal growth, but negative remodeling is not directly linked to any change in intimal hyperplasia at Year 1. Glagov et al originally found from autopsy studies that human native coronary arteries enlarge in response to atheroma plaque area.[20] Positive remodeling may be a compensatory mechanism in the early development of native coronary artery disease and CAV that prevents luminal loss.[21-23] This compensatory remodeling is generally inadequate to compensate for the effects of plaque growth in recipients.[12,14]

The ability to undergo compensatory vessel enlargement in response to plaque formation is dependent on intact endothelial function.[24] Coronary endothelial dysfunction has been found in the early post-transplantation period before the development of intimal thickening.[25] Coronary endothelial dysfunction is an early marker for the development of intimal thickening and graft atherosclerosis.[26] The prevalence of epicardial endothelial dysfunction is 30% to 40% in patients during the first year post-OHT and persists at long-term follow-up.[27] If compensatory positive remodeling is influenced by endothelial dysfunction in the first year after transplantation, this may explain why >50% of sites did not enlarge sufficiently in the presence of intimal growth. On the other hand, adventitial inflammation and subsequent fibrosis may inhibit vessel enlargement, and cause vessel shrinkage.[22,28] Progression to symptomatic CAV is in part due to the lack of vessel compensatory dilation or even shrinkage in the setting of intimal proliferation.

The relative contribution of vascular remodeling and intimal hyperplasia as the cause for luminal narrowing in CAV is controversial. One study demonstrated that lumen loss in transplant coronary artery disease is a biphasic process involving early intimal thickening and late constrictive remodeling.[13] In the present study we

found that 20% of the sites had lumen enlargement of >10% from baseline, and 36% of the sites had lumen loss of >10% from baseline at Year 1. Lumen enlargement was associated primarily with an increase in EEM area. The contribution to lumen loss was due more to a decrease in EEM area than intimal thickening, which supports the finding by Pethig and colleagues.[10] Thus, in CAV, the change in vessel remodeling is a major factor influencing the change in lumen area at the first year after OHT.

In addition, the discordant remodeling patterns within the same artery seen in 76% of the arteries is in agreement with previous studies.[9,15,29] Endothelial function may not be uniformly disturbed after cardiac transplantation.[30] Different vascular remodeling patterns could be observed in the same artery due to variable responses of the local vessel and the interaction of systemic immunologic processes with pre-existing pathology.[29]

The randomized trial that formed the basis of this IVUS core laboratory data showed that MMF, an immunosuppressive agent that inhibits cellular proliferation, was more efficacious than Aza in reducing rejection episodes and improving survival among heart transplant recipients.[19] The present study is an expansion of the IVUS results from that clinical trial. The IVUS data demonstrate that the MMF-treated patients showed a trend for lower maximal MIT per patient compared with the Aza-treated patients (p-value was borderline, most likely due to small sample size). MMF also decreased the degree and incidence of vessel shrinkage. The mechanism of MMF in decreasing the development of CAV may be due to the inhibitory effects on both lymphocyte proliferation and smooth muscle cell proliferation.[31-33] In addition, the benefit of MMF may partly contribute to the decrease in systemic inflammatory activity as indicated by reduced levels of highly sensitive C-reactive protein in MMF-treated patients.[34]

Study Limitations

This is not a natural history study of CAV because the patients were treated with different medications. However, all studies of CAV are confounded by the multiple drugs these patients receive. All IVUS images were performed with manual pullback of the IVUS catheter because motorized pullback devices were not available during the study period. This could lead to difficulty in matching sites from the baseline and follow-up studies. However, the only sites chosen were those with physical characteristics that could be identified on both studies. In addition, automated pullback studies do not guarantee correspondence between sites based on the distance from reference markers. This study did not analyze the relation between vascular remodeling and clinical characteristics.

Table 6. Concordance of Vascular Remodeling Patterns Within Each Artery

Examined sites/arteries	1 compensatory pattern	2 compensatory patterns	3 compensatory patterns
2 (n = 15)	8	7	—
3 (n = 103)	27	67	9
4 (n = 72)	10	48	14
Total (n = 190)	45 (24%)	122 (64%)	23 (12%)

ΔEEM area per site could increase, decrease or remain constant ($\leq$10%). 1 compensatory pattern = all sites from the same artery had same direction of ΔEEM; 2 compensatory patterns = 2 sites from the same artery had different ΔEEM patterns; 3 compensatory patterns = 3 sites from the same artery had different ΔEEM patterns.

In conclusion, in CAV, the vascular remodeling pattern is the major factor influencing the change in lumen area at Year 1 after OHT. Vascular remodeling is a complex process determined by many factors, and the pathophysiologic mechanisms are not fully understood. In the first year after cardiac transplantation, vascular remodeling occurred in 48% of coronary artery sites and the majority of coronary arteries had discordant vascular remodeling patterns. When the lumen narrows, the contribution from the decrease in EEM area is greater than that of intimal thickening, whereas lumen enlargement results primarily from an increase in EEM area, and not from regression of baseline intima thickening.

Compensatory enlargement (positive remodeling) is associated with intimal growth, and vessel shrinkage (negative remodeling) is not directly linked to any change in intimal hyperplasia. Angiography alone cannot distinguish the mechanism of lumen narrowing and it requires IVUS cross-sectional imaging to clarify these issues. These results support the hypothesis that negative remodeling post-transplantation is due to the inflammatory process of CAV. Mycophenolate mofetil was more efficacious than azathioprine in preventing the development of CAV by reducing the degree and incidence of vessel shrinkage and the progression of intimal hyperplasia in the first year after cardiac transplantation. (Table 6).

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