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Authors

Li, Hai-yan
Tanaka, Koji
Oeser, Brandy
et al.

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Original article

Compensatory enlargement in transplant coronary artery disease: an intravascular ultrasound study

LI Hai-yan, Koji Tanaka, Brandy Oeser, Brett Wertman, Jon A. Kobashigawa and Jonathan M. Tobis

Keywords: *transplant coronary artery disease; compensatory enlargement; intravascular ultrasound*

Background It is unclear to what extent the "Glagov phenomenon" occurs in transplant coronary artery disease (TCAD). The objective of this study was to evaluate the relationship between intimal hyperplasia and compensatory enlargement in TCAD.

Methods Intravascular ultrasound imaging was performed on 190 cardiac transplant recipients at (1.4±0.6) months and again (12.1±0.7) months after cardiac transplantation. Studies 1 year apart were matched at 625 sites. There were 345 coronary artery sites that had an increase in intimal area >10% from baseline to one year, and this comprised the data set of the present study.

Results At the first year, 91% of coronary artery sites with intimal growth had a total cross-sectional area stenosis ⩽40%, but 38% of the sites showed a decrease of >10% in lumen area. Receiver operating characteristic curve demonstrated that the change in cross-sectional area stenosis cut-off level at year 1 was 8% with a sensitivity of 75% and a specificity of 82% in predicting lumen loss. At a total cross-sectional area stenosis of 20%, sensitivity was 65% with a specificity of 81% in predicting lumen loss.

Conclusions In TCAD, vessel enlargement as a compensatory mechanism for plaque growth is generally inadequate. Instead of continued vessel expansion, luminal narrowing develops when there is more than 8% cross-sectional area filled with intimal hyperplasia. In distinction to native coronary artery atherosclerotic disease, the transition point in transplant vasculopathy where the lumen is diminished by increasing intimal growth, occurs at a lower threshold, 20% vs 40% of vessel cross-sectional area.

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Transplant coronary artery disease (TCAD) is the primary limitation to long-term survival in heart transplant recipients.[1,2] Intravascular ultrasound (IVUS) detects abnormal intimal thickening in 50% of patients at 1 year.[3] Following orthotopic heart transplantation (OHT), coronary artery narrowing is ultimately determined not only by an increase in intimal hyperplasia but also by the direction of vascular remodeling.[4] Compensatory enlargement (expansive remodeling) is described as a mechanism in early native coronary artery disease that prevents luminal loss despite plaque accumulation.[5,6] Glagov et al[7] originally noted this phenomenon in an autopsy study of 136 patients left main coronary arteries, showing that in the early stages of native coronary atherosclerosis, coronary arteries enlarged in relation to plaque area to preserve lumen size until plaque area occupied ⩾40% of the vessel area. Although the importance of compensatory enlargement as a major factor for preventing coronary luminal narrowing has been established in heart transplant recipients,[8-12] it is unclear to what extent the "Glagov phenomenon" occurs in TCAD. The objective of this study was to evaluate the relationship between intimal hyperplasia and compensatory enlargement in TCAD at the first year after OHT.

METHODS

Patient population

A total of 190 *de novo* cardiac transplant recipients came from a randomized multicenter double-blind controlled trial of mycophenolate mofetil (MMF) in

Division of Cardiology, Department of Medicine, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, California 90095, USA (Li HY, Tanaka K, Oeser B, Wertman B, Kobashigawa JA and Tobis JM)

Department of Cardiology, Peking University Third Hospital, Beijing100083, China (Li HY)

Correspondence to: Jonathan M. Tobis, Division of Cardiology, University of California Los Angeles, 10833 Le Conte Avenue, BL-394 CHS, Los Angeles, California 90095, USA (Tel: 310-794-4797. Fax: 310-267-0384. Email: jtobis@mednet.ucla.edu)

heart transplant recipients.[13] IVUS imaging was performed in all recipients at (1.4±0.6) months and again at (12.1±0.7) months after OHT. All patients received cyclosporine and prednisone and were randomized to receive either MMF or azathioprine (AZA). A total of 625 sites from 190 arteries (mean 3.3 sites per artery) were matched from baseline to 12 months. Of the 625 sites, 345 (55%) coronary artery sites with an increase in intimal area >10% from baseline to one year were selected. The 345 sites were from 161 patients (134 men, 27 women) with a mean age of (51.4±9.3) years. The mean donor age of the 161 patients was (29.0±12.7) years. 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 － 8 weeks and 12 months post-transplantation. After full anticoagulation 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 sublingual nitroglycerin and/or 200 μg intracoronary nitroglycerin before advancing the IVUS catheter. A 30 MHz ultrasound transducer was inserted into a distal position of the selected vessel where the luminal diameter exceeded 2 mm. A manual and continuous (>30-second) slow 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 by the echoPlaque program (echoPlaque™ version 2.5, INDEC System Inc., California, USA). 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 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 between the intima and the lumen, and the boundary between the media and adventitia. In each site, maximum intimal thickness (MIT), intimal area (IA), external elastic membrane area (EEM area) and lumen area (LA) were measured. Cross-sectional area stenosis was defined as (IA/EEM area)×100%.

The reproducibility of measurement in terms of mean interobserver variability was －1.4 (－11.7, 10.8) for lumen area and －2.7 (－9.6, 9.9) for EEM area. Therefore, a change >10% was chosen as representing a measurable difference of the interobserver variability. Based on the interobserver value, all sites were categorized into 3 subgroups depending on the change±10% for lumen area from the baseline to 12 months. Lumen gain was defined as sites with an increase >10% in lumen area from baseline to 12 months; lumen loss was defined as sites with a decrease >10% in lumen area; no significant change was defined as a change ≤10% in lumen area.

Statistical analysis

The mean±standard deviation or mean (minimum, maximum) was calculated for all numerical data. Comparisons between baseline and follow-up were determined by paired *t* test. Comparisons between MMF-treated and AZA-treated patients were performed using Mann-Whitney U test. A linear regression was used to describe the correlation between measured variables. Receiver operating characteristic (ROC) curves were employed to analyze the prediction of lumen loss at the first year after heart transplantation using cross-sectional area stenosis and to estimate a cross-sectional area stenosis cut-off value at optimized sensitivity and specificity. ROC area under the curve was reported as mean±standard error (SE). All analyses were performed using SPSS statistical software, version 11.5 (SPSS, Inc, USA). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Serial changes in IVUS parameters at year 1

At the first year post-transplant, in the sites that developed intimal hyperplasia, the average intimal area increased by 98% [from (1.66±1.58) mm^2 at baseline to (3.29±2.84) mm^2, P<0.001]; the average EEM area enlarged by 4% [from (15.92±6.91) mm^2 at baseline to (16.53±7.01) mm^2, P<0.001]; and the average lumen area decreased by 7% [from (14.25 ±6.30) mm^2 at baseline to (13.24±5.81) mm2, P<0.001]. Of the 345 sites with intimal growth, 132 (38%) sites showed lumen loss, 149 (43%) sites had no significant change in lumen area, and 64 (19%) sites had lumen gain although 91% of all sites had a total cross-sectional area stenosis ≤40% at year 1. Fig. 1 shows the matched IVUS images between baseline and one year.

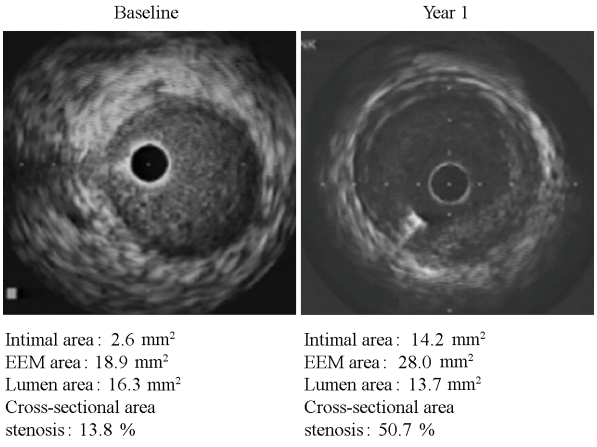

Fig. 1. An example of compensatory enlargement in transplant coronary artery disease. EEM area: external elastic membrane area.

Influence of MMF and AZA on lumen loss

Of the 345 sites, 174 sites came from 80 MMF-treated patients, and 171 sites came from 81 AZA-treated patients. At the first year after transplantation, the average increase in EEM area was greater in the MMF group than in the AZA group (P=0.006), whereas there was no significant difference in intimal hyperplasia between the two groups, P=0.50 (Table). Consequently, the average decrease in lumen area was greater in the AZA group than in the MMF group, P=0.009.

Cut-off value for the change in cross-sectional area stenosis as a predictor for lumen loss

The percent change in lumen area correlated closely with the change in cross-sectional area stenosis at the first year post-transplant (r=−0.704, P<0.001, Fig. 2). The ROC curve in Fig. 3 demonstrated that the change in cross-sectional area stenosis cut-off level at year 1 was 8% with a sensitivity of 75% and a specificity of 82% in predicting lumen loss. The result showed that above an 8% increase in cross-sectional area stenosis at year 1, the EEM of the vessel did not show a complete compensatory enlargement for a further increase in plaque area, and the lumen area decreased.

Table. Geometric features in MMF-treated and AZA-treated patients at year 1

Parameters	MMF (n=174 sites)	AZA (n=171 sites)	P value
ΔMIT (mm)	0.16 (−0.82, 1.17)	0.21 (−0.31, 1.60)	0.180
ΔIA (mm^2)	1.55 (0.04, 9.15)	1.70 (0.04, 11.02)	0.500
ΔEEM area (mm^2)	1.08 (−8.74, 11.25)	0.13 (−9.86, 6.23)	0.006
ΔLA (mm^2)	−0.47 (−10.27, 10.23)	−1.57 (−13.30, 5.15)	0.009
ΔIA/EEM area (%)	7.86 (−4.08,39.24)	9.62 (−2.10, 66.55)	0.630

MIT: maximum intimal thickness; IA: intimal area; EEM area: external elastic membrane area; LA: lumen area; IA/EEM area: cross-sectional area stenosis.

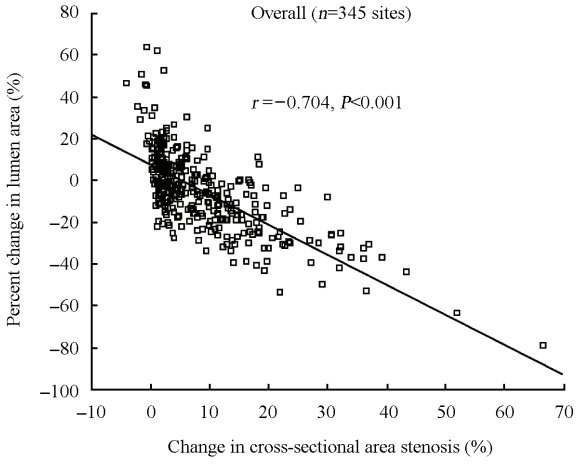

Fig. 2. The percent change in lumen area correlated closely with the change in cross-sectional area stenosis at the first year after transplantation.

Cut-off value for the total cross-sectional area stenosis as a predictor for lumen loss

Of the 345 sites, at the first year, the total cross-sectional area stenosis correlated closely with the change in cross-sectional area stenosis (r=0.80, P<0.001). While plotting luminal narrowing against the total cross-sectional area stenosis at the first year, an inverse correlation was demonstrated (r=−0.56,

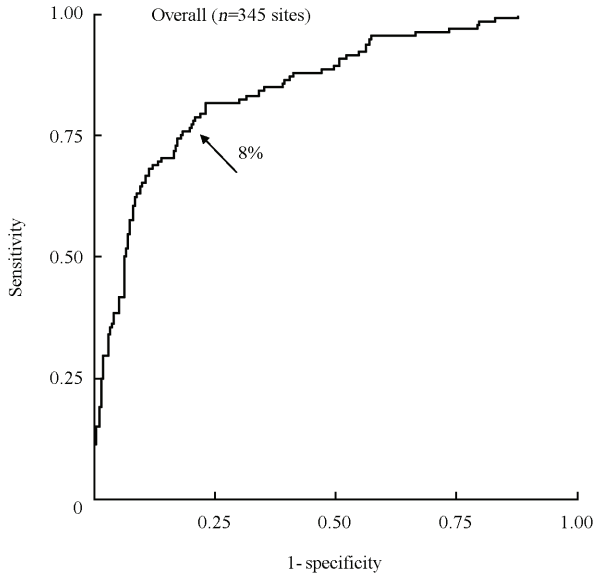

Fig. 3. Receiver operating characteristic curve values for the change in cross-sectional area stenosis in predicting lumen loss at the first year after transplantation. At a change in cross-sectional area stenosis of 8%, sensitivity was 75% with a specificity of 82% (ROC area under the curve: 0.85±0.02).

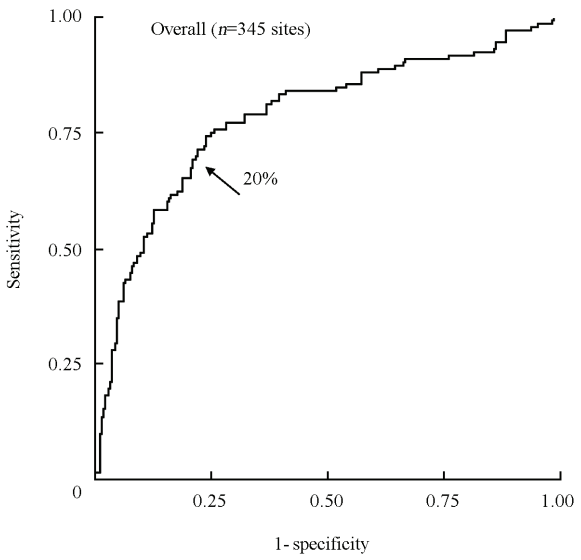

Fig. 5. Receiver operating characteristic curve values for the total cross-sectional area stenosis in predicting lumen loss at the first year after transplantation. At a total cross-sectional area stenosis of 20%, sensitivity was 65% with a specificity of 81% (ROC area under the curve: 0.78±0.03).

P<0.001, Fig. 4). At a total cross-sectional area stenosis of 20%, sensitivity was 65% with a specificity of 81% in predicting lumen loss (Fig. 5). The finding demonstrated that above 20% cross-sectional area stenosis at year 1, luminal narrowing occurred predominantly.

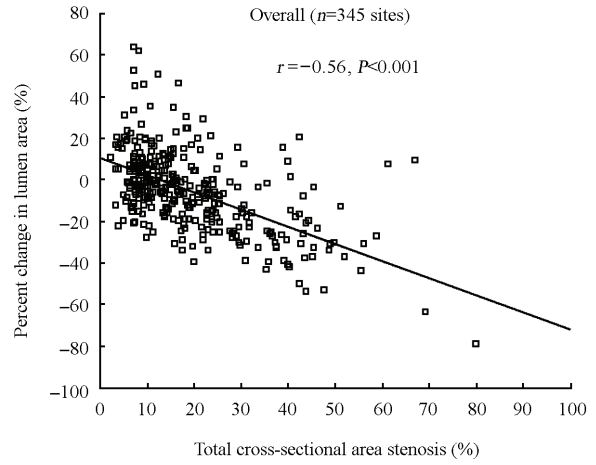

Fig. 4. Percent change in lumen area against the total cross-sectional area stenosis at the first year after transplantation.

DISCUSSION

The present study confirmed that expansive remodeling is a compensatory response for intimal hyperplasia formation in the early development of TCAD.[6] But this compensatory enlargement for plaque growth is less robust than in native coronary artery atherosclerotic disease. In the first year post-transplant, although a total cross-sectional area stenosis of ⩽40% was present in 91% of all coronary artery sites, 38% of all sites developed lumen loss. The explanation for the inadequate compensatory enlargement in TCAD as intimal hyperplasia develops is unclear. Several factors may contribute to this phenomenon. First, the ability to undergo compensatory vessel enlargement in response to plaque formation is dependent on intact endothelial function.[14] 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.[15] Second, TCAD is characterized by diffuse and concentric intimal thickening that may involve all portions of the coronary arteries and veins, including the intramyocardial branches.[16] Concentric plaques have less ability to remodel and preserve luminal area compared with eccentric plaques.[17] Third, the central process in the development of TCAD is the inflammatory response to immune or nonimmune-mediated endothelial damage.[2] Adventitial inflammation and subsequent fibrosis in transplant

coronary arteries may inhibit vessel enlargement, and even cause shrinkage of the vessel.[10-12] Fourth, the relationship between luminal narrowing and the total cross-sectional area stenosis in transplant coronary arteries is different from that of native coronary arteries. Preexisting donor atherosclerosis may influence this difference. Vessel compensatory enlargement for plaque formation is already initiated at donor lesion sites. The presence of preexisting donor atherosclerosis may impede compensatory enlargement as intimal thickening progresses post-transplant.[18] Finally, it is important to note that the compensatory enlargement for increasing plaque accumulation in TCAD was limited. The present study found that when an increase in coronary artery cross-sectional narrowing from baseline to one year was greater than 8%, the EEM of the vessel did not show a complete compensatory enlargement as intimal hyperplasia continued to increase, and luminal narrowing occurred.

The ability of compensatory enlargement of the EEM to protect lumen size was seen in sites with a lower degree of stenosis (≤20%), whereas in sites with higher stenosis (>20%) the compensatory mechanism was lost and lumen area markedly diminished with increasing plaque area. These results demonstrate that the transition point where intimal hyperplasia growth produces a lumen decrease tends to be lower in TCAD (total cross-sectional area stenosis≈20%) than in native coronary artery disease (total cross-sectional area stenosis≈40%), which may be attributed to the inflammatory response post-transplant.

The randomized trial showed that MMF was more efficacious than AZA in reducing rejection episodes and improving survival among heart transplant recipients.[13] The present study is an expansion of the IVUS results from this clinical trial. The IVUS data demonstrated that MMF decreased the degree of vessel shrinkage and resulted in a lower luminal narrowing. The mechanism of MMF in decreasing the development of TCAD may be due to the inhibitory effects on both lymphocyte proliferation and smooth muscle cell proliferation.[19,20] In addition, the benefit of MMF may partly contribute to the decrease in systemic inflammatory activity as indicated by reduced levels of high-sensitive C-reactive protein in MMF-treated patients.[21]

This is not a natural history study of TCAD because the patients were treated with different medications. In this study, all IVUS images were performed with manual pullback of the IVUS catheter because motorized pullback devices were not available during the period of this study. This could lead to difficulty in matching sites from the baseline and follow up studies. However, sites were chosen 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.

In conclusion, as in native coronary artery disease, enlargement of the EEM (expansive remodeling) is a compensatory mechanism in the early development of transplant vasculopathy that prevents luminal narrowing despite intimal hyperplasia accumulation. However, this compensatory mechanism is inadequate. In TCAD, when the change in coronary artery cross-sectional area stenosis approaches 8%, this protective mechanism fails to compensate for further increases in plaque formation and the lumen narrows. The transition point at which the lumen decreases with further increase in intimal hyperplasia tends to be lower in TCAD (total cross-sectional area stenosis≈20%) than in native coronary artery disease (total cross-sectional area stenosis≈40%).

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