REVIEW

Diagnosis and management of coronary allograft vasculopathy in children and adolescents

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Received: June 9, 2014   Revised: August 12, 2014
Accepted: September 16, 2014
Published online: December 24, 2014

Abstract

Coronary allograft vasculopathy remains one of the leading causes of death beyond the first year post transplant. As a result of denervation following transplantation, patients lack ischaemic symptoms and presentation is often late when the graft is already compromised. Current diagnostic tools are rather invasive, or in case of angiography, significantly lack sensitivity. Therefore a non-invasive tool that could allow early diagnosis would be invaluable.This paper review the disease form its different diagnosis techniques,including new and less invasive diagnostic tools to its pharmacological management and possible treatments.

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Key words: Cardiac transplantation; Allograft vasculopathy; Paediatrics; Diagnosis; Management which reflect the content of the study

Core tip: Coronary allograft vasculopathy remains the leading cause of great loss in children after the first year post transplant. This paper offers a state of the art review of the disease from diagnosis including most recent and less invasive tools to management.

## DEFINITION AND PHYSIOPATHOLOGY

In children, coronary allograft vasculopathy (CAV) remains the main limiting survival factor after heart transplantation and the major cause of mortality after the first year post transplant leading ultimately to graft loss[1,2].

One elegant etiological description of CAV is that of "immunologic mechanisms operating in a milieu of non-immunologic risk factors"[3]. The process is believed to start off as a response to endothelial injury in the graft, originated by a complex interaction of multiple donor and recipient factors. The resulting endothelial dysfunction, leads to altered endothelial permeability and subsequent intimal hyperplasia as a consequence of the vascular remodeling originated by the inflammatory response. The immunologic events constitute the original trigger and non-inflammatory events such as cytomegalovirus infection, ischemic time (reperfusion injury), increased donor age and classical cardiovascular risk factors (*i.e.,* diabetes, dyslipidemias, smoking and hypertension), perpetuate the inflammatory response and increase the endothelial injury[4].

Typical lesions (Figures 1 and 2) consist of diffuse intimal proliferation leading to the development of luminal stenosis and small vessels occlusion which then limits blood supply to the graft causing chronic vascular injury and ultimately myocardial ischemia[5]. The lesions develop earlier and quicker than atherosclerotic lesions.
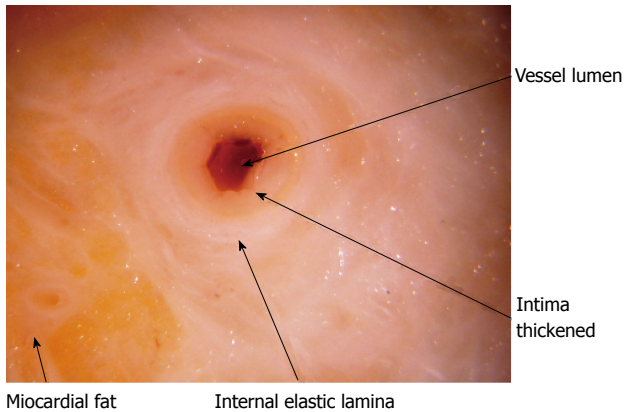
Figure 1 Stenotic coronary artery macroscopic aspect in post mortem study of explanted heart.
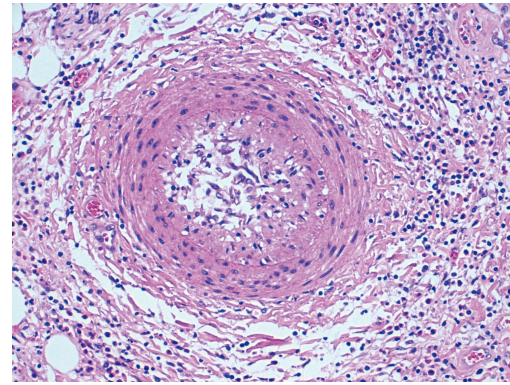
Figure 2 Histopathologic example of stenotic microvasculopathy: Medial thickening and endothelial swelling with evidence of luminal stenosis (hematoxylin-eosin stain).

In addition, progression is often silent due to the lack of ischemic symptoms from the denervated heart and often, the first clinical manifestation is an adverse cardiac event[6].

The real incidence of CAV among the pediatric population remains unknown, with a reported incidence varying between studies from 3% to 43%[7]. According to an angiographic multicenter study, the incidence of CAV would be 2%, 9% and 17% at 1, 3 and 5 years[1]. Looking at the incidence reported in studies that use intravascular ultrasound (IVUS), this is even higher, with 75% incidence of detectable intimal thickening at 5 years, with half of these representing at least mild disease[8]. The most current angiographic data estimates the incidence of CAV in the pediatric cohort of 13% at 5 years, 25% at 10 years and 54% at 15 years[9].

According to the ISHLT registry, using angiographic definitions, 65% of recipients are free of CAV at 10 years, but after a diagnosis of CAV, the 2-year graft survival rate is less than 50%[2].

Age at transplantation has a strong influence on survival with a 74% 8-year freedom of CAV in younger recipients compared to 56% in recipients older than 10 years[10].

As CAV lesions are preceded by endothelial dysfunction, it is essential to identify and characterize this as early as possible for targeted therapy and ultimately to improve patient survival.

DIAGNOSIS

The diagnosis of CAV is challenging. As a result of the denervation inherent to heart transplantation, patients fail to display classical clinical warning signs of angina[11]. The ability of early diagnosis is essential but unfortunately, the majority of the diagnostic techniques lack sensitivity or are rather invasive. A reliable and repeatable non-invasive method that detects CAV and its functional significance would have a huge impact on the follow up of heart transplant recipients. However, sensitivity and specificity of the currently available non-invasive tests remain limited.

Screening protocols vary among centers and the majority of units use a combination of diagnostic modalities, depending mainly on local preferences and expertise.

Angiography

For many years, until the introduction of IVUS, this has been the cornerstone of CAV diagnosis[12,13]. Despite its relatively low sensitivity[14,15] and resulting delay in diagnosis, coronary angiography remains the most widely used diagnostic technique for CAV in the majority of transplant centers.

Angiography is known to underestimate the disease[16]. Adults series display a low sensitivity and negative predictive value. St Goar *et al*[14] found that 50% of patients with normal angiographies had moderate to severe intima thickening on IVUS. In a series by Tuzcu *et al*[17] the sensitivity of angiography for CAV detection (defined by maximal intimal thickness > 0.5 mm) was 43%, specificity was however high with 95%.

Similarly in a most recent paper, Gregory *et al*[18], using the same definition, showed a sensitivity even lower of 11% with a negative predictive value of 57%. Defining CAV as mean intimal thickness > 0.3 mm, Störk *et al*[19] found a sensitivity of 44% and a negative predictive value of 28% when compared to the IVUS data.

Its main limitation arises from the fact that it assesses the vessel lumen. The contrast fills the patent lumen without direct visualisation of the vessel wall. By the time a filling defect appears and there is significant stenosis, the graft is already compromised. CAV tends to be diffuse and concentric affecting large and medium size vessels as well as the microvasculature[14,20]. Typically there is initial vessel expansion: as the intima thickens, the external elastic membrane expands preserving initially the lumen area (Glagov-type positive remodeling)[21-24]. This explains why the coronary angiography result can be normal in the presence of significant disease demonstrated by IVUS. Nevertheless, angiography is inexpensive, readily available across centers and findings have proven prognostic implications regarding graft survival and adverse cardiac events[25,26].

One of the largest experiences in pediatric patients has been published by Pahl *et al*[1] in 2005 and included

Table 1 ISHLT consensus grading for coronary allograft vasculopathy (Mehra *et al*[13] 2010)
Grade
0 (Not significant) No detectable angiographic lesion
I (Mild) Angiographic LM < 50% stenosis, or primary vessel with maximal lesion of < 70%, or any branch stenosis of < 70% (including diffuse narrowing)
II (Moderate) Angiographic LM 50%-69% stenosis, a single primary vessel ≥ 70% stenosis, or isolated branch stenosis of ≥ 70% in branches of 2 systems
III (Severe) Angiographic LM ≥ 70%, or 2 or more primary vessels ≥ 70% stenosis, or isolated branch stenosis of ≥ 70% in all 3 systems, or mild/moderate angiographic disease with LVEF < 45% or evidence of significant restrictive physiology (*i.e.*, symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (> 1.5 in children), shortened isovolumetric relaxation time (< 60 ms), shortened deceleration time (< 150 ms), or restrictive hemodynamic values (Right Atrial Pressure > 12 mmHg, Pulmonary Capillary Wedge Pressure > 25 mmHg, Cardiac Index < 2l min/m^2)

LM: Left main.

Table 2 Stanford score (severity based on the localization of the most severe disease		
Grade	**Severity**	**Intimal thickness**
I	Minimal	< 0.3 mm and < 180 degrees
II	Mild	< 0.3 mm and > 180 degrees
II	Moderate	0.3-0.5 mm OR 0.5-1 mm and < 180 degrees
IV	Severe	> 1 mm OR 0.5-1 mm and > 180 degrees
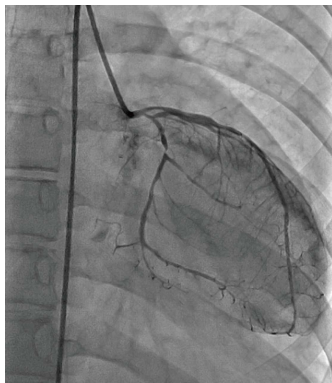
Figure 3 Left coronary angiography showing severe epicardial disease with multiple stenosis in left anterior descending artery and left circumflex artery.

multicenter data proceeding from the Pediatric Heart Transplant Study database. Two thousand and forty-nine angiograms from 751 patients were analysed. The incidence of angiographic abnormalities at 5 years was 17%. However, moderate-to-severe disease occurred in only 6% at 5 years[1]. The use of IVUS in children is limited and they showed a sensitivity of angiography to detect CAV when compared to IVUS data between 18% and 30%[8,27].

In 2010, the ISHLT published new guidelines for CAV including a new classification (Table 1) in view to provide a more refined definition and prognostic value[13]. Figures 3 and 4 showed angiography of two grats with severe disease.

IVUS
IVUS is more sensitive than angiography for early CAV detection and allows delineation of the vessel wall as well as measurement of intimal thickness[14]. Even if it might provide an oversimplified picture of the disease process, the intimal thickening measured *via* IVUS remains the most sensitive diagnostic modality available[13].

As mentioned above, Glagov-type positive remodeling occurs in response to the vessel wall disease. This serves to maintain initial lumen patency and the angiographic appearance of the vessel can therefore be normal despite significant CAV. This is particularly significant in the first year post transplantation. Later on in the disease process, constrictive negative remodeling of the vessel will occur and lead to the stenosis of the vessel[23].

IVUS parameters reported in the literature include: intimal thickness, mean intimal index (ratio of the mean intimal area to the sum of the mean intimal and luminal areas), total atheroma volume and percentage of atheroma volume. In 1995, the Rickenbacher *et al*[28] demonstrated that, in an adult cohort, moderate to severe intimal thickening diagnosed by IVUS was predictive of the future development of angiographically detectable disease (Table 2). This article describes CAV as being present when maximal intimal thickness is ≥ 0.3 mm. A further finding was that maximal intimal thickness (MIT) ≥ 0.3 at 1 year was associated with a 4 year survival of 73% compared to 96% within the group of MIT < 0.3 mm[28]. Two more recent studies published in 2005[17,29] reported that a change of MIT ≥ 0.5 mm over the first year post-transplant was an independent predictor for subsequent angiographic development of CAV; for myocardial infarction and for all-cause death at 5-years post-transplant. Patients with a change in MIT > 0.5 mm had a 5-year incidence of 21% for death or graft loss, 46% for all major adverse events and 65% for the development of subsequent angiographic disease compared to 6%, 17% and 35% respectively for patients without a 0.5 mm change[29].

Interestingly, however, intimal proliferation evaluated in IVUS does not always correlate with microvascular or small artery disease in biopsies specimens[13,30]. Looking specifically at Pediatric data, IVUS has not shown yet
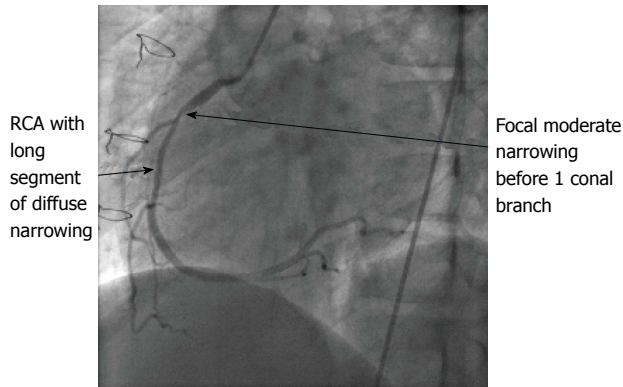
RCA with long segment of diffuse narrowing

Focal moderate narrowing before 1 conal branch

Figure 4 RCA angiography.

Intima thickened

Catheter

Vessel lumen

Figure 5 Intravascular ultrasound still frame showing severe intimal thickening (Stanford grade IV).

impact on prognosis[27] and this probably relates to the limited number of studies, each with differing analysis methodology.

According to published data, sensitivity increases with the number of vessels imaged[31]. However, our experience in children suggests that this is not the case and multi-vessel imaging increases risk without substantially altering sensitivity. Therefore, in our usual practice, we only image the left main and proximal left anterior descending. We use automatic pullback to enhance consistent sampling and identification of branch vessels that are used as landmarks in order to be able to compare serial investigations. We analyze 30 cross-section images taken at 1.5 mm intervals and identified (as mentioned above) by branch points. Additionally, image analysis is performed during mid-diastolic rest period for consistency. In addition to maximal intimal thickness, mean intimal thickness, and mean intimal index, Stanford grading score (Table 2) and percentage of atheroma are recorded. We also use a semi-automatic interactive edge detection software (QIVUS) to improve reproducibility of measurements[32] (Figure 5).

Unfortunately, IVUS remains rather unused in clinical routine: the higher cost and potential morbidity added to the requirement of a trained operator, limits its use currently. This is particularly true in the pediatric population, where the size of the patient is an additional limitation. Nicolas *et al*[27], have reported feasibility in patients ≥ 10 kg but in our institution, we normally do not proceed in patients under 10 years of age[8,27].

Echocardiography
The usefulness and accuracy of several echocardiographic techniques, as diagnostic methods for CAV have been explored. Published data have shown disparate results but more recent reports involving dobutamine stress echocardiography have demonstrated greater prognostic value[33-40].

Dobutamine stress echocardiography (DSE) allows assessment of wall motion, inducible ischemia and viability. Nevertheless, the sensitivity, specificity positive predictive value and negative predictive value vary significantly among these studies. Despite these limitations, Spes *et al*[35] noted, in
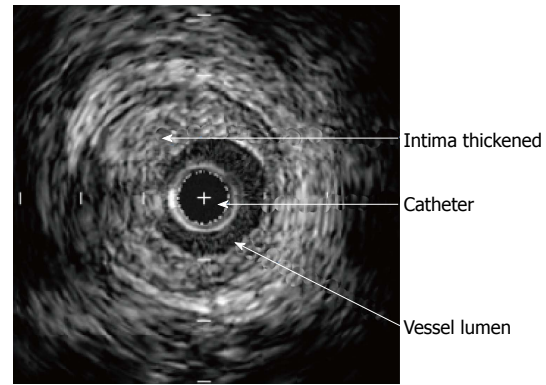
an adult cohort, that in patients with abnormal DSE, 90% had significant CAV by IVUS, but only 49% by angiography again demonstrating the relative insensitivity of angiography. Furthermore, they showed that a normal pharmacological stress echocardiography after heart transplantation has a high negative predictive value for any major adverse cardiovascular event. This suggests that if a strict DSE protocol is followed, a selective invasive angiography/IVUS policy may be adopted[34,35,37,38,41]. This was corroborated in a Pediatric cohort by Pahl *et al*[39]. Some authors have pointed out that endothelial dysfunction might be the cause of abnormal wall motion detected by DSE and normal angiography[42].

In children, the variability when compared to angiography, is even higher than that showed in adult series. Sensitivity rates vary between 35% and 71%, specificity between 80% and 94%, positive predictive value between 45% and 91% and negative predictive value between 81% and 92%[37,43,44]. If reliability within a given department is established, then it certainly appears to be an attractive option for children due to its non-invasive nature. However, it does require a good set up, effective sedation, expertise in images acquisition, expertise in interpretation and a standardised, reproducible protocol.

Sensitivity and specificity of stress echocardiography techniques can be improved by quantitative analysis using strain imaging. This modality can quantify regions of wall motion abnormality, (*i.e.*, a reduction in peak systolic strain % will be seen in LV segments associated with inducible ischemia and accurate measurements of time to peak strain may also give information on regional wall motion abnormalities). Eroglu *et al*[40], showed that, in adults, the accuracy of DSE can be improved using strain analysis (Figure 6).

Combined use of contrast-enhanced echocardiography with adenosine mediated hyperemia in order to assess coronary flow reserve has shown encouraging results in adults. Tona *et al*[45] demonstrated feasibility and prognostic value of coronary flow reserve measured by contrast enhanced echocardiography with good correlation with major acute cardiac events. Severe Coronary Flow Reserve (CFR) alteration was shown to precede acute cardiac event
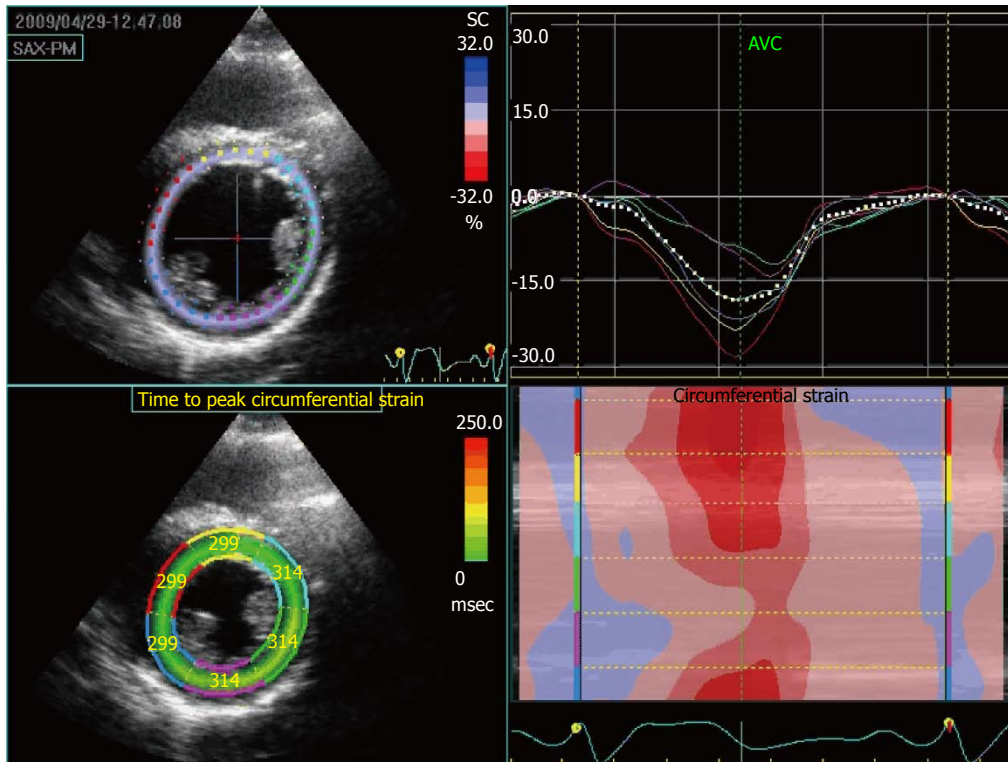
Figure 6 Speckle-tracking echocardiographic analysis of myocardial deformation showing circumferential strain in a patient with coronary allograft vasculopathy. On the top right image we can appreciate the dyssinchrony (later contraction compared to the rest of the segments) and lower contractility of the green and purple segment corresponding to LCX territory. On the bottom right figure, we can appreciate how the same green and purple segments have significant lower contractility than the others (red corresponds to the maximum contractility and blue to the absence of it). The left superior panel shows the color coding for each of the segments. The left inferior panel shows the time interval between beginning of QRS and maximal strain value.

onset. On a more recent study, the same group, showed high sensitivity and specificity for this technique in the detection of significant CAV (defined by Media Intimal Thickness > 0.5 in IVUS)[46]. Although these results are really encouraging, more studies are needed to establish the reproducibility. Interestingly, a separate small study in adults showed that transesophageal echocardiographic measurement of CFR impairment could identify CAV but it did not allow grading of severity[47]. However, this approach will be more difficult to implement in children, owing to difficulty in imaging due to the small size of the coronary arteries and the need for sedation in many patients.

The application of tissue Doppler techniques to the transplant population is also worth mentioning. Dandel *et al*[48,49] showed the utility of power Doppler TDI for the diagnosis of CAV in adults. Systolic Tissue Doppler Imaging (TDI) parameters at basal lateral LV wall level showed the highest diagnostic accuracy. Peak systolic motion velocity (Sm) and time to peak systole (TSm) differed significantly between patients with and without CAV as identified by IVUS. Furthermore, with Sm > 11 cm/s and TSm > 110 cm/s^2, angiographic disease can be excluded and, in the absence of any rejection, an Sm < 10 cm/s has a positive predictive value of over 97% for CAV (as detected by IVUS or angiography)[48,49]. The main limitations for the widespread use of this technique arise from the inter-observer and inter-departmental variability. These techniques have been applied to adult cohorts mainly and the available literature in the pediatric population is still very limited. One small retrospective study has shown that tricuspid annulus velocity was the best predictor of graft failure in pre-terminal patients. However, conventional echocardiographic parameters such as increase in tricuspid regurgitation severity and a reduction in left ventricular ejection fraction were also associated with increased mortality[50]. However, another recent study in a pediatric cohort showed poor correlation between TDI and hemodynamics parameters[51], highlighting the need for further confirmatory studies in children.

Exercise stress echocardiography (ESE) in adult patients was initially found to have unacceptably low sensitivity for the detection of CAV[33,52]. However, Chen *et al*[53] showed recently a sensitivity higher than 88% with almost 92% specificity in detecting significant epicardial angiographic CAD among pediatric heart transplant recipients. The positive predictive value of ESE was 72.7%, and the negative predictive value was 97.1%[53]. These results need wider confirmation prior to consideration as a screening tool.

Invasive coronary hemodynamics
CAV is a complex and diffuse process that leads to concentric luminal stenosis and occlusion of epicardial large and medium sized vessels. It also affects the intramyocardial microvasculature. Microvascular disease is present in heart transplant recipients early after transplant, even in
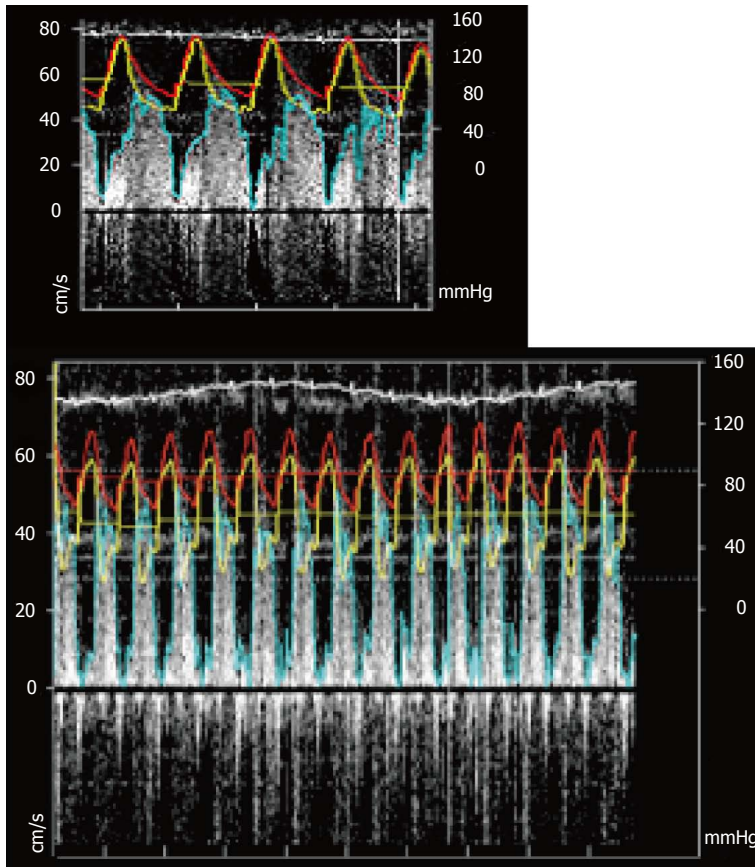
Figure 7 (A) Resting pressure and flow recording (Red: Aortic pressure; Yellow: Distal coronary pressure; Blue: Pulse wave Doppler envelope) and (B) during hyperemia note that the aortic pressure has decrease as well as the distal coronary pressure. FFR: Ratio of the mean distal coronary pressure at a point past the stenosis the aortic pressure during maximal hyperemia; CFR: Ratio of hyperemic blood flow to resting myocardial blood flow.

asymptomatic patients[20,54] and it is known to be associated with CAV, ischemia and death.

Fractional flow reserve (FFR) is defined as the ratio of maximum flow in the presence of a stenosis to normal maximum flow. It is a lesion-specific index of stenosis severity that can be calculated by simultaneous measurement of mean arterial, distal coronary, and central venous pressure, during pharmacological vasodilation. FFR is a well established tool to assess hemodynamic significance of coronary focal stenosis and has been recommended since 2010 by European Society of Cardiology for the physiological assessment of moderate coronary stenosis when functional information is lacking[55] in atherosclerotic disease.

In such cases, pressure gradients and FFR are recorded throughout the length of the artery through a pull back of the wire during maximum pharmacologically-induced hyperemia.

The Combowire® XT also allows simultaneous measurement of flow and pressure and FFR simultaneously to the coronary flow reserve (CFR) (Figure 7).

In transplanted patients, the exact value of FFR to determine epicardial disease is difficult to establish and results have been inconsistent between series[56,57]. In a publication by Hirohata *et al*[20], FFR improved as the microvascular disease deteriorated and therefore, due to the particular interaction between microvascular and epicardial disease that occurs in CAV, FFR might not be the best reflection of epicardial affectation in this situation.

CFR reflects the ability of the myocardium to increase blood flow in response to maximal exercise or stress. It is expressed by the ratio of the myocardial blood flow at peak stress, or maximal vasodilatation, to the flow at rest. Decrease in CFR, after Adenosine administration to achieve maximum vasodilation, in the absence of significant epicardial stenosis (normal fractional flow reserve) indicates microvascular dysfunction[58]. If the significance of decreased CFR is well established in the atherosclerotic population[59,60]. Although theoretically more important for CAV, the exact significance of CFR measurement remains to be determined. Using acetylcholine-mediated, endothelium-dependent, coronary vasodilatation measurement of CFR, Hollenberg *et al*[61] showed that endothelial microvascular dysfunction was more common in the group suffering adverse outcomes (death or angiographic evidence of CAV) than in those without adverse outcome. However, published data are not consistent between studies. Kübrich *et al*[62], in a larger cohort, found no correlation between epicardial and microvascular disease and found that, whilst microvascular dysfunction demonstrated by CFR was a predictor of outcome (death or adverse cardiovascular event) in the univariate analysis, it did not predict outcome in the multivariate analysis.

The pediatric population offers very limited data for CFR. In a small cohort, a decrease in CFR correlated with microvasculopathy seen in endomyocardial biopsy specimens[63]. The invasive nature of Doppler wire flow measurements to determine CFR makes it an unattractive tool for children.

Several groups have presented data of CFR quantified

by CMRI of the coronary sinus showing good correlation with PET or flow phantoms[64-66]. More recently, Ishida *et al*[67] presented data on CFR as independent predictor of MACE in patients with known or suspected CAD. Kennedy *et al*[68] have translated this idea into the transplant population: they found that CFR determination by Cardiac Magnetic Resonance Imaging (CMRI) in the coronary sinus, was significantly decreased inpatients with severe CAV and therefore, it may be a useful tool in non-invasively evaluating coronary allograft vasculopathy in heart transplant recipients.

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is a useful clinical tool for myocardial perfusion imaging to detect and risk-stratify of coronary atherosclerotic disease for management guidance[69]. Either exercise or pharmacological stress can be employed and, most commonly, one of theTc-99m-labeled tracers is used. Numerous studies in adult population with coronary atherosclerotic disease have assessed the relative accuracies of stress imaging using nuclear cardiology techniques: for stress SPECT, sensitivity is around 87% with a specificity of 73% (compared to coronary angiography)[70]. Recently, it has been recognized that some patients with non-critical coronary artery stenosis can have abnormal stress perfusion imaging. This is due to microvascular and endothelial dysfunction causing abnormal flow reserve[71].

When applied to CAV, SPECT has a high negative predictive value in adults[72-77]. When using Dobutamine stress and 99m technetium tetrofosmin, abnormal perfusion is associated to a risk ratio of 3.5 in predicting cardiac death[78-80]. A reversible perfusion defect on stress SPECT is an independent predictor of mortality or graft loss[72,81-83] and it seems that stress SPECT at one year post transplantation could be an earlier prognostic indicator[84].

In Pediatrics, the experience with SPECT is largely anecdotal. The small size of the heart might be a limiting technical factor and the radiation related to the technique itself makes it a rather unattractive diagnostic tool.

Positron emission tomography

Positron emission tomography (PET) has established itself as the gold standard for noninvasive assessment of myocardial perfusion measuring myocardial blood flow at rest and during stress. As well as myocardial perfusion reserve, perfusion of the epicardial arteries and the microvasculature can be determined[85,86]. In patients after heart transplantation, myocardial perfusion reserve measured with PET has been performed in a few studies[87-89]. Wu *et al*[88] found good correlation between IVUS and myocardial perfusion reserve even in the absence of angiographic lesions. Published data is very limited even in adults, related to the limited availability of the technique and the expertise required.

Multidetector computed tomography

In the atherosclerotic population, multidetector computed tomography (MDCT) has shown high sensitivity and specificity in the diagnosis of angiographic coronary arteriopathy and characterization of the stenotic disease[90]. Recent studies also indicate that detection and characterization of the plaque is possible although challenging[91,92] increasing potential value as a diagnostic tool.

The literature provides some data regarding the heart transplant population: Sigurdsson *et al*[93] used a 16-detector MDCT to identify coronary stenosis and compared to angiographic disease (defined by luminal stenosis > 95%). Sensitivity, specificity, positive and negative predictive values were 86%, 99%, 81% and 99% respectively, unfortunately only a few subgroup of patients underwent IVUS.

Gregory *et al*[18], on the other hand, did use IVUS to compare 64-slice MDCT results in 20 patients at 1 year post-transplant. They defined CAV as maximal intimal thickness > 0.5 mm and found that MDCT has a sensitivity of 70% and a specificity of 92% with a positive predictive value of 89% and negative predictive value of 77%. However, in this study, slightly less than 20% of coronary segments (mainly distal) could not been analysed due to poor image quality (probably in relation with elevated heart rate)[18].

Recent studies showed that dual source MDCT allows good image quality of vessel lumen[94,95] and, when validated against IVUS, high diagnostic accuracy[96]. A small study, just under 20 patients, demonstrated that MDCT, using 64-slices, was superior to angiography for the identification of non-obstructive vessel wall disease. However, they did not use IVUS for comparison[94]. Schepis *et al*[96] compared 64 channels dual source MDCT with IVUS to look at vessel wall thickness. Defining CAV as intimal thickness > 0.5 mm on IVUS they established sensitivity, specificity, negative predictive value and positive predictive value of MDCT of 85%, 84%, 76% and 91% respectively.

Therefore, MDCT appears to be a useful tool for CAV screening. Although not as sensitive as IVUS, it is non-invasive and clearly superior to angiography. However, the elevated heart rate post-transplantation, especially in pediatric patients, compromises image quality and the need for potentially nephro-toxic contrast agent adds concern for heart transplant recipients, for whom renal impairment is a frequent comorbidity[97,98].

There is preliminary data available in children using MDCT compared to angiography and IVUS to identify coronary luminal stenosis, although the size of the series was very small[99] and results would require further studies to be validated.

Again, the implied repeated radiation dosage makes it a less attractive screening option in children.

Optical coherence tomography

Optical coherence tomography (OCT) is an intravascular high resolution imaging modality that measures reflected light waves intensity and converts these into a high resolution tomographic image[100]. In CAD patients, OCT has been used to characterize plaque composition and differentiate between intimal hyperplasia, fibrous plaque, lipid-rich plaque or calcifications[101,102] (Figure 8).
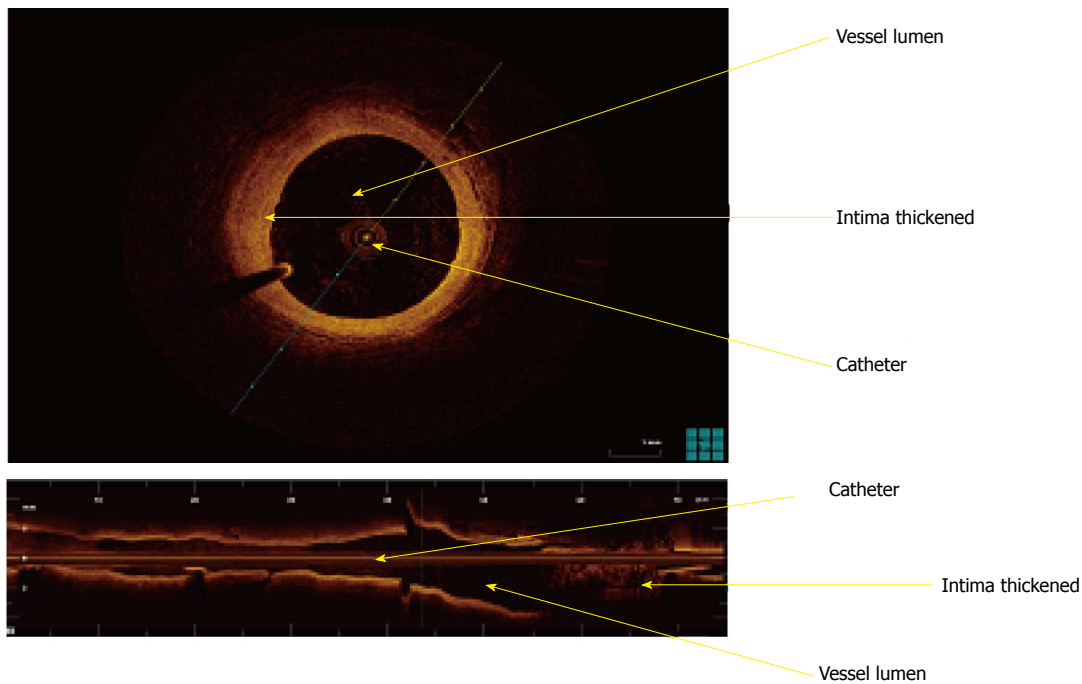
Figure 8 Optical coherence tomography images showing intima hyperplasia. The superior image shows a transverse cut of the coronary. On the inferior part of the image, longitudinal cut.

Recent studies have evaluated the use of OCT in heart transplant recipients with promising results. The OCTAV study demonstrated, in 15 patients early post-transplant (with no angiographic evidence of CAV), that early quantification of intima-media ratio and characterization of the plaque is possible. There was no IVUS performed for comparison[103]. Garrido *et al*[104] compared OCT to IVUS in 21 patients, later post-transplant, and not only found good correlation with IVUS but also postulated that OCT offers better plaque characterization and less inter-observer variability.

Cassar *et al*[105] compared OCT to IVUS and angiography in 53 patients, showing that OCT was superior to angiography but not to IVUS. IVUS and OCT were strongly correlated with 100% agreement.

Further prospective and larger studies are needed to define the exact role of OCT in the diagnosis of CAV and, more importantly, to define its prognostic implications.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) coronary angiography in the context of CAD has proved its capacity to detect atherosclerotic plaque and proximal to mid-coronary artery stenoses[106-108]. Uribe *et al*[109] have demonstrated the feasibility and accuracy of MR coronary angiography in the detection of coronary anomalies in children, despite elevated heart rates with whole heart dual phase cardiac imaging[109,110]. Greil *et al*[111], have also previously shown the utility of coronary magnetic resonance angiography (CMRA) in patients with Kawasaki disease.

These studies undoubtedly open the door for the application of CMRA in CAV including in pediatric cohorts. Unfortunately, when compared to MDCT, CMRA does not seem to be as sensitive or robust in the detection of coronary stenoses, although limited studies have been done. CMRI offers several advantages: it provides functional information on myocardial characterization and contractility as well as wall motion performance; it allows quantitative measurements of ventricular volumes and it is radiation-free, which is especially valuable in a population already exposed to repeated X-ray angiography.

In conventional atherosclerosis, perfusion imaging has shown to be effective in detecting myocardial ischemia and to assess microvascular dysfunction as it detects downstream microvacular blood flow within the myocardium. The MR-IMPACT study demonstrated that CMRI is superior to SPECT in identifying perfusion defects within the myocardium for atherosclerotic patients[112]. Perfusion stress with adenosine also provides prognostic data: a normal CMR stress perfusion scan showed 99% event free survival at 3 years[113].

The use of adenosine for myocardium stress perfusion after heart transplantation has not been widely reported. Nevertheless, Muehling *et al*[114] showed a reduced myocardial perfusion reserve in patients with CAV with good correlation between MRI and invasive measurements. Unfortunately, microvascular disease in this study could not be assessed. They also demonstrated that patients with CAV have a reduced myocardial perfusion even during rest conditions[114].

In regards to CMR tissue characterization, Steen *et al*[115] showed that more than 80% of patients with severe angiographic CAV had a late gadolinium enhancement pattern suggesting subendocardial infarction with a distribution consistent with the angiographic pattern. Furthermore, he was able to identify silent myocardial
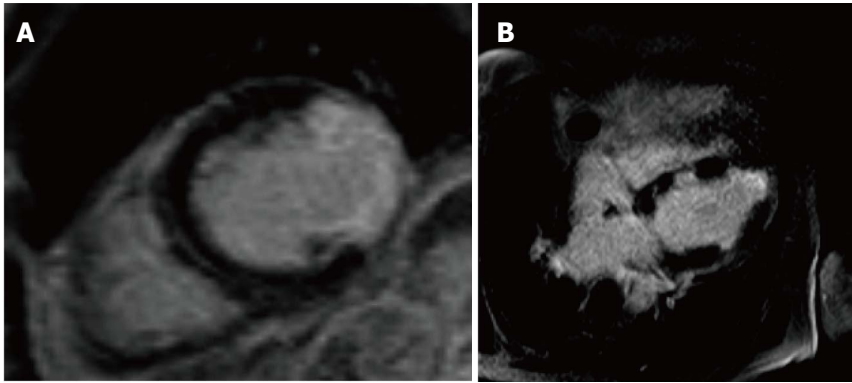
Figure 9 Late gadolinium enhancement scar imaging. A: Typical infarct pattern Late enhancement with > 75% transmurality; B: Atypical pattern with diffuse pattern of late enhancement.
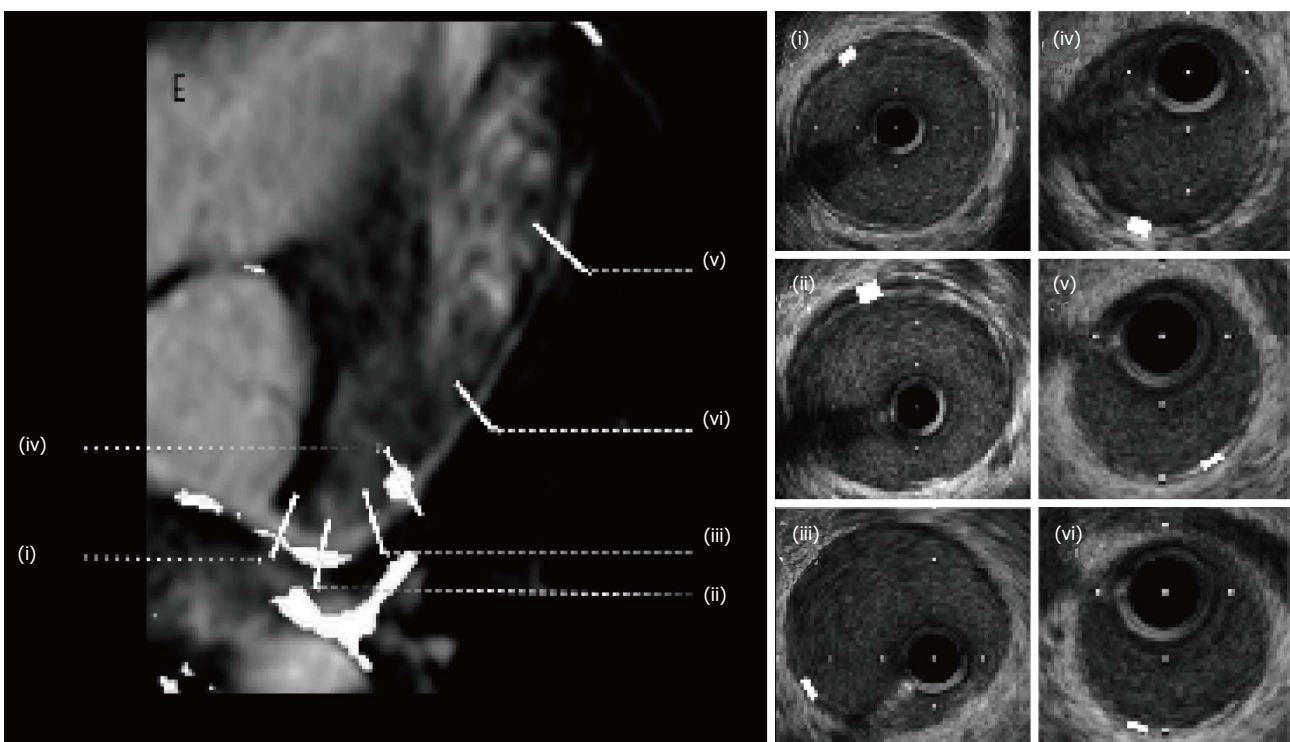
Figure 10 Late gadolinium enhancement in the coronary vessel wall showing corresponding positions for intravascular ultrasound: Illustrates intimal thickening corresponding to enhancement on overlay picture on the left.

infraction in otherwise apparently event-free patients (Figure 9). In a more recent publication, the same group looked at infarct-atypical myocardial involvement that they were not able to correlate with coronary angiographic pattern in the prior study. According to their findings, within the 4 different patterns of infarct-atypical LGE-CMR, only the diffuse form was significantly higher patients early post transplantation, but they could not establish a definite reason for the findings[116].

Hussain *et al*[117], have taken this technique further showing that high resolution late gadolinium enhancement (LGE) can be used to show vessel wall disease in CAV with good correlation with IVUS Figure 10. LGE scores correlated well with the maximal intimal thickness and mean intimal index [Pearson coefficient 0.80 (P < 0.001) and 0.92 (P

< 0.001), respectively]. An enhancement diameter > 7.5 mm gave promising sensitivity and specificity values of 86% and 93%, respectively, for the detection of significant CAV.

A recently published paper, evaluated in 48 transplanted patients both epicardial and microvacular disease concomitantly. The patients underwent coronary angiography, invasive coronary physiological assessment, IVUS and multi-parametric cardiac MRI that includes, tissue characterization, perfusion analysis and tissue tagging. They found that cardiac MRI-based myocardial perfusion reserve was independently predictive of both epicardial and microvacular components of CAV and furthermore that diagnostic performance was significantly higher than angiography[118].

More studies are needed to establish CMRI as a reliable non-invasive tool for CAV diagnostic but certainly the latest

data are encouraging and more work needs to be achieved in this direction.

PREVENTION AND TREATMENT

Rapid progression of CAV within the first year post transplant is a strong indicator of severe CAV, graft loss and mortality[17]. Therefore, prophylactic strategies are paramount and must been introduced early to improve long-term outcomes and prognosis.

Similar to native coronary disease, primary prevention includes control of traditional cardiovascular risk factors such as hypertension, smoking, diabetes and hyperlipidemia. This can be challenging, as many of these factors are also side effects of the immunosuppressive therapy. Tobacco should be avoided and care should be taken to avoid passive smoking in children. Modifications of specific risk factors related to the transplant include prevention and aggressive treatment in case of cytomegalovirus (CMV) sero-conversion[118]. In addition, it is essential to treat any episode of rejection early and aggressively.

Psychological care
Psychological support is crucial in transplanted children and their families throughout all the transplant journey: Leaving with a reduced life expectancy when compared to peers is often complicated and despite good quality of life can be a source of distress for the recipients. In the context of CAV psychological support is especially important: Prevention is paramount; and, if it is essential to treat aggressively any rejection episode, it is also vital for the patients to be compliant with the antirejection therapy. However, it is well known that often therapy compliance declines in adolescence and case of sudden death have been reported related to antirejection treatment discontinuation. In these patients psychological support is essential to ensure therapy obeisance. In cases of advanced CAV the ineluctability of the graft loss and its implication lead to severe depression and negation that also frequently required psychological input.

Statins
Most transplant protocols nowadays include statin, independently of the lipid level. Several studies have highlighted their benefits beyond lipid lowering effects[119-121]; including reduced incidence of severe rejection episodes, reduced CAV progression and improved long term survival[122-124]. Consensus guidelines unequivocally recommend statin therapy[125].

CMV
CMV infection results in acceleration of CAV as the result of the host immune response. Aggressive treatment with ganciclovir reduces progression of CAV[126] and the lack of prophylaxis is associated with increased lumen loss[127]. Our institution, as with most of the transplant centers, uses acyclovir for CMV prophylaxis during the first 3 mo post-transplantation.

Vasodilators
A few reports indicate a potential role for vasodilators in preventing and slowing CAV progression. Calcium channels blockers and ACE inhibitors have been reported in the literature to be beneficial but large prospective trials are needed to determine their exact role[128-130]. Most transplant institutions use both of these to treat hypertension, which develops frequently as side effect of calcineurin inhibitors therapy.

Immunosuppression
Most of the data are from adult studies with limited evidence in the pediatric population.

Calcineurin inhibitors
Tacrolimus not only offers better protection against acute rejection compared to cyclosporine[131-133], but it is also superior against CAV[134]. Moreover, Petrakopoulou *et al*[135] showed that tacrolimus is better than cyclosporine in the prevention of microvascular endothelial dysfunction.

Mycophenolate mofetil
Mycophenolate mofetil (MMF) has demonstrated superiority to azathioprine in mortality and graft loss[136]. In the re-analysis of the same study, it also showed less intimal thickening and wider lumen area[137]. Finally, Kaczmarek *et al*[138], in 2006 demonstrated that MMF decreased CAV incidence.

Proliferation signal inhibitors
Contrary to Calcineurin Inhibitors (CNIs) that blocks T-cell activation and proliferation by suppressing lymphokines production, proliferation signal inhibitors (PSIs) inhibit Tcell and B cell proliferation by impairing their response to growth promoting lymphokines[139]. In addition, PSIs have also a significant cytostatic effect on the immune system[134,140]. In 2003, Eisen *et al*[141] published the first data in favor of PSIs, using everolimus de novo after heart transplantation. They showed preservation of the coronary lumen at 1 year with significant lower incidence of CAV in the everolimus group compared to the aziathropine group. A sub-study published in 2007 confirmed the results at 24 mo[142] and the same group has also shown reduced incidence of cardiovascular events in the everolimus group[143]. Nevertheless, despite the promising results of these studies, all of them compared PSIs to Azathioprine, which is not used as first line therapy anymore and known to be associated to higher rate of rejection than newer immunosuppressive agents. The results of an eagerly awaited clinical trial comparing everolimus de novo to cyclosporine has been recently published showing marked improvement in renal function at 12 mo in the everolimus group without increased of adverse events as well as demonstrated, *via* IVUS, significantly reduced CAV progression at 12 mo in the everolimus group[144].

Mancini *et al*[145], in a randomized study reported that sirolimus (as a secondary immunosuppressant) slows progression of CAV and reduces the incidence of clinically significant events, such as death or graft failure. Keogh *et al*[146], using randomized de novo treatment between

sirolimus or azathioprine reported significantly reduced progression in intimal and medial proliferation at 6 mo post-transplant and a reduction in the number of acute rejection episodes of around 50%. The effect was sustained at 2 years post transplant using IVUS to quantify vessel wall proliferation.

Although a combined regime CNIs + PSIs appears to be attractive in preventing and slowing CAV, serious concerns with this regimen should be raised regarding nephrotoxicity. PSIs have shown in several studies to increase side effects of CNIs, especially for nephropathy[147-151].

Raichlin *et al*[152] have published encouraging data with sirolimus-based immunosuppression, and even postulated that a CNI free regimen would be safe, well tolerated and associated with less CAV progression, coronary events and graft failure, when initiated beyond the first year (and within the first 2 years).

In a more recent study, the same group showed that early conversion to sirolimus attenuated plaque progression, improved overall survival, and increased freedom from cardiac events. However, the retrospective nature of the design and the differences in criteria for the therapy changes, make the results less generalizable[153]. Moreover, a recent study reported that late conversion to PSIs is associated with necrotic plaque core and calcification of the plaque[154].

Hence, safety of early CNI withdrawal with PSI conversion remains uncertain, especially in the first year post-transplant with concerns also raised about acute rejection. Therefore, many continue to recommend against withdrawal of CNIs during the first 12 mo post transplantation[155].

Side effects from PSIs are not infrequent: anemia, dyslipidemia, increased incidence of bacterial infections, peripheral oedema, pericardial or pleural effusion, pneumonitis and delayed wound closure. They seem to be dose-related and reversed by discontinuation of the drug, although most can be controlled with dose adjustments[155].

PSIs have also been attributed with a reduction in CMV infections and an inhibition of Epstein-Barr virus-infected tumorigenic cell lines[156-158]. In the Pediatric population, PSI use is still limited to a rescue therapy for post-transplant complications such as CAV or renal impairment secondary to therapy.

Coronary revascularization

In contrast to native coronary disease, CAV is progressive and revascularization procedures are only palliative with no survival benefit[159,160]. Moreover, the concentric, diffuse and distal nature of CAV precludes the majority of patients for revascularization procedures.

Percutaneous interventions

Percutaneous intervention in transplanted patients are characterized by good short term results but high restenosis rates[160-165].

Unfortunately, stents do not offer better long-term results with a late re-stenosis rate around 70%. Drug eluting stents appear to have slightly better results with less restenosis[57,166]. However, only the minority of CAV lesions are amenable for percutaneous revascularization as outlined above and stent angioplasty might only be an option in selected patients.

Bypass grafting

Surgical revascularization is associated with a very high mortality (up to 40%)[162,167,168] and limited success. Indication is then reserved to highly selected patients.

Re-transplantation

Re-transplantation is the only definitive treatment for CAV. Unfortunately it is associated with lower survival than with the primary graft[169] (relative risk for 10 years mortality according to ISHLT 2012 data is 1.56) and the probability of CAV recurrence is higher (50% at 3 years)[167,170].

The scarcity of donors, and prior antigen sensitization means that, in practice, re-transplantation occurs infrequently.

CONCLUSION

Despite a wide range of new diagnostic techniques, angiography remains, to date, the most commonly used diagnostic tool for CAV. Not only is it invasive, costly and radiation-prone but it also fails to identify the disease in its early phase. IVUS is the most sensitive technique but requires trained operators and it is, again, an invasive technique requiring ionizing radiation.

Overall, the available published evidence support a role for MDCT or DSE as non-invasive screening test to reduce the number of invasive angiograms (and IVUS). However, an accurate and reproducible non-invasive diagnostic tool is yet to be widely established. CMR offers anatomical, histological and physiological assessments and, in the future, it could be valuable in the detection and grading of CAV.

Early detection is paramount but remains challenging. It may allow us to identify those requiring modification in immunosuppression, such as early introduction of PSIs for those with more aggressive CAV.

Unfortunately CAV remains the primary cause of graft failure after the first year post-transplantation and the only definitive treatment is re-transplantation.

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