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Vascular remodelling after cardiac transplantation: a 3-year serial intravascular ultrasound study

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KEYWORDS
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Aims To assess the time-course of intimal hyperplasia and vascular remodelling, and their relative contributions on luminal narrowing in transplant coronary artery disease (TCAD) by a 3-year serial intravascular ultrasound (IVUS) study.
Methods and results Serial IVUS examinations were performed in 90 cardiac transplant recipients at 1.4 ± 0.6 months after transplantation and again annually thereafter for 3 years. From 90 arteries, 304 sites were matched from baseline to the third year post-transplant. Based on the change in external elastic membrane (EEM) area $\pm 10\%$ at 1 year, 304 sites were divided into three groups: sites with no remodelling (52%); early constrictive remodelling (26%); and early compensatory enlargement (22%). Greater intimal growth was seen at 1 year in sites with early compensatory enlargement, whereas there was no change in intimal area in sites with early constrictive remodelling. Over 3 years, the cumulative lumen loss was greater in sites with early constrictive remodelling than in sites with early compensatory enlargement or no remodelling ($P < 0.001$). When luminal narrowing occurred for each annual interval, the contribution from the decrease in EEM area was greater than that due to intimal thickening ($P < 0.001$).
Conclusion During the first 3 years post-transplant, the largest intimal growth occurs in the first year, mostly in sites with early compensatory enlargement. The contribution to luminal loss in TCAD is greater from constrictive remodelling than from intimal hyperplasia. The type of remodelling pattern that occurs in transplanted coronary arteries within the first year post-transplant may be a predictor of the progression of luminal narrowing during subsequent years.

Introduction

Transplant coronary artery disease (TCAD) is the major cause of death in heart transplant recipients beyond the first year after transplantation.[1–4] Intravascular ultrasound (IVUS) detects abnormal intimal thickening in 50% of patients at 1 year.[5] Angiographic evidence of TCAD is present in 42% of heart transplant recipients at 5 years.[6] 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 remodelling.[7,8] Although the importance of vascular remodelling as a factor for influencing coronary luminal narrowing has been established in heart transplant recipients,[9–15] it is unclear what the relative importance is of intimal hyperplasia and vascular remodelling on the development of TCAD during the long-term follow-up after OHT. The objective of this study was to assess the time-course of intimal hyperplasia and vascular remodelling, and their relative contributions on luminal narrowing in the development of TCAD by a 3-year serial IVUS study.

Methods

Patient population

There were 650 cardiac transplant recipients who were enrolled between 1994 and 1995 in a randomized trial comparing mycophenolate mofetil and azathioprine.[16] Of the 650 patients, 90 patients had serial IVUS studies over 3 years and were included in the present analysis. The trial was approved by the Institutional Review Board of each participating centre, and signed informed consent was obtained from all patients.

Angiography

Coronary angiography was performed at 1–8 weeks and at annual intervals during the 3-year follow-up. The angiograms were analysed by quantitative coronary angiographic methods by an independent core laboratory at Stanford University. The angiographic diagnosis of TCAD was based on observing a new lesion $\geq 50\%$ diameter narrowing of a major epicardial vessel.

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IVUS imaging procedure

IVUS imaging was performed at 1–8 weeks and at annual intervals during the 3-year follow-up. After full anticoagulation with 100 units/kg of heparin, 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 (4.3 Fr, CVIS, Sunnyvale, CA, USA; 3.5 Fr, Hewlett-Packard, Palo Alto, CA, USA) was inserted into a distal position of the selected vessel where the luminal diameter exceeded 2 mm. A manual and continuous slow pullback (>30 s) 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. Only one vessel per patient was imaged by IVUS. The left anterior descending artery (LAD) was primarily selected. If the LAD could not be used, the IVUS study was performed on the left circumflex artery (CX) or right coronary artery (RCA).

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., CA, 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 (LM), 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 third year IVUS study, and then these selected frames were matched with sites from baseline and the first and second year IVUS studies. 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%. *Figure 1* shows sequential IVUS images from a matched site over the 3-year studies.

The reproducibility of measurement in terms of mean interobserver variability was 1.4 ± 3.8% for LA and 2.7 ± 3.3% for EEM area. Therefore, a change >10% was chosen as representing a measurable difference >2 SD of the interobserver variability. On the basis of the interobserver value, all sites were categorized into three remodelling patterns depending on the change ±10% for EEM area from the baseline to 12 months after transplantation. For each annual interval, expansive remodelling was defined as sites with an increase >10% in EEM area; constrictive remodelling was defined as sites with a decrease >10% in EEM area; no significant remodelling was defined as an absolute change ≤10% in EEM area.

Statistical analysis

Descriptive statistics were presented as the mean value ± SD for continuous variables and as frequencies and percentages for categorical variables. The change for each year in the same group was tested using a paired *t*-test. For all matched sites, comparisons of IVUS measurements between the four timepoints were determined by repeated measures followed by pairwise comparisons with the Bonferroni *post hoc* test. Comparisons among the three vascular remodelling patterns were performed using one-way ANOVA followed by multiple comparisons with the Bonferroni *post hoc* test for continuous variables and Fisher's exact or χ^2 tests for categorical data. A two-sided *P*-value <0.05 was considered statistically significant.

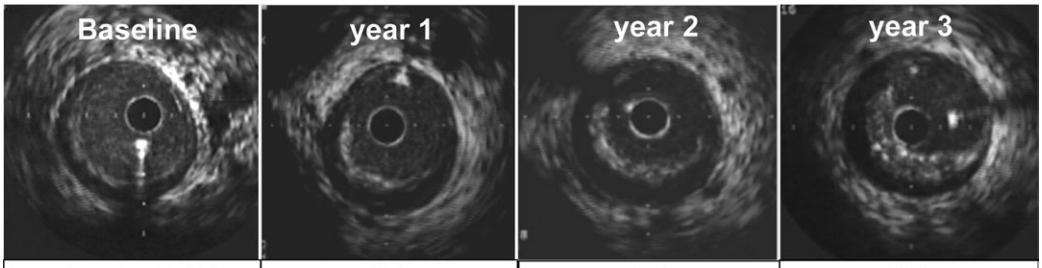
Results

Patient enrolment

A total of 90 patients (71 men, 19 women, with a mean age of 51.3 ± 9.6 years) were analysed. The first IVUS study was performed at 1.4 ± 0.6 months after transplantation and again annually thereafter for 3 years. From 90 arteries, 304 sites (72 LADs, 14 left CXs, and 4 RCAs) were matched from baseline to the third year post-transplant.

The yearly course of IVUS measurements for all studied sites

After heart transplantation, the yearly increase in IA accounted for 34% (year 1), 9% (year 2), and 14% (year 3) of the total intimal thickening ($F = 75.08$, $P < 0.001$, *Figure 2 Panel A*). The average EEM area did not change significantly each year ($F = 1.31$, $P = 0.27$, *Panel B*). Significant lumen losses were observed at year 1 and between year 1 and year 3 ($F = 28.74$, $P < 0.001$, *Panel C*). The yearly increase in cross-sectional area stenosis accounted for 27% (year 1), 16% (year 2), and 10% (year 3) of the total cross-sectional area stenosis ($F = 102.49$, $P < 0.001$, *Panel D*). The incidence of expansive remodelling for each year was similar during the 3-year follow-up (22, 21, and 23%, respectively). In contrast, the incidence of constrictive remodelling was lower at year 3



	Baseline	year 1	year 2	year 3
Intimal area (mm^2)	7.6	8.6	10.6	12.5
EEM area (mm^2)	18.3	19.0	19.8	20.3
Lumen area (mm^2)	10.8	10.4	9.2	7.8
Stenosis (%)	41.2	45.4	54.0	61.6

Figure 1 An example of sequential IVUS images from a matched site over the 3-year studies.

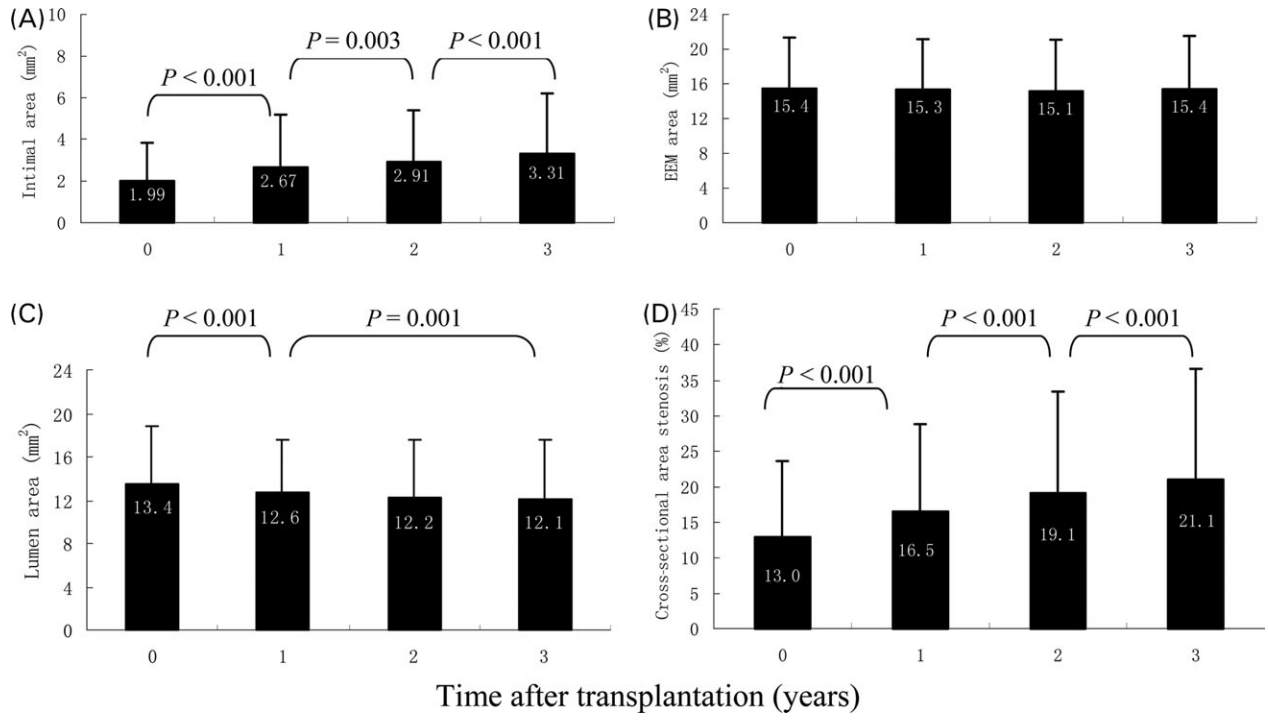


Figure 2 Serial changes in IA (Panel A), EEM area (Panel B), LA (Panel C), and cross-sectional area stenosis (Panel D) in all sites studied during the 3-year follow-up. *P*-value, using repeated measures followed by pairwise comparisons with Bonferroni *post hoc* test.

(15%) than in the first 2 years (year 1 and year 2 were the same, 26%), $P = 0.001$. In those sites with constrictive remodelling for each year, there was no significant change in IA (ΔIA: year 1 to year 0 $= 0.10 \pm 0.82$ mm^2; year 2 to year 1 $= -0.01 \pm 1.39$ mm^2; year 3 to year 2 $= -0.12 \pm 0.88$ mm^2, respectively).

Lumen loss during the 3-year follow-up

A decrease >10% in LA (lumen loss) for each year was seen in 119 (39%), 106 (35%), and 72 (24%) sites in the first, second, and third year, respectively. At year 3, the incidence of lumen loss tended to decrease (year 3 vs. year 1, $P = 0.02$; year 3 vs. year 2, $P = 0.09$). When luminal narrowing occurred for each annual interval, the contribution from the decrease in EEM area was greater than that of intimal thickening (year 1 to year 0 = 63% vs. 37%; year 2 to year 1 = 77% vs. 23%; year 3 to year 2 = 63% vs. 37%, all $P < 0.001$, *Figure 3*).

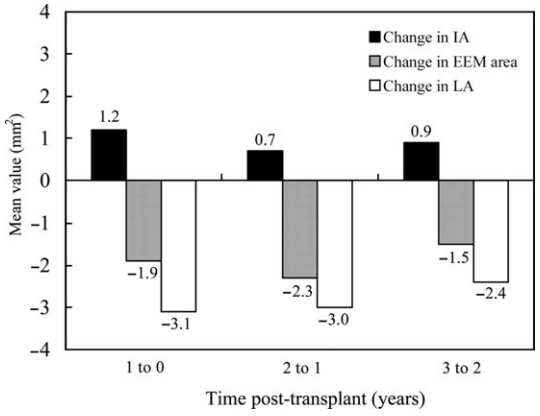


Figure 3 Serial changes in IA, EEM area, and LA in sites with lumen loss for each year. Year 1 to year 0, 119 sites; year 2 to year 1, 106 sites; year 3 to year 2, 72 sites.

Early expansive or constrictive remodelling of the vessel

In the first year after transplantation, of the 304 sites, 157 (52%) sites had no significant remodelling, 79 (26%) sites exhibited shrinkage (early constrictive remodelling), and 68 (22%) sites showed compensatory enlargement (early expansive remodelling). The average EEM area at baseline was smaller in sites with early expansive remodelling than in sites with no remodelling or early constrictive remodelling (13.33 ± 4.93 mm^2 vs. 15.99 ± 6.03 mm^2, $P = 0.005$; 13.33 ± 4.93 mm^2 vs. 16.17 ± 5.85 mm^2, $P = 0.009$).

The 90 patients were classified into four groups depending on vascular remodelling patterns: (i) 36 patients with constrictive or constrictive and no remodelling patterns within the same artery; (ii) 20 patients with no remodelling within the same artery; (iii) 25 patients with expansive or expansive and no remodelling patterns within the same artery; (iv) 9 patients with constrictive and expansive remodelling patterns within the same artery. There was no significant difference in clinical characteristics among the three types of vascular remodelling (*Table 1*).

Annual changes in IA

In sites with early expansive remodelling or no remodelling, a greater degree of intimal hyperplasia was seen

Table 1 Clinical baseline demographic characteristics of recipients

Characteristics	Group 1 ($n = 36$) (constriction)	Group 2 ($n = 20$) (no remodelling)	Group 3 ($n = 25$) (expansion)	Group 4 ($n = 9$) (mixed)
Baseline demographics				
Donor age (years)	25.8 ± 11.5	24.8 ± 10.3	29.0 ± 14.8	31.3 ± 15.3
Recipient age (years)	49.3 ± 9.6	48.9 ± 10.5	53.1 ± 8.1	54.8 ± 12.4
Recipient gender, male/female	26/10	16/4	24/1	6/3
HLA mismatch	4.41 ± 1.16	4.79 ± 1.03	4.64 ± 1.36	4.78 ± 0.97
The aetiology of heart failure CAD	15 (41.7)	10 (50.0)	11 (44.0)	4 (44.4)
Recipient with CMV mismatch (D)	4 (11.1)	1(5.0)	5 (20.0)	0 (10.0)
Cold ischaemic time (h)	3.1 ± 1.2	3.3 ± 0.8	3.1 ± 0.7	3.3 ± 0.5
At year 1				
Cholesterol (mean value) (mmol/L)	5.35 ± 0.81	5.24 ± 0.67	5.28 ± 0.92	5.65 ± 0.99
Diabetes	19 (52.8)	7 (35.0)	15 (60.0)	5 (55.6)
Hypertension	33 (91.7)	18 (90.0)	23 (92.0)	8 (88.9)
Statins	18 (50.0)	10 (50.0)	15 (60.0)	6 (66.7)
Azathioprine	21 (58.3)	9 (45.0)	13 (52.0)	5 (55.6)
Rejection 3A or greater	16 (44.4)	9 (45.0)	16 (64.0)	5 (55.6)
At year 3				
Angiographic TCAD	1 (2.7)	2 (10.0)	4 (16.0)	0 (0.0)

$P > 0.05$ for overall comparison by one-way ANOVA for continuous variables and Fisher's exact or χ^2 tests for categorical data. Values are either *n* (%) or mean ± SD. CMV, cytomegalovirus; D+, donor positive; R−, recipient negative; HLA, human leukocyte antigen.

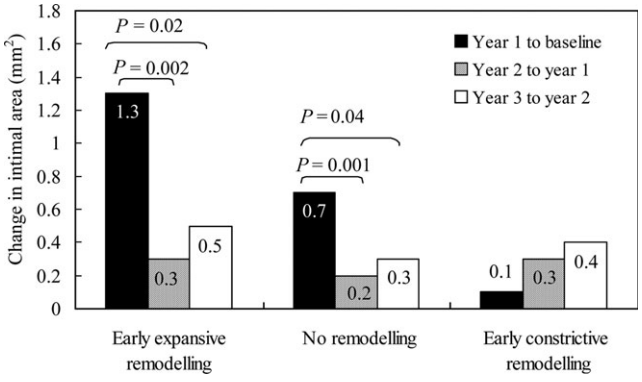


Figure 4 Annual changes in IA among the three vascular remodelling patterns.

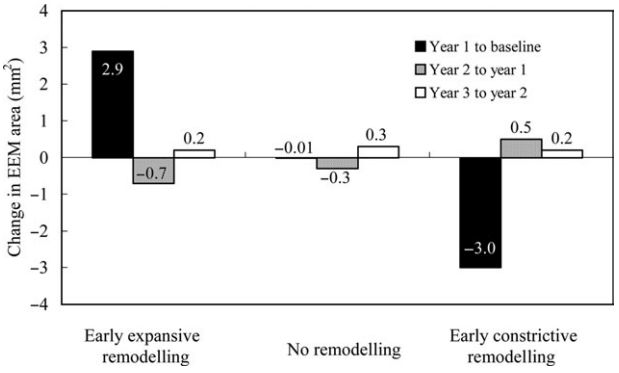


Figure 5 Annual changes in EEM area among the three vascular remodelling patterns.

at year 1 (*Figure 4*). In contrast, in sites with early constrictive remodelling, the average IA increased mildly but significantly at year 2 and year 3 (ΔIA: year 2 to year 1 = 0.34 ± 1.00 mm^2, $P = 0.004$; year 3 to year 2 = 0.44 ± 0.95 mm^2, $P < 0.001$), whereas there was no change in IA at year 1 (0.10 ± 0.82 mm^2, $P = 0.30$).

Annual changes in EEM area

At year 2, the sites with early expansive remodelling had a trend towards vessel shrinkage that did not reach statistical significance ($P = 0.07$), whereas sites with early constrictive remodelling showed mild compensatory enlargement ($P = 0.03$, *Figure 5*) despite the same degree of progression of intimal hyperplasia (0.32 ± 1.37 mm^2 vs. 0.34 ± 1.00 mm^2, $P = 1.0$). At year 3, there was no significant change in EEM area in sites with early expansive or constrictive remodelling despite further progression of intimal hyperplasia. In sites with no remodelling, there was no significant change in EEM area in the first 2 years, but the EEM of the vessel enlarged mildly but significantly at year 3 ($P = 0.04$).

Cumulative change in LA

Cumulative changes from baseline to year 3 are shown in *Figure 6*. In sites with early expansive remodelling, the cumulative intimal growth was well compensated by the enlargement of EEM, and LA had no change ($P = 0.7$). In sites with no remodelling, there was no significant change in EEM area ($P = 0.8$), intimal growth caused lumen loss. In sites with early constrictive remodelling, the mild intimal growth plus a decrease of EEM area resulted in a greater decrease in the total LA ($P < 0.001$).

Cumulative change in cross-sectional area stenosis

There was no significant difference in the cumulative increase of cross-sectional area stenosis from baseline to year 3 among sites with early expansive remodelling, without remodelling, and early constrictive remodelling (10.4 ± 14.2%, 7.3 ± 10.4%, and 7.6 ± 8.5%, respectively, $P = 0.14$ by one-way ANOVA).

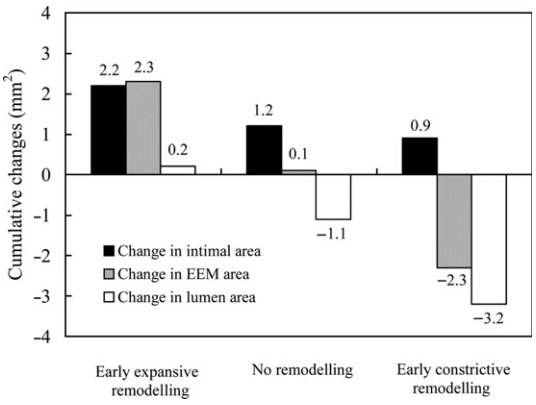


Figure 6 Cumulative changes from baseline to year 3 in IA, EEM area, and LA among the three vascular remodelling patterns.

Discussion

This IVUS core laboratory study analysed the multicentre data from 90 OHT patients who were randomly assigned treatment with mycophenolate or azathioprine. The matched IVUS cross-sectional images were separated according to the first year change in EEM of the vessel. In the first year post-transplant, coronary artery sites with an increase $>$10% in EEM were defined as early expansive remodelling, a decrease $>$10% in EEM was defined as early constrictive remodelling, and an absolute change $\leq$10% in EEM was defined as no remodelling. These groups were then compared with the changes in intimal hyperplasia, EEM area, and LA over the subsequent 2 years. This method differs from prior studies that segregated the sites into only two groups, those with expansive remodelling or constrictive remodelling. We believe that this provides a more appropriate description of alterations in vessel geometry because changes $<$10% can occur due to interobserver measurement variance.

The present study showed that a greater rate of progression of intimal hyperplasia occurred in sites with early expansive remodelling, primarily during the first year after transplantation. The incidence of constrictive remodelling for each year was lower at year 3 than in the first 2 years, whereas the incidence of expansive remodelling for each year was similar during the 3-year follow-up. Most importantly, the present study found that the degree of cumulative lumen loss was associated with the direction of early remodelling of transplant coronary arteries. This study also found that when luminal narrowing occurred, the contribution from the decrease in EEM area was greater than that of intimal thickening during the 3-year follow-up.

Intimal thickening occurs rapidly during the initial 2 years after cardiac transplantation, primarily in the first year.[12,13] The central process in the development of TCAD is believed to be the inflammatory response to immune or non-immune-mediated endothelial damage.[3,4] These processes are active in the first year after transplantation and induce vascular smooth muscle cell proliferation and migration from the media to form a neointima.[4] Interestingly, the present study found that in the first year post-transplant, a rapid progression of intimal hyperplasia occurred mainly in sites with early expansive remodelling, whereas there was no change in IA in sites with constrictive remodelling. Similarly, in the second and third year, sites with constrictive remodelling for each year also did not have a significant change in IA. These findings of the present study support the concept that expansive remodelling is associated with intimal growth, but constrictive remodelling is not directly linked to the change in intimal hyperplasia. It is likely that constrictive remodelling in transplant coronary artery is due to the diffuse inflammatory process associated with cardiac transplantation.

Several IVUS studies have described the serial changes in EEM area in the development of TCAD. One study compared the findings of two IVUS examinations 1–3 years apart in 75 patients after heart transplantation.[9] This study showed that compensatory dilation tended to occur in the early phase (2.0 ± 0.3 years) after heart transplantation, whereas no compensatory enlargement or shrinkage of the vessel occurred later (3.2 ± 0.5 years).[9] Another study analysed 135 segments (average length 12.5 ± 5.4 mm) among 5-year serial IVUS studies in 38 heart transplant recipients, and found that the average changes in the EEM area showed a biphasic response, consisting of early expansion (between years 1 and 3) and late constriction (between years 3 and 5).[13] In contrast, Pethig *et al.*[11] analysed the IVUS data of 30 heart transplant recipients by volume, and showed that the average vessel volume decreased in the first year post-transplant and increased thereafter. In fact, the three vascular remodelling patterns do occur in subgroups of coronary artery sites at each year after transplantation. The present study found that the incidence of constrictive remodelling was higher in the first 2 years after transplantation, whereas the incidence of expansive remodelling for each year was similar. Consequently, the incidence of lumen loss was lower at the third year post-transplant.

The relative contribution of vascular remodelling and intimal hyperplasia as the cause for luminal narrowing in TCAD is controversial. One study demonstrated that lumen loss in transplant CAD is a biphasic process involving early intimal thickening (within the first year) and late constrictive remodelling (between years 4 and 5).[13] Another IVUS study found that inadequate compensatory enlargement rather than intimal hyperplasia was the major predictor of coronary artery stenosis.[10] It is important to note that lumen loss occurs in a subgroup of transplant coronary artery sites. In the present study, 24–39% of sites showed lumen loss during the 3-year follow-up. The contribution to lumen loss was predominantly because of the decrease in EEM area when compared with the growth of intimal hyperplasia.

The first year after transplantation, 52% of coronary artery sites had no significant remodelling, 26% had constrictive remodelling, and 22% showed expansive remodelling. Beyond the first year, the late remodelling pattern was different between sites with early compensatory enlargement vs. shrinkage despite a similar amount of intimal growth. Glagov *et al.*[17] originally noted compensatory enlargement of human atherosclerosis in an autopsy study of LM coronary arteries. He noted 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 $\geq$40% of vessel area. Subsequently, IVUS studies have demonstrated that expansive remodelling is a compensatory mechanism in the early development of

native CAD and TCAD that prevents luminal loss.[18–20] This compensatory remodelling is generally inadequate to compensate for the effects of plaque growth in transplant recipients.[12,14] The ability to undergo compensatory vessel enlargement in response to plaque formation is dependent on intact endothelial function.[21] The prevalence of epicardial endothelial dysfunction is 30–40% in patients during the first year post-transplant and persists at long-term follow-up.[22] However, the pathophysiologic mechanisms of the remodelling process of native atherosclerosis and transplant vasculopathy are not completely understood. The findings of the present study demonstrate that the development of intimal hyperplasia is one of the multiple factors influencing the direction of vessel remodelling in TCAD. Importantly, this study found that a cumulative lumen loss after transplantation was associated with the direction of early remodelling. A greater cumulative lumen loss was seen in sites with early constrictive remodelling, whereas there was no significant change in the mean LA in sites with early expansive remodelling despite a greater progression of the mean IA, which was similar to the observation by Tsutsui *et al*.[23] These findings demonstrate that the early remodelling pattern after cardiac transplantation may be a predictor of the progression of transplant coronary artery luminal narrowing during subsequent years.

Previous studies have demonstrated that statin treatment is associated with lower risks of death, serious rejection, and the development of TCAD.[24–26] Mycophenolate mofetil was more efficacious than azathioprine in reducing progression of TCAD and improving survival among heart transplant recipients.[16,27] In the present study, there was no significant difference in the use of statins or azathioprine, total cholesterol levels, the incidence of diabetes, and hypertension, CMV infection, as well as acute allograft rejection, among the three types of early remodelling pattern. Recently, Kobashigawa *et al*.[28] found that rapid progression of intimal thickening in the first year after transplantation (an increase of $\geq$0.5 mm in MIT from baseline to 1 year measurement) predicts all cause-mortality, non-fatal myocardial infarction, and the subsequent development of angiographically severe TCAD. In the present study, there was no significant difference in the incidence of angiographic TCAD between patients with early expansive remodelling and patients with early constrictive remodelling during the 3-year follow-up. The relatively small number of patients in the present study may impact this observation. Therefore, further studies with a larger number of patients should assess the relationship between early vascular remodelling patterns seen at year 1 after transplantation and clinical outcomes.

The difference in observations between these IVUS studies could be due to different medical regimens in the patient populations. Different definitions, such as using biphasic (expansive or constrictive) remodelling vs. three remodelling patterns (expansive, constrictive, and no remodelling) could also affect the findings.

Limitations

This is not a natural history study of TCAD because the patients were treated with different medications. However, all studies of TCAD are confounded by the multiple drugs these patients receive. In the present 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 only included with physical characteristics that could be identified on serial studies. In addition, automated pullback studies do not guarantee correspondence between sites based on the distance from reference markers. Serial ultrasound studies are not available beyond 3 years to determine the sequential changes in the artery that eventually develops clinically significant transplant vasculopathy. Finally, the relatively small number of patients with the same remodelling pattern within the same artery may impact this assessment of the relationships among vascular remodelling patterns, clinical characteristics, and outcomes.

Conclusions

The mechanisms of vessel remodelling in TCAD may be more complex than in native CAD. After cardiac transplantation, a greater rate of progression of intimal hyperplasia occurs in the first year compared with subsequent years, primarily in coronary artery sites with early EEM enlargement. Constrictive remodelling primarily occurs in the first 2 years after transplantation. Of note, constrictive remodelling is responsible for a greater percentage of transplant coronary artery luminal loss than is intimal hyperplasia. Over 3 years a greater cumulative lumen loss was seen in sites with early constrictive remodelling, whereas there was no significant change in the mean LA in sites with early expansive remodelling despite a greater progression of the mean IA. These findings demonstrate that the early remodelling pattern of transplant coronary arteries may be a predictor of the progression of luminal narrowing during subsequent years. The patterns of early remodelling of the coronary arteries in transplanted hearts represent the variable responses to the underlying pathologic mechanisms of transplant vasculopathy.

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Conflict of interest: none declared.

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