5

IVUS in the Assessment of Coronary Allograft Vasculopathy

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1. Introduction

Cardiac allograft vasculopathy (CAV) is a unique form of accelerated atherosclerosis and remains the leading cause of late morbidity and mortality in heart transplant patients accounting for 30% mortality at 5 years (Miller et al., 1993), (Taylor et al., 2007).
Although the pathogenesis of CAV is not fully elucidated, it seems to result from a complex interplay between immunologic and nonimmunologic factors, with consequent repetitive vascular injury and a localized sustained inflammatory response (Costanzo et al., 1998), (Julius et al., 2000). CAV affects large epicardial vessels and the microcirculation which results in a progressive luminal narrowing (Gao et al., 1990) and reduces myocardial blood flow (Kushwaha et al., 1998). CAV may be present in intramyocardial vessels even if epicardial disease is not evident (Clausell et al., 1995). Autopsy findings have demonstrated the presence of CAV in nearly all specimens at two years and changes are seen as early as 6 weeks after cardiac transplant (Baldwin et al., 1987), (St. Goar et al., 1992).
Early CAV is clinically silent, and ischemia is usually not evident until the disease is far advanced (Ciliberto et al., 1993), (Collings et al., 1994, (Mairesse et al., 1995), (Smart et al., 1991), (Stark et al., 1991) and graft failure tends to develop as a late manifestation of the disease. Therefore, identification of the asymptomatic patient at early stages of the disease is an important strategy for the prevention of irreversible detrimental effects on the graft.

2. IVUS and allograft vasculopathy

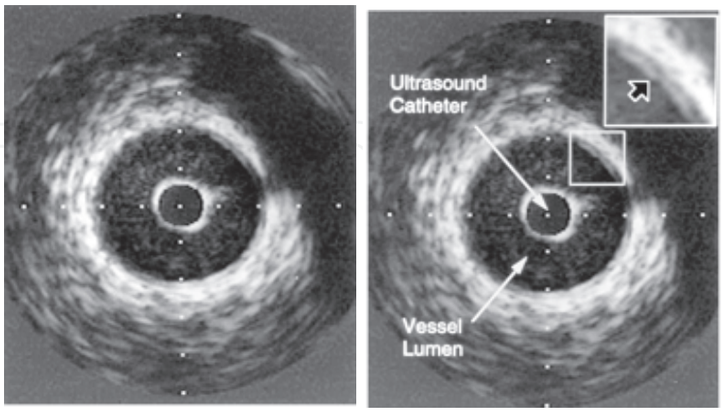
2.1 Limitations of coronary angiogram

Noninvasive screening tests for CAV such as the exercise electrocardiogram, thallium scintigraphy, and exercise radionucleotide ventriculography have shown insufficient sensitivity and specificity for reliable detection of CAV (Smart, 1991). Traditionally, **coronary angiography** has been used for the diagnosis of CAV and, according to the amount of stenosis in the most severely affected vessel, CAV is usually classified as absent (0% stenosis), mild (up to 30% stenosis), moderate (30–70% stenosis), or severe (>70% stenosis).
However, coronary angiography, given that it basically provides images in the form of a lumenogram, has been shown to systematically underestimate the presence of coronary atherosclerosis in transplant recipients as validated in autopsy studies (St. Goar et al., 1992), (Dressler et al., 1992). No information on vessel wall structure and intimal thickening is provided by coronary angiography. Being a highly specific (97.8%) tool, the diffuse nature of

CAV limits the sensitivity of coronary angiography to 79.3% (Sharples et al., 2003), (St. Goar et al., 1992). As a result, one fifth of patients with CAV have false normal coronary angiography (Sharples et al., 2003). Moreover, the reported 50% negative predictive value (Cale et al. 2010) limits the clinical utility of routine angiographic surveillance for CAV in heart transplant recipients. Based on these limitations, at least one transplant center has abandoned coronary angiogram for routine monitoring of heart-transplant recipients (Clague et al., 2001).
Intravascular ultrasound (IVUS) is a safe and reproducible imaging technique (Batkoff et al., 1996) that is more sensitive than angiography and useful for the early diagnosis of CAV, morphometric and volumetric analysis, assessing plaque composition and vessel remodeling (Miller et al., 1995), (Pflugfelder et al., 1993), (St. Goar et al., 1992), (Yeung et al., 1995). Whereas angiographic disease is present in 10% to 20% of patients at 1 year and 50% by 5 years after transplantation (Gao et al., 1988), (Uretsky et al., 1987) the prevalence of abnormal intimal thickening is seen in 50% of patients by 1 year in IVUS imaging (Gao et al., 1988), (Tuzcu et al., 1996), (Yeung et al., 1995). Therefore, IVUS is now considered the "gold standard" for the evaluation of CAV (Kapadia et al., 2000).

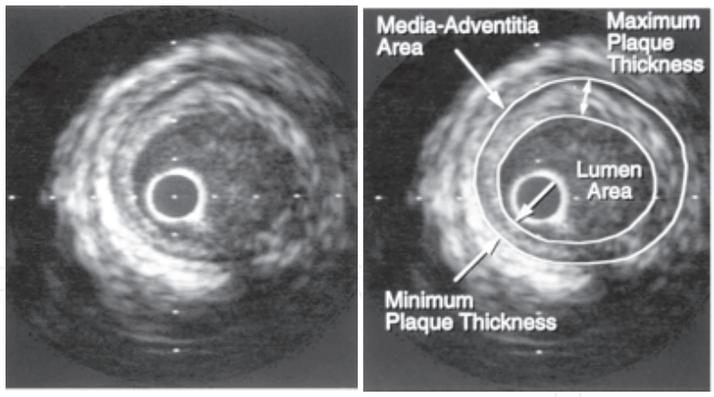
2.2 Lesion morphology and quantitative analysis

IVUS reveals cross sectional coronary artery image, which in post-transplant patients typically have tri-laminar appearance (Figure 1) with bright inner layer (intima), an echo-fine middle layer (media) and a bright dense outer layer (adventitia); and allows the following measurements: (1) maximal intimal thickness (MIT) as the greatest distance from the intimal leading edge to media-adventitia border, (2) minimal intimal thickness as the shortest distance from the intimal leading edge to media-adventitia border, (3) minimal luminal diameter as the shortest distance between opposing intimal leading edges, (4) lumen area as the area within the boundaries of the intimal leading edge, (5) vessel area as the area within the media-adventitia border, (6) plaque cross-sectional area as the difference between vessel and lumen areas, (7) plaque index as (lumen area/vessel area) X 100, and (8) eccentric index: [(maximal plaque thickness - minimal plaque thickness)/ maximal plaque thickness] X 100 (Figure 2).



Adapter from Tuzcu et al., 1995
Inset shows the three layers of the vessel wall (black arrow). The thin echogenic inner layer corresponds to the intima, the thin echolucent middle layer to the media, and the echogenic outer layer to the adventitia

Fig. 1. Ultrasound image of a normal coronary artery



Adapted from Tuzcu et al., 1995

Fig. 2. Measurements of lumen and vessel wall dimensions in an ultrasound image

The maximal intimal thickness (MIT) assessed by 2D-IVUS is a commonly used measure to describe the severity of lesions and has been defined as a clinically useful surrogate for clinical outcome (Mehra et al., 1995a), (Rickenbacher et al., 1995a). The threshold of MIT > 0.5 mm is usually acceptable (Kapadia et al., 2000), but this categorical classification of MIT, a continuous variable, into normal or abnormal is inherently arbitrary. This definition, however, is based on information provided by histological and ultrasound studies. In an autopsy study, normal intimal thickness, not including media, ranged between 0.10 and 0.30 mm in individuals between 21 and 40 years of age (Sims et al., 2002), (Velican et al., 1985). Therefore, intimal thickness > 0.3 mm is considered to represent significant CAV. A classification of the vascular disease severity according to **intimal thickness** and degree of vessel circumference involved was proposed by the Stanford group (Table 1).
The thickness of the **media** is usually about 0.02-0.23 mm and is unchanged or decreased with the development of CAV. Thus, the thickness of the normal **intima plus media** in young and middle age individuals ranges from 0.45 to 0.50 mm. (Sims et al., 2002), (Velican et al., 1985).

	Class			
	I	II	III	IV
Severity	Minimal	Mild	Moderate	Severe
Intimal thickness	<0.3 mm <180°	>0.3 mm >180°	0.3–0.5 mm or >0.5 mm, <180°	>1.0 mm or >0.5 mm, >180°

Adapted from St. Goar, 1992

Table 1. Ultrasound classification of CAV in cardiac transplant recipients)

Despite this immense value of IVUS in the detection of CAV, there is controversy regarding the methodology and imaging protocols. Site selection and adequate sampling for quantitative analysis is crucial. Most studies have selectively visualized the LAD, making the assumption that CAV occurs uniformly throughout the coronary tree. It has been demonstrated, that multi-vessel imaging is definitely more sensitive in detecting transplant vasculopathy lesions compared to single-vessel imaging (Kapadia, 2000), and sampling of a single coronary artery for imaging may not be sufficient to adequately

assess the prevalence of CAV. However, multi-vessel imaging is time consuming, adds to the cost of the procedure and, although procedural complications other than occasional spasm resolved with intracoronary nitroglycerin did not occur, the long-term safety of the multi-vessel imaging remains unknown. Thus, the limitations of single vessel imaging should be weighed against the potential benefits from adequate sampling of multi-vessel imaging.

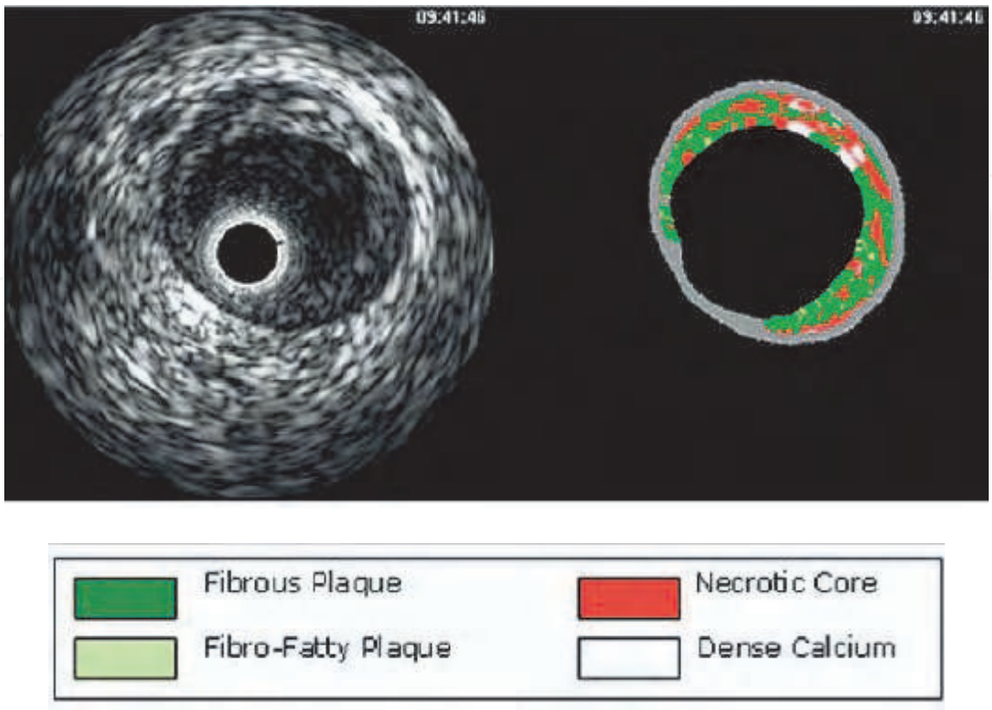
2.3 Three-dimensional reconstruction (3D-IVUS)

2D-IVUS has limitation in spatial registration and the inability to assess the full extent of vascular disease (Tuzcu, 2005) which reduces its sensitivity to detect the changes of atherosclerotic burden in CAV. Three-dimensional (3D-IVUS) reconstruction allows rapid and accurate measurement of volume and plaque dimensions with full extent of atherosclerotic pathology. Automated pullback with a known pullback speed is necessary. The vessel, lumen and plaque volume can be calculated using the Simpson rule for images that are 1 mm apart. Since the histology literature does not commonly depend on volumetric indices, currently, there is no well-defined threshold for these measurements and the information is not readily obtainable. Because of its superior reproducibility, however, 3D-IVUS may be used to assess the progression of coronary artery disease and allow for more accurate evaluation of interventions aimed at preventing or attenuating coronary artery disease (Bae et al., 2006), (White et al., 2003).

2.4 Virtual Histology Intravascular Ultrasound (VH-IVUS)

Grayscale IVUS is able to visualize coronary atherosclerosis in vivo and allows rapid and accurate assessment of plaque area and distribution, lesion length, and coronary remodelling (Bae et al., 2006), (Kapadia et al., 2000), (White et al., 2003), but has a significant limitation in the evaluation of atherosclerotic plaque composition.

VH-IVUS is a novel technology to characterize the different types of plaque morphology in vivo which based on the spectral analysis of the radiofrequency ultrasound signals in a frequency domain (Nair et al., 2002), (Nasu et al., 2006), (Rodriguez-Granillo et al., 2005). It displays the reconstructed color coded tissue map of plaque composition overlaid on a grey-scale image and groups plaque components into 4 basic tissue types: fibrous tissue (green), fibro-fatty tissue (light green), necrotic core (red), and dense calcium (white). (Figure 3) This approach has not been validated with histological techniques in heart transplant patients, however in the non-transplant population the overall predictive accuracies were 90.4% for fibrous tissue, 92.8% for fibrolipidic, 89.5% necrotic core, and 90.9% for dense calcium (Nair et al, 2001), (Nair et al, 2002), (Nasu et al, 2006). In native coronaries morphological composition of atherosclerotic plaque is a useful determinant of the plaque vulnerability (Ehara et al., 2004), (Naghavi et al., 2003), (Valgimigli et al., 2007), and identified plaques with a high-risk of future clinical events (Bae et al., 2008), (Kawaguchi et al., 2007), (Kawamoto et al., 2007). After heart transplantation, simultaneous assessment of virtual histology with IVUS provides detailed information about plaque morphology and composition, may improve the risk stratification of heart transplant recipients (Konig et al., 2008) and add important information in the clinical evaluation of heart transplant recipients (Raichlin et al., 2009).



(Left) Gray scale IVUS cross-section imaging shows concentric plaque: a (PV/SL) of 6.79 and a PI of 32% was calculated

(Right) The corresponding VH-IVUS image depicts specific color-coded plaque components and demonstrates fibrous plaque of 47%, fibrofatty plaque of 20%, dense calcium of 14%, and necrotic core of 27%.PV/SL, plaque volume normalized for segment length; PI, plaque index

Adapted from Raichlin et al., 2007b

Fig. 3. Gray scale IVUS cross-section imaging shows concentric plaque with corresponding VH-IVUS image

2.5 Impact of IVUS in understanding coronary allograft vasculopathy

Morphologic studies performed with IVUS have led to important insights into the etiology and pathogenesis of CAV.

Coronary artery vasculopathy (CAV) is a multifactorial phenomenon with variable morphologic features. Previous histological ex-vivo studies described two microscopic types of coronary allograft lesions (Johnson, 1989). One type of coronary lesion is confined to the proximal region of epicardial arteries and indistinguishable from typical atherosclerosis of native vessels. The second type is characterized by the presence of vasculitis, involving the entire coronary arterial system and has been suggested to represent the immune mediated vessel injury (Higuchi et al., 1999). The ability to differentiate between the existence of classic atherosclerosis and transplant-specific immunologically mediated CAV holds both prognostic and therapeutic values and this

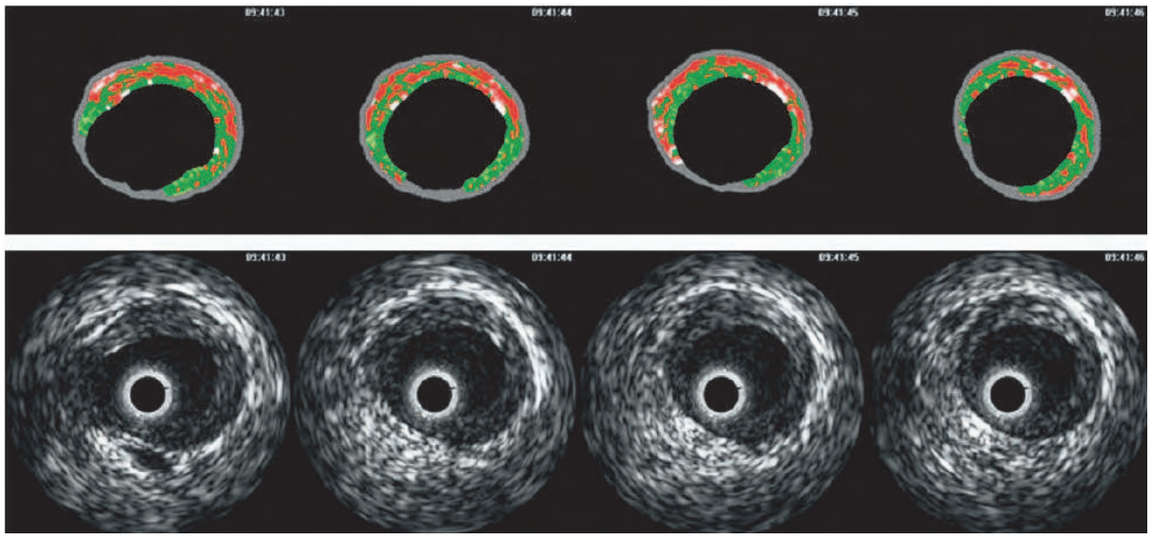
morphologic heterogeneity has been evident in gray scale (Tuzcu et al., 1996) and VH-IVUS study (Raichlin et al., 2009).

Typical atherosclerosis has been detected in 56% of donor hearts despite a mean donor age of thirty-two years (Tuzcu et al., 1995) and IVUS studies have demonstrated that atherosclerotic lesions located in proximal segments, involved the bifurcation sites with eccentric focal plaques, appeared similar to conventional atherosclerosis, were associated with fibrotic and fibro-fatty tissues in VH-IVUS (Konig et al., 2008), (Raichlin et al., 2009) positively correlated with the donor age and probably related to donor-derived coronary atherosclerosis (Kapadia et al., 1998), (Tuzcu et al., 1996).

On other hand de novo lesions assessed by IVUS were diffuse and circumferential, involved more commonly the mid and distal segments of the coronary arteries (Kapadia et al., 1998) and were associated with necrotic core and dense calcium burden ≥ 30%, which presumably reflects the inflammatory burden of the cardiac allograft atherosclerotic plaque (Raichlin et al., 2009). (Figure 4)

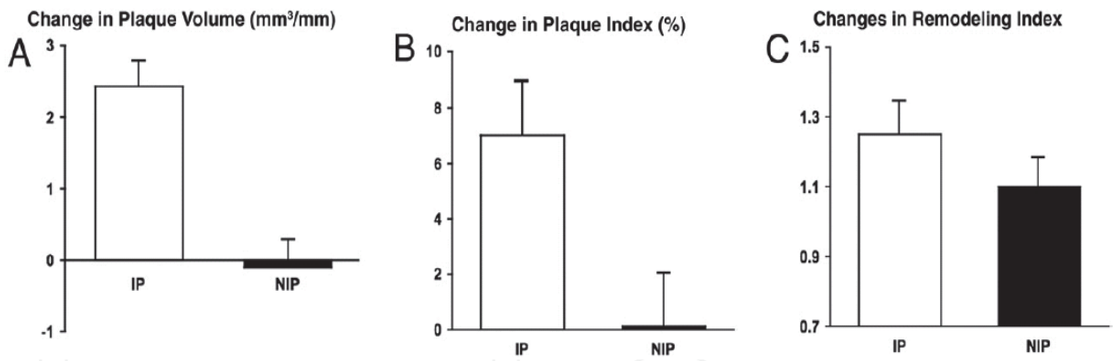
Previous studies have demonstrated that early immunological events surrounding engraftment lead to an inflammatory process in the vascular endothelium (Brunner-La Rocca et al., 1998), (Caforio et al., 2004), (Hornick et al., 1997), (Jimenez et al., 2001), (Narrod et al., 1989), (Opelz et al., 1997), (Vassalli et al., 2003), (Yamani et al., 2002). Although CAV may develop at any stage after transplantation, events during the first year, resulting most likely from initial and ongoing immunologically mediated injury to the vascular endothelium appear to be important in CAV pathogenesis (Kobashigawa et al., 2003) leading to more rapid progression in intimal thickening during the first year after transplantation (Kobashigawa et al., 1995), (Mehra et al., 1995d), (Rickenbacher et al., 1995a). A cross-sectional study demonstrated a mean absolute increase of 0.23 mm 10% in intimal thickening and intimal index respectively (Kobashigawa, 1995) during the first year of transplantation. After the first year, the intimal thickness and intimal area do not increase rapidly but new lesions continue to develop at previously normal sites (Kapadia SR et al., 1998). This underscores the importance for continued surveillance for transplant vasculopathy beyond first year after transplantation.

A relationship between immune events and an increase in systemic inflammatory markers following heart transplantation has been shown in several clinical studies (Eisenberg, 2000), (Labarrere, 2002) suggesting that chronic inflammation may be a central event in cardiac allograft vasculopathy. Experimental evidence demonstrated that acute cellular allograft rejection and CAV are closely related processes (Brunner-La Rocca et al., 1998), (Caforio et al., 2004), (Hornick et al., 1997), (Jimenez et al., 2001), (Narrod et al., 1989), (Opelz et al., 1997), (Vassalli et al., 2003), (Yamani et al., 2005) and elevated systemic levels of the inflammatory markers were predictive not only of cardiac allograft vasculopathy but also of allograft failure (Eisenberg & Pethig, 2000), (Hognestad et al., 2003), (Labarrere et al., 2002), (Raichlin et al., 2007b). An association between early recurrent cellular rejections and an increase in intimal thickening (Mehra et al., 1995a) and the presence of necrotic plaque (Raichlin et al., 2007b) has been revealed in 2D and VH-IVUS studies. Moreover, focal inflammation as assessed by VH-IVUS resulted in subsequent progression of CAV. Thus, VH-IVUS can be used for in-vivo identification of patients with increased burden of "inflammatory plaque" and the predicting the progression of CAV following heart transplantation (Raichlin et al., 2009). (Figure 5)



Adapted from Raichlin et al., 2009

Fig. 4. Grayscale intravascular ultrasound (IVUS) cross-section imaging (bottom) and corresponding virtual histology (VH)-IVUS images (top) from patients with VH-IVUS–derived inflammatory plaque



A Progression in plaque volume in VH-IVUS derived inflammatory plaque (IP) and noninflammatory plaque (NIP) groups
Change in Plaque Volume (mm3/mm) **IP** (n=21) 2.42 ± 1.78; **NIP** (n=17) -0.11±1.65; p=0.01
B Progression in plaque index in the in VH-IVUS derived inflammatory plaque (IP) and noninflammatory plaque (NIP) groups
Change in Plaque Index (%): **IP** (n=21) 7± 9; **NIP** (n=17) 0.1± 8; p=0.04
C Remodeling index in VH-IVUS derived inflammatory plaque (IP) and noninflammatory plaque (NIP) groups
Remodeling Index: **IP** (n=21) 1.24 ± 0.44, **NIP** (n=17) 1.09 ± 0.36; p=0.03

Adapted from Raichlin et al., 2009

Fig. 5. Progression in Plaque Volume, Plaque Index, and Remodeling Index in IP and NIP Groups

The natural history of donor lesions after transplantation is largely unknown. In the 2010 ISHLT registry older donor age is an independent risk factor for early CAV (Stehlik et al.,

1089). Several studies, however, have found no significant difference in the rate of intimal thickening between patients with donor hearts having pre-existing coronary artery disease and those without (Botas et al., 1995), (Li et al., 2006). From multiple variables only serum triglyceride level and pre-transplant body mass index were found to be significant predictors for the progression of donor atherosclerosis (Kapadia SR et al., 1998). A VH-IVUS study has demonstrated relatively slow progression of CAV in a group of patients with fibrous, presumably donor-derived plaque (Raichlin et al., 2009).(Figure 5) Several studies, however, have shown that the presence of donor lesions leads to the more frequent development of de novo transplant vasculopathy lesions (Botas et al., 1995), (Escobar et al., 1994), (Gao et al., 1997). The impact of donor and recipient gender on transplant vasculopathy has also been assessed. Male recipients of a female allograft had a higher degree of vascular intimal hyperplasia compared with either male or female recipients of a male allograft as detected by IVUS imaging 1 year after heart transplantation (Mehra et al., 1994).

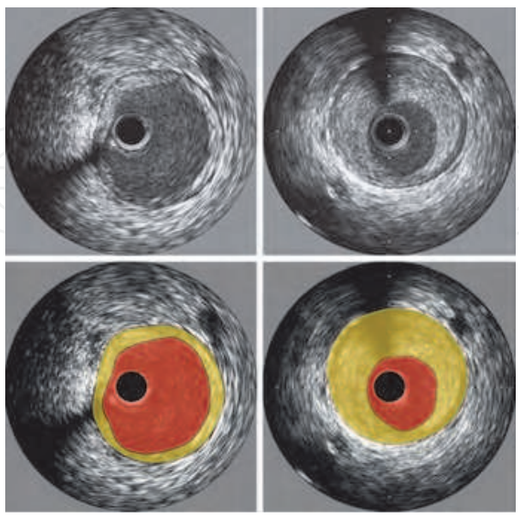
Arterial remodeling has been studied in the transplant population in serial and cross-sectional IVUS study designs. In its early stages, CAV shows no decrease in luminal diameter due to vascular remodeling, thus limiting the ability of angiography to detect and diagnose early CAV (Nissen et al., 2001). Three year serial IVUS studies have shown that the rate of remodeling of donor lesions is different from CAV. Furthermore, the rate of remodeling is different depending on the time interval from transplantation (Ziada et al., 1997). Both compensatory local vessel enlargement (positive remodeling) and vascular constriction (negative remodeling) have been demonstrated and it is thought that inadequate compensatory enlargement probably contributes significantly to luminal obstruction (Pethig et al., 1998). In a study of 3D-VH-IVUS, the coronary arteries with "inflammatory plaque" showed positive remodeling compared to "non-inflammatory plaque" (Raichlin et al., 2009).(Figure 5) These data are consistent with previous findings from a non-transplant population, which showed that inflammation is associated with expansion of the internal elastic lamina and positive remodeling closely correlates with plaque vulnerability (Burke et al., 2004), (Rodriguez-Granillo et al., 2006).

IVUS imaging has also have been used to evaluate the impact of non-immunological factors in the development of transplant vasculopathy lesions. Total cholesterol, low-density lipoprotein cholesterol, triglyceride levels, obesity indexes, donor age greater than 35, and years following cardiac transplantation were independent predictors of the severity of cardiac allograft vasculopathy as determined by the severity of intimal thickening (Escobar et al.,, 1994), (Hauptman et al., 1995), (Mehra et al., 1995), (Rickenbacher et al., 1995b), (Valantine et al., 1995).

2.6 Clinical applications

Studies performed using IVUS have shown a strong association between the severity of the disease and the clinical outcome. Severe intimal thickening predicted both events (death, MI, and re-transplantation) and survival in patients after transplantation (Mehra et al., 1995b), (Mehra et al., 1995c) regardless of the presence of angiographic CAV (Rickenbacher et al., 1995b). Moreover, rapidly progressive vasculopathy, defined as an increase of ≥ 0.5 mm in intimal thickness within the first year after transplantation, was a powerful predictor of all-cause mortality, nonfatal MI, and the subsequent development of angiographic coronary obstructions independent of other confounding variables, including rejection episodes, age, gender, and conventional risk factors (Kobashigawa et al., 2005), (Tuzcu et al.,

2005). (Figure 6 and 7) Thus, the prognostic value of IVUS has significant clinical utility in the identification of a high-risk population and underscores the importance of serial IVUS examinations (Kapadia et al., 1999).



Adapted from Tuzcu et al., 2010

Fig. 6. Serial intravascular ultrasound examination at baseline (left side panel) and 1 year follow-up (right side panel) demonstrates significant plaque development at the first year. Transplant vasculopathy at the same site in a coronary vessel segment

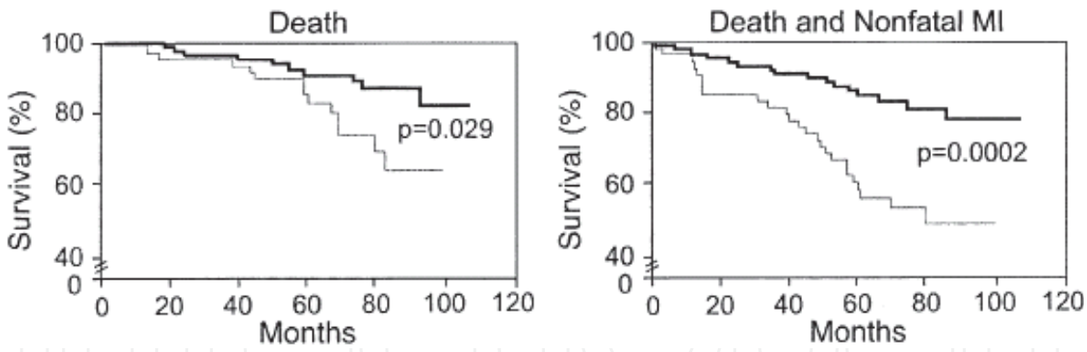


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Fig. 7. Kaplan-Meier all-cause mortality **(left)** and death and myocardial infarction (MI) **(right)** rates of patients with and without rapidly progressive transplant vasculopathy. Thick lines - without rapid progression; thin lines - with rapid progression

IVUS also provides a sensitive tool to evaluate the effectiveness of different therapeutic and preventive modalities influencing CAV and various clinical protocols have incorporated IVUS findings as surrogate end-points for clinical events. Serial IVUS has been essential as a research tool in studies that assess emerging transplant vasculopathy therapies (Bae et al., 2006), (Eisen et al., 2003), (Fang et al., 2002), (Mehra et al., 1995c), (Raichlin et al., 2007a). The effects of early use of pravastatin on CAV have been assessed by IVUS imaging in a randomized study (Kobashigawa, 1995). 2D-IVUS measurements at baseline and 1 year after

transplantation showed less increase in MIT and maximal intimal index with pravastatin therapy. The incidence of coronary vasculopathy as determined by angiography and at autopsy also was lower (Kobashigawa, 1995).

The influence of angiotensin-converting enzyme inhibitors and calcium blockers on the development of CAV has also been assessed. Mehra et al., using IVUS, demonstrated that heart transplant recipients treated with either diltiazem or angiotensin-converting enzyme inhibitors, or both have significantly less intimal hyperplasia 1 year after cardiac transplantation than matched untreated control subjects (Mehra et al., 1995b), (Mehra et al., 1995c). Another IVUS study has demonstrated that a combination of a calcium channel blocker and an angiotensin-converting enzyme inhibitors is more effective in CAV prevention than the individual use of either drug alone. This effect was independent of mean arterial pressure, suggesting these drugs have a synergistic anti-proliferative effect beyond the anti-hypertensive efficacy (Erinc et al., 2005). Moreover, a 3D-IVUS study demonstrated that lower serum lipid levels and angiotensin-converting enzyme inhibitors use in patients after heart transplantation is associated with CAV plaque regression (Bae et al., 2006). The question of whether supplementation with antioxidant vitamins C and E retards the early progression of CAV has also been assessed by 2D-IVUS (Fang et al., 2002).

IVUS imaging has been used to evaluate the effect of immunosuppressive therapy on the development of CAV. A randomized, double-blind trial, comparing mycophenolate mofetil with azathioprine as adjuvant to cyclosporine, revealed that the change in mean MIT was less for the mycophenolate mofetil group than for the azathioprine group ($p = 0.056$) (Eisen et al., 2005).

The first clinical evidence that proliferation signal inhibitors (PSIs) could limit the development of CAV in heart transplant recipients was provided by an international multicenter randomized, double-blind study (Eisen et al., 2003) comparing everolimus with azathioprine as adjuvant to full dose of cyclosporin in 634 de-novo heart transplant patients. The results of the intravascular substudy with matched analysis of baseline and 1-year images were available for 211 patients. The average increase in intimal thickness was significantly larger with azathioprine than with everolimus. The 12 months of double-blind period of this study were followed by 12 month of open-labeled period (Vigano et al., 2007) in 149 patients and showed that continued treatment with everolimus limits the progression of intimal thickening and lowers the incidence of allograft vasculopathy at 24 months when compared with azathioprine.

Similar benefits have also been seen in patients treated with sirolimus. In an open-labeled study (Keogh, 2004) of 136 de-novo transplant patients randomized to sirolimus or azathioprine, IVUS showed that the use of sirolimus significantly reduced the progression in intimal and media proliferation by six months, whereas azathioprine therapy resulted in increased plaque volume and plaque burden over time. This effect was sustained at two years.

The first evidence of using sirolimus for primary immunosuppression after heart transplantation demonstrated that complete CNI withdrawal and replacement with SRL results in attenuation of CAV progression by reducing intimal hyperplasia as evidenced by 3D-IVUS. Treatment with azathioprine or mycophenolate mofetil did not significantly affect the results. A CNI-free regimen was more effective when initiated within the first two years following transplantation (Raichlin et al., 2007a).

3. Conclusion

Coronary angiography has a high specificity of 97.8% but only moderate sensitivity of 79.3% in CAV detection. The intimal changes in CAV are best detected by intravascular ultrasound, which has become the gold standard for the early diagnosis of CAV. The prognostic value of IVUS has significant clinical utility in identification a high-risk population and underscores the importance of serial IVUS examinations during annual routine screening of heart transplant recipients. 3D-IVUS with simultaneous assessment of virtual histology may add important information in the clinical evaluation of heart transplant recipients.

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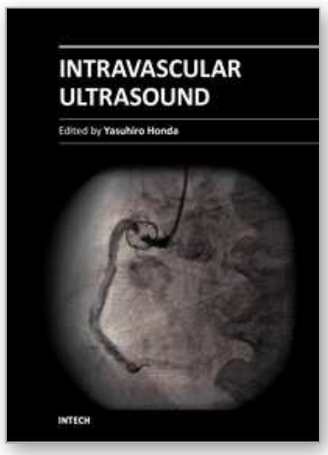

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Intravascular ultrasound (IVUS) is a cardiovascular imaging technology using a specially designed catheter with a miniaturized ultrasound probe for the assessment of vascular anatomy with detailed visualization of arterial layers. Over the past two decades, this technology has developed into an indispensable tool for research and clinical practice in cardiovascular medicine, offering the opportunity to gather diagnostic information about the process of atherosclerosis in vivo, and to directly observe the effects of various interventions on the plaque and arterial wall. This book aims to give a comprehensive overview of this rapidly evolving technique from basic principles and instrumentation to research and clinical applications with future perspectives.

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