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ISHLT CONSENSUS STATEMENT

International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy—2010

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From the ISHLT Working Group on Classification of Cardiac Allograft Vasculopathy commissioned by the Education Committee and Board of Directors of the Society

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The development of cardiac allograft vasculopathy remains the Achilles heel of cardiac transplantation. Unfortunately, the definitions of cardiac allograft vasculopathy are diverse, and there are no uniform international standards for the nomenclature of this entity. This consensus document, commissioned by the International Society of Heart and Lung Transplantation Board, is based on best evidence and clinical consensus derived from critical analysis of available information pertaining to angiography, intravascular ultrasound imaging, microvascular function, cardiac allograft histology, circulating immune markers, non-invasive imaging tests, and gene-based and protein-based biomarkers. This document represents a working formulation for an international nomenclature of cardiac allograft vasculopathy, similar to the development of the system for adjudication of cardiac allograft rejection by histology.
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The development of cardiac allograft vasculopathy (CAV) remains the Achilles heel of cardiac transplantation. This entity, characterized by intimal proliferation, develops early after transplant, is progressive, and accounts for major morbidity and mortality late in the transplant natural history.[1] Initially, the diagnosis of CAV was made pathologically and was discovered in its most aggressive form of a vasculitis in an era of sub-optimal immunosuppression. As immunosuppression improved and post-cardiac transplant survival increased, angiographic diagnosis became the norm. In the mid-1990s, several groups began to use the innovative technique of intravascular ultrasound (IVUS) to define the early development of angiographically silent cardiac allograft vasculopathy, and this led to an era of greater understanding of this disease.[2] In the 21st century, pathologic definitions of the disease began to surface with the advent of immunohistologic biomarkers and circulating biomarkers.

Despite these advances, there are no standards in the nomenclature of CAV. Much confusion abounds. An early attempt at angiographic classification was not widely adopted due to its lack of prognostic direction and was overshadowed by the advent of IVUS technology. The lack of a standard language has led to confusion in the interpretation of various studies and several unanswered questions persist (Table 1).

Objective

This effort, commissioned by the International Society of Heart and Lung Transplantation (ISHLT) Board and reviewed by Standards and Guidelines Committee as well as

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Table 1 Unanswered Questions in Cardiac Allograft Vasculopathy

- What is significant angiographic cardiac allograft vasculopathy?
- How does allograft function play a role in the nomenclature for defining severity?
- Is there a "histopathologic" definition of cardiac allograft vasculopathy?
- How does intravascular ultrasound fit into the current diagnostic schema?
- What is the value of new non-invasive tests and gene-based or protein-based biomarkers?

the Education Committee, is based on best evidence and clinical consensus. This effort is designed to develop a working formulation for an international nomenclature of CAV, similar to the development of the system for adjudication of cardiac allograft rejection by histology.[3]

Consensus

Consensus #1

Coronary angiography coupled with assessment of cardiac allograft function maintains the highest level of evidence and consensus opinion for inclusion in the final nomenclature. The advantages of angiography are that it is universal in availability for both adult and pediatric patients, clinically accepted, and applicable at any time in the post-transplantation process (favorable for longitudinal and snap-shot assessments).

Consensus #2

IVUS-detected maximal intimal thickening may be most useful for its negative predictive value at any time after transplant; however, we do not see a role for routine IVUS surveillance. IVUS may define evidence of sub-clinical CAV but is unlikely to provide incremental information when the angiogram is negative in the presence of allograft dysfunction. IVUS-defined intimal thickening is predictive of developing angiographic CAV and may guide treatment, but this remains speculative. If performed, maximal intimal thickening evaluation should be based on automated pullback in 1 or more epicardial vessels over a 40- to 50-mm segment.

Consensus #3

IVUS-detected first-year change in maximal intimal thickening (6 weeks to 1 year) is a putative surrogate marker for prognosis, but evaluation as a robust marker for reliable late outcomes is uncertain and at present should be considered investigational.

Consensus #4

Non-invasive computed tomography-based angiography should not be used in a manner equivalent to invasive coronary angiography for the assessment of CAV. There is lack of adequate branch vessel assessment accuracy, sensitivity and specificity still remain uncertain in cardiac transplantation, and concerns for excess radiation in this vulnerable population exist. Furthermore, data providing prognostic outcomes are lacking.

Consensus #5

Endomyocardial biopsy findings, immune-based markers, gene-based and protein-based biomarkers (B-type natriuretic peptide, cardiac-specific troponins, high-sensitivity C-reactive protein), microvascular function testing, and stress-based imaging are not recommended for inclusion in the current nomenclature algorithm as markers for defining severity of CAV. This decision was reached due to lack of standardized platforms of assessment, lack of specificity for diagnosis, and issues of inherent broad reproducibility (single-center data).

These consensus statements provide the foundation for the recommended nomenclature as outlined in Table 2. Implementation of this nomenclature is recommended using the structure provided below:

1. The nomenclature is based on a combination of visual angiographic vessel descriptors in concert with measures of cardiac allograft function.
2. Each angiographic description must include a description of the maximum stenosis at the level of the Left Main artery, Primary Vessels and Secondary Branch Vessels.
3. For optimal assessment, resting vasospasm in the coronary vessels must be excluded.
4. Allograft function must be defined by allograft imaging (left ventricular ejection fraction (LVEF) coupled with hemodynamic assessment (restrictive physiology*)

**Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2 (>1.5 in children), shortened isovolumetric relaxation time (<60 msec), shortened deceleration time (<150 msec), or restrictive hemodynamic values (Right Atrial Pressure >12mmHg, Pulmonary Capillary Wedge Pressure >25 mmHg, Cardiac Index <2 l/min/m^2).*

Background

Angiography

Coronary angiography has been the cornerstone of the diagnosis of CAV vasculopathy (CAV) before the advent of IVUS.[1,2] Although coronary angiography is not perfect, it provides a screening tool to grossly detect the presence of CAV. The main problem with coronary angiography is that the contrast agent merely fills the vessel lumen and does not inform us of the anatomy of the arterial wall. In addition, vascular remodeling (including vasodilation) occurs due to the development of CAV, which may obscure its detection by angiography.[4] Coronary vasospasm can sometimes mimic CAV lesions, and if suspected, administration of intracoronary nitroglycerin is indicated.

The angiographic definition of CAV has been somewhat elusive. In the literature, CAV has been defined as any luminal irregularity or a stenosis > 30%, 40%, 50%, or 70%. An early study in the pre-statin era by Keogh et al[5]

Table 2 Recommended Nomenclature For Cardiac Allograft Vasculopathy

ISHLT CAV_0 (Not significant): No detectable angiographic lesion
ISHLT CAV_1 (Mild): Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
ISHLT CAV_2 (Moderate): Angiographic LM <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction
ISHLT CAV_3 (Severe): Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific; see text for definitions)

Definitions

a). A "Primary Vessel" denotes the proximal and Middle 33% of the left anterior descending artery, the left circumflex, the ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches.
b). A "Secondary Branch Vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches or any portion of a non-dominant right coronary artery.
c). Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2 (>1.5 in children), shortened isovolumetric relaxation time (<60 msec), shortened deceleration time (<150 msec), or restrictive hemodynamic values (Right Atrial Pressure >12mmHg, Pulmonary Capillary Wedge Pressure >25 mmHg, Cardiac Index <2 l/min/m2)

suggested that moderate or severe proximal or mid-vessel CAV at angiography (> 40% stenosis) predicted an overall mortality rate of > 50% at 2 years.

The initial description of angiographic CAV by Gao et al[6] coded anatomic abnormalities into type A, B1, B2, and C lesions. Type A was discrete or tubular stenosis and multiple stenoses in the proximal, middle, or distal segment branches; type B1 was a proximal vessel maintaining normal diameter with abrupt onset of distal concentric narrowing and obliteration; type B2 was a gradual transition from the normal proximal vessel with tapering, concentric narrowing progressively increasing in severity distally; and type C was a diseased vessel, diffusely irregular that lost small branches with terminations often non-tapered, squared off, and ending abruptly (Figure 1). Many clinicians used this anatomic coding for descriptive purposes, but it did not have prognostic value.

The largest assessment of CAV by coronary angiography was a multi-institutional study of 4637 postoperative angiograms at 39 centers from Costanzo and the Cardiac Transplant Research Database (CTRD).[7] CAV was categorized as normal (n = 3821, 82%), mild (n = 574, 12%), moderate (n = 181, 4%), or severe (n = 61, 1%). Mild CAV was defined as left main (LM) < 50%, or primary vessel with maximum lesion < 70%, or isolated single-branch stenosis > 70%, or any branch stenosis < 70% (including diffuse narrowing). Moderate CAV included LM 50% to 69%, or a single primary vessel > 70%, or isolated branch stenosis > 70% in branches of 2 systems. Severe CAV included LM > 70%, or ≥ 2 primary vessels > 70%, or isolated branch stenosis > 70% in all 3 systems. The term "primary vessels" refers to the proximal or middle 33% of the left anterior descending, left circumflex, and dominant or codominant right coronary artery. "Branch vessels" refer to the diagonal branches, obtuse marginal branches, or the distal 33% of a primary vessel or any part of a non-dominant right coronary artery.

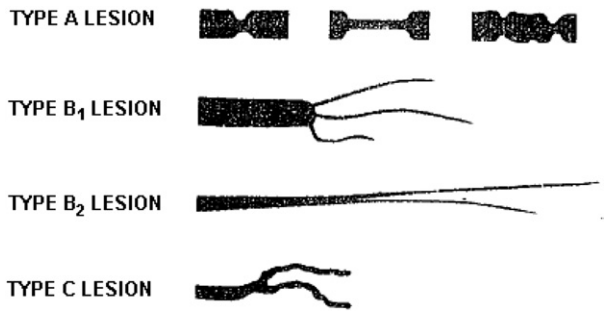

Figure 1 Anatomic abnormalities in transplant coronary vascular disease.[6] Type A lesion: discrete, tubular or multiple stenoses. Type B_1 lesion: abrupt onset with distal diffuse concentric narrowing and obliterated vessels. Type B_2 lesion: gradual, concentric tapering with distal portion having some residual lumen. Type C lesion: narrowed irregular distal branches with terminations that are often non-tapered and squared off, ending abruptly.

The overall likelihood of death or retransplantation (as result of CAV) at 5-year follow-up was 7%. In patients with severe CAV, 50% experienced these end points. Therefore, this CAV classification scheme appears to have prognostic significance, and we hope that use of the ISHLT CAV classification will allow for more refined prospective and contemporary validation.

CAV has protean presentations. It can occur early after heart transplant (< 1 to 2 years), and this is more likely to represent an inflammatory vasculitis, with distinctly bad outcomes.[2] CAV may also present later (> 2 years) after transplant and have an indolent course with relatively good prognosis. Rapidly progressive or fulminant CAV, defined as a lesion > 70% within 1 year of a benign angiogram (< 30% previously) may occur after transplant and can portend a poor prognosis. Thus, the speed of CAV development and the time after transplant are the primary determinants of adverse outcomes.[8]

However, anatomic CAV must be viewed as only a part of the syndrome, with cardiac allograft dysfunction in the setting of anatomic CAV as a further determinant of prognosis. Patients with CAV > 2 years after transplant and a LVEF < 40% had significantly lower subsequent 5-year survival compared with CAV patients without LV dysfunction and patients without CAV (60% vs 90% vs 92%, respectively, $p < 0.05$). Mortality was spread evenly across the 1-, 2-, or 3-vessel CAV sub-sets.[9]

Even when systolic function is preserved, a restrictive cardiac physiology in the setting of large- or small-vessel CAV also appears to play a role in prognosis. Patients with restrictive cardiac physiology, defined as symptomatic heart failure with an echocardiographic E/A velocity ratio > 2, shortened isovolumetric relaxation time (< 60 msec), shortened deceleration time (< 150 msec), or restrictive hemodynamic values (right atrium > 12 mm Hg, pulmonary capillary wedge pressure > 25 mm Hg, cardiac index, < 2 liters/m^2) have a lower 5-year survival than heart transplant patients without restrictive cardiac physiology.[10] It should be noted, however, that restrictive physiology is not specific for the presence of CAV, and thus, its presence should not automatically infer the presence of significant epicardial or small-branch CAV.

IVUS imaging

Developed almost 20 years ago, IVUS was found to be an excellent in vivo tool to investigate the anatomy and physiology of the human coronary vasculature. Several studies have found that IVUS findings, even when the visual angiography result is apparently normal, have value in predicting both CAV-related and other cardiovascular end points.[11–13] The non-immunologic milieu influences the predictive value of intimal thickness measured by IVUS, and serial assessments using early baseline examination are essential to distinguish early CAV from donor-transmitted conventional atherosclerosis. Others have reported that the intimal index determined by IVUS does not correlate with small-artery disease by histologic or immunohistochemical analysis. Intimal proliferation detected by IVUS may represent an oversimplification of the disease processes involved in CAV but remains one of the best available surrogate markers for predicting outcomes from CAV. However, interpretation of intimal thickening by IVUS should be made in the context of the interventions being studied and the background non-immunologic milieu.[2]

The safety of IVUS has been demonstrated in cardiac transplant recipients; serial studies do not pre-dispose to progression of disease.[14] Numerous reports have shown that significant changes in the intimal thickness, intimal area, intimal index, and vessel area can occur in the initial year after transplant. Typically, the vessel area will enlarge (vessel expansion) as the intima thickens and the lumen area is hence preserved. This explains why the coronary angiography result, which is based upon the appearance of the lumen, may be deemed normal, whereas IVUS can demonstrate significant CAV. During the next 2 to 4 years, "constrictive remodeling" occurs as the vessel area and lumen area are reduced.[15]

These observations provided the enthusiasm to use IVUS as a secondary end point in clinical trials to determine if CAV parameters in the first year after transplant would be predictive of subsequent CAV detected by coronary angiography and hard clinical end points including death, myocardial infarction, and revascularization. Two confirmatory series of prior findings reported that a change in maximal intimal thickness of ≥ 0.5 mm at a specific site in the coronary tree that occurred in the first year after transplant predicted outcomes at 5 years related to angiographic CAV, mortality, and myocardial infarction.[12,13]

The yield of IVUS is related to the number of vessels that are imaged. The prevalence of transplant vasculopathy lesions was determined to be 27%, 41%, and 58% at 1 year, 39%, 55% and 71% at 2 years, and 39%, 55%, and 74% at 3 years for patients with 1-, 2-, and 3-vessel imaging, respectively.[16] Clinical trials stipulate the imaging of the left anterior descending artery, followed by the right coronary artery and the circumflex when possible, using automated pullback to enhance consistent sampling and identification of branch vessels that are used as landmarks.[17]

Published IVUS parameters include (1) intimal thickness, (2) intimal index, (3) change in maximal intimal thickness at a reference point, (4) total atheroma volume, (5) percentage of atheroma volume (PAV), and (6) rapidly progressive CAV (described above). PAV is emerging as a favored end point in clinical trials but requires a rigorous core laboratory for analytic evaluation and reporting. Pilot data in a contemporary transplant population of 93 patients from the Cleveland Clinic showed the PAV increased by 3.11% (standard deviation, 5.196%) over 1 year. This represents a dramatic rate of change compared to the non-transplanted population that exhibits a 1% increase in PAV annually.

Thus, although IVUS remains an experimental tool to help investigators evaluate the outcome of various therapeutic conditions, clinical utility is limited, and importantly, may be used at any point in the transplant process for excluding significant disease when the angiogram appears ambiguous. It is unlikely, however, that the IVUS will define flow-limiting epicardial disease that is not demonstrated by a high-quality coronary angiogram. Although IVUS remains very sensitive to define CAV, we cannot advocate routine IVUS at this time because its value as a surrogate marker remains investigational. IVUS holds promise, pending further research, as a guide to therapy as well as a valid surrogate marker.

Microvascular function evaluation

CAV diffusely affects vessels of different size and function: the epicardial vessels, intramyocardial arteries (50–20 μm), arterioles (20–10 μm), and capillaries (< 10 μm). In addition, resting coronary flow velocity is increased after transplant, making interpretation of coronary flow velocity reserve difficult. The terms "flow" and "flow velocity" are not

strictly applied, although the relation between the 2 depends on the local cross-sectional area at the site of measurement. Doppler flow velocity measurements provide selective assessment in target vessel territories. Testing is done for endothelial-dependent vasodilatation with acetylcholine and substance P, whereas endothelial-independent vasodilatation is assessed with nitroglycerine, adenosine, or papaverine. Endothelial and microvascular smooth muscle cell dysfunction are often both defined as coronary flow velocity reserve (CFR) of < 2 or < 2.5.[18]

In a large cohort, Kubrich et al[19] found no correlation between epicardial and microvascular function. Most studies correlated endothelial-independent CFR with epicardial CAV using IVUS or angiography that showed either negative or positive results. Prospective analysis in a pediatric population showed CFR was decreased in patients with microvasculopathy detected in biopsy specimens (detailed in the Pediatric section).

A thermodilution-derived index of microvascular resistance was established in 2003 to investigate microvascular physiology, but diabetes, ischemic time, and back pressure influence index of microvascular resistance and, therefore, affect accurate estimation of microvascular tone.[20]

Another assessment tool is the thrombolysis in myocardial infarction (TIMI) myocardial perfusion grade estimating TIMI contrast washout from the myocardium as a surrogate marker for microvascular function. However, the technique has been applied only for detection of stenotic epicardial CAV.[21] The TIMI frame count, derived from patients undergoing percutaneous coronary intervention or thrombolysis, has failed to predict CFR.

In other data, endothelial dysfunction is not associated with abnormal CFR.[22] However, 2 recently published studies have found a better correlation between microvessel disease and prognosis. In 2007, Hiemann et al[23] showed that the presence of stenotic microvasculopathy (defined as obliteration of arterioles mainly due to thickening of the media on endomyocardial biopsy specimens) was associated with adverse clinical outcomes in a large series of patients. A further step was taken by Escaned et al,[24] who performed simultaneous physiologic and histologic studies of microcirculation in a small group of cardiac transplant recipients. In their study, arteriolar obliteration and a striking reduction in the number of capillaries both contributed to deterioration of microcirculatory indices. Interestingly, absolute indices, such as instantaneous hyperemic diastolic velocity pressure slope, correlated well with histologic microvasculopathy and clinical events, whereas relative indices such as CRF did not.[24]

In summary, microvascular dysfunction is frequent after transplant and there is little evidence that invasive or noninvasive techniques are reliable tools to reflect the post-transplant physiology of microvessels. Flow velocity reserve tested by agents acting in resistance vessels seems to be preserved even as microvasculopathy is diagnosed by biopsy specimen, and its prognostic value is uncertain during the early and intermediate post-transplant course. Newly described Doppler-derived indices showing a better correlation with histology and prognosis are still in need of confirmation.

Non-invasive imaging

The commonly studied non-invasive techniques include perfusion scanning with technetium-99m sestamibi, stress echocardiography (usually with dobutamine), and multidetector computed tomography (MDCT).

Perfusion scanning

Resting electrocardiographic abnormalities (especially right bundle branch block) are common in heart transplant recipients, and stress testing with electrocardiogram alone is rarely useful in the detection of CAV. Dipyridamole technetium-99m sestamibi tomography was studied by Ciliberto et al[25] in patients who also underwent coronary angiography. The angiogram was normal in 53 patients, showed non-significant coronary disease in 13, and significant CAV (stenosis $> 50\%$) in 12. Resting wall motion abnormalities were detected in 9 patients and perfusion defects in 20 on scanning. The sensitivity and specificity of the test was 92% and 86% for significant CAV, with a negative predictive value (NPV) of 98% and positive predictive value (PPV) of 55%. For any CAV, the sensitivity fell to 56% whereas specificity was 89%. Combining the test with resting echocardiography increased the NPV to 100%. During the 6.5 ± 2 years of follow-up, there were 19 deaths, and 6 were ascribed to CAV. Three patients underwent retransplant for severe CAV, and heart failure developed in a further 11. An abnormal resting echocardiogram increased the relative risk of a major cardiac event 10-fold, whereas a positive dipyridamole single photon emission CT (SPECT) scan conferred a relative risk of 4.1.

Wu et al[26] studied dobutamine thallium-201 SPECT in 47 patients at a mean of 34 ± 21.4 months after heart transplant. Coronary angiogram results were normal in 37 patients, non-significant CAV was detected in 1, and significant CAV in 9. The test for the detection of CAV had sensitivity of 89%, specificity of 71%, NPV of 96%, and PPV of 42%.

Dobutamine stress echocardiography

Akosah et al[27] studied 22 patients who underwent serial dobutamine stress echocardiography (DSE) performed ≤ 24 hours of routine endomyocardial biopsies from the time of transplant. Mean follow-up was 32 ± 11 months. Patients also underwent annual coronary angiography. Seven patients had no inducible wall motion abnormalities on any DSE study, 4 patients had abnormalities that were not persistent, and the other 11 patients had inducible abnormalities that were persistent. Events occurred in 8 of 11 patients in the third group, including death, myocardial infarction, and angiographic coronary artery disease. No events occurred in the first 2 groups.

Spes et al[28] studied 109 heart transplant recipients 39 ± 37 months after surgery with serial DSE, coronary

angiography, and IVUS. A normal DSE result predicted an uneventful clinical course. DSE detected CAV with a sensitivity of 72%. Cardiac events were significantly more frequent in patients with abnormal DSE results. Patients with worsening serial DSE had an inferior outcome.

Derumeaux et al[29] enrolled 37 patients 40 ± 20 months after heart transplant and performed DSE, followed by coronary angiograms 24 hours later. Of these, 23 had normal coronary angiogram results (Group 1), and DSE detected abnormalities in 2 patients. Angiogram results were abnormal in 14 patients, comprising 7 with focal stenoses < 50% or minor diffuse abnormalities (Group 2), and 7 with stenoses > 50% (Group 3). DSE correctly identified the hypoperfused segments in Group 3 and showed hypokinesia in 5 patients in Group 2. DSE had a sensitivity of 86% and specificity of 91%. A myocardial infarct occurred in 1 patient in Group 1 and in 1 patient in Group 3 during follow-up, and both had abnormal findings on DSE.

Multidetector computed tomography

Sigurdsson et al[30] performed MDCT in 54 heart transplant recipients within a few days of quantitative coronary angiography.[30] MDCT correctly identified 15 of 16 patients classified by quantitative coronary angiography as having significant CAV and 29 of 37 patients without significant stenosis. The sensitivity, specificity, PPV, and NPV, of MDCT for the detection of segments with stenoses >50% were 86%, 99%, 81%, and 99%, respectively.

Iyengar et al[31] studied 19 heart transplant recipients with 64-slice MDCT within 2 weeks of coronary angiography. MDCT identified plaques in 13 patients, and angiography identified disease in 11 patients (2 with stenosis > 50%). MDCT detected more CAV than angiography in 4 patients.

Romeo et al[32] enrolled 53 consecutive heart transplant recipients in a study comparing 16-slice MDCT with coronary angiography. Adequate images could not be obtained in 3 patients. Of 450 angiographic segments, 432 (96%) were evaluable by MDCT. Complete analysis of the coronary tree was possible for 44 of the 50 patients. For detection of stenoses > 50%, sensitivity was 83%, specificity was 95%, PPV was 71%, and NPV was 95%. Of 9 coronary stents in 7 patients, CT correctly identified 3.

Gregory et al[33] compared 64-slice MDCT with coronary angiography plus IVUS in 20 patients who were greater than 1 year after transplant. The image quality of 83% of the coronary segments was graded as excellent or good. Using IVUS as the reference standard, MDCT had a sensitivity of 70%, specificity of 92%, PPV of 89%, and NPV of 70% for the detection of CAV. MDCT vessel diameter measurements correlated well with quantitative coronary angiography.

Schepis et al[34] used dual-source CT and IVUS to study 30 patients who had survived at least 1 year after heart transplant, having excluded significant coronary stenoses by angiography. IVUS was performed in any 1 vessel (selected by the operator). CAV on dual-source CT was defined as the presence of any coronary plaque. Of the 459 segments that were evaluated in the 30 patients, 96% were considered to have excellent or good image quality. IVUS detected CAV in 17 of 30 patients and in 41 of 110 coronary segments studied. Using IVUS as the reference standard, the sensitivity, specificity, PPV, and NPV of dual-source CT were 85%, 84%, 76%, and 91%, respectively.[34]

In summary, non-invasive testing, particularly with MDCT or dual-source CT, can be used to exclude significant CAV but is not as sensitive as IVUS. DSE can be used as a prognostic tool; a patient with a normal DSE study result is unlikely to have prognostically important CAV.

Cardiac allograft histology

Yamani et al[35] developed computerized scoring of endomyocardial biopsy specimens for predicting epicardial CAV that was validated by IVUS. The authors developed a mathematic model computing a biopsy specimen score for each patient based on the duration and severity of cellular rejection, vascular rejection, ischemia, and fibrosis and demonstrated that this score is an effective method for predicting the development of CAV and for predicting outcome in cardiac transplant recipients. Histologic correlates of CAV seen in endomyocardial biopsy specimens are primarily limited to small study populations and include unspecific changes, such as concentric intimal thickening with or without foamy macrophages, sub-endothelial accumulation of lymphocytes—the so-called endothelialitis—and perivascular fibrosis.[36] Furthermore, evidence of myocardial ischemia is sometimes present, such as myocytolysis, coagulation necrosis, and healing ischemic lesions, as well as interstitial, perivascular, and replacement fibrosis.[37,38] However, endomyocardial specimen findings are considered to have only limited sensitivity in the recognition of microvascular CAV.

Coronary arteries from healthy or naïve hearts may appear to have intimal thickening that is histologically characteristic of CAV. Longitudinally oriented cushions of smooth muscle have been observed in several mammalian species and have been characterized in human coronary arteries as normal and as pathologic findings.[39–49] Whelan et al[50] described these "coronary endocardial cushions" in humans and in swine and suggested that these cushions may play a functional role in intramural coronary arterial blood flow and predispose to ischemic heart disease.

Houser et al[51] quantified the small but notable prevalence of vessels in naïve porcine and human myocardium that have morphologic features of CAV despite the hearts being otherwise normal. These longitudinally oriented smooth muscle cushions varied in morphology, and depending on the manner in which a vessel with these cushions was cut in cross-section, an apparent intimal thickening might be concentric or eccentric. Vessels with these muscular cushions, particularly if they produce a more or less concentric morphology in cross-section, could clearly mimic histologic features of CAV and affect one's assessment of prevalence

of CAV in human grafts or by surrogate markers such as IVUS.

Immune monitoring markers

The endothelial cells of the cardiac vasculature express major histocompatibility complex (MHC) antigens and others, such as vimentin and MHC class I-related chain A (MICA), and appear to be primary targets of cell-mediated and humoral immune responses after heart transplant.[52–55] The possibility of using titers of these or other antibodies against known antigens for CAV-grading purposes is limited by a number of deficits in our knowledge of their behavior, clinical significance, and diagnostic or prognostic value.

Vasilescu et al[56] conducted a prospective study in 285 heart transplant patients and assessed anti-human leukocyte antigen (HLA) antibodies by the complement-dependent microlymphocytotoxicity method at the time of each endomyocardial biopsy. CAV was defined by angiography. The presence of circulating anti-HLA class II antibodies was an independent risk factor for CAV. The probability of a patient remaining disease-free 5 years after heart transplant was 90% without and 65% with anti-class II antibodies. Neither class I incompatibilities nor anti-class I antibodies showed significant correlation with CAV.

Tambur et al[57] prospectively studied 71 heart transplant patients and used the FlowPRA (One Lambda Inc, Canoga Park, CA) panel reactive antibody assay to investigate anti-HLA antibodies. De novo anti-class II antibodies were associated with IVUS-documented CAV. McKay et al[58] retrospectively observed that anti-HLA class I antibody was associated with higher risk of stenosis after percutaneous coronary interventions in CAV (hazard ratio, 11.3, $p = 0.01$) in 62 de novo lesions in 40 patients.

Vimentin is abundantly expressed in the intima of vessels with CAV but not on the healthy endothelial cell surface.[53] Anti-vimentin antibodies are produced by about 30% of patients after heart transplant and have been associated with CAV, as have high levels before heart transplant. Among 167 heart transplant patients, 91% of those with CAV after 2 years were anti-vimentin positive compared with 42% of those without CAV ($p = 0.0066$).[59] In a 213-patient study, Kaczmarek et al[60] observed that circulating HLA-directed donor-specific antibodies, assayed with a Luminex test (Luminex Corp, Austin, TX), correlated with increased mortality and CAV. The cumulative incidence of formation of alloantibodies, in most cases anti-class II, was 10.8%. Kaplan-Meier CAV-free rates at 1, 5, 10, and 15 years after transplant were 94.4%, 81.5%, 41.2%, and 10.3% for recipients with anti-class II antibodies, and 96.3%, 83.1%, 67.3%, and 32.9% for those without ($p = 0.02$).

Poggio et al[61] performed a cross-sectional analysis of 65 patients using enzyme-linked immunosorbent spot assay to assess anti-donor cellular immunity and FlowPRA for humoral immunity, and 53.1% of patients with angiographic CAV were immunoreactive vs 12.1% without ($p < 0.001$). No large prospective studies have evaluated the association of antibodies with CAV. Serial assessments of anti-donor immunity using different methods are necessary, and larger prospective studies using more sensitive CAV-detecting methods (ie, IVUS rather than angiography) are required to enhance our understanding.

The key limitations of current investigations include the diverse use of various methods with different sensitivities and specificities, lack of standards for the diagnosis of CAV, and lack of consistent correlation with intragraft histology. Studies have been incomplete in that uncertainty has remained concerning whether the relations observed are causal or epiphenomenal. Temporal association between an alloimmune response and transplant rejection do not prove that the autoimmune response is directly pathogenic to the graft. Thus, the establishment of a standardized nomenclature for CAV will allow for more enhanced correlation studies.

Gene-based and protein-based biomarkers

Although a simple biomarker would be of great interest, no gene-based or protein-based biomarker rises to a level of definition as a detector of CAV. Patients with persistent elevation in cardiac-specific troponin I in the first year after transplant have greater progression of CAV and earlier graft failure than patients whose troponin levels normalize within the first 3 months.[62] Elevated levels of C-reactive protein, a sensitive marker of systemic inflammation, have been associated with the development of CAV and predict cardiac allograft failure late after transplant.[63]

Elevated plasma B-type natriuretic peptide (BNP), which reflects ongoing wall stress and structural remodeling of the allograft, is correlated with the development of CAV in the late post-transplant period, and gene-based correlations suggest elevation of vascular transcriptomes.[64] The predictive value of BNP is enhanced in combination with angiographic findings, with 50% of patients with high BNP levels and angiographic CAV experiencing cardiac death. The cut point of BNP of < 250 pg/ml or ≥ 250 pg/ml for predicting cardiac events has 89% sensitivity and 72% specificity. Although the PPV was only 35%, it yields an excellent NPV of 97%.[65] The problem, however, is in the variability of BNP levels as a result of obesity, gender, or renal function.[66]

Transcriptional signals in peripheral blood mononuclear cells provide information on the presence or absence of immunologic quiescence of the cardiac allograft.[62] The informative genes represent a number of biologic pathways, including T-cell activation (*PDCD1*), T-cell migration (*ITGA4*), and mobilization of hematopoietic precursors (*WDR40A* and microRNA gene family *cMIR*), as well as steroid-responsive genes such as *IL1R2*, the decoy receptor for interleukin-2. These molecular signals may provide predictive insight to future cardiac allograft events when assessed early after heart transplantation.[67,68] Whether, these

signals also correlate with CAV remains the subject of ongoing study.

Pediatric considerations

Commensurate with the adult experience, CAV remains the leading cause of late mortality in pediatric heart transplant recipients.[69] Moderate to severe CAV by angiography is associated with a poor prognosis, with the most comprehensive multicenter registry report from the Pediatric Heart Transplant Study (PHTS) citing graft survival with an angiographic diagnosis of severe CAV of 50% at 2.8 years after diagnosis or less than 30% freedom from death or graft loss within 4 years.[70] In addition to the overarching data provided earlier in this document, focused pediatric experience is outlined below. As is often the challenge in the pediatric population, numbers are small, and the number of patients with significant disease and disease-related events is even smaller.

CAV in children exhibits some key differences compared with the adult heart transplant population. First, reported prevalence by angiography is lower, with data on 751 patients within the PHTS showing an angiographic incidence of any degree of CAV of 2%, 9%, and 17% at 1, 3, and 5 years after transplant, and only 5% meeting criteria for moderate to severe disease at 5 years. Given the low incidence of moderate to severe disease, freedom from graft loss due to CAV was 99%, 96%, and 91% respectively at 1, 3, and 5 years.[70] Other reports cite freedom from CAV of 66% and 79% at 10 years, and 72% at 15 years.[69,71] This variability is likely related to challenges with diagnosis of CAV.

Age at transplant has a strong influence, with an 8-year freedom for CAV in infancy or early childhood of 74% compared with 56% for age older than 10 years. The largest cohort reported from the ISHLT database for 1999 to 2008 showed a freedom from CAV at 6 years of 88% for infants younger than 1 year old, 81% for ages 1 to 10 years, and 70% for those older than 11 years at transplant.[69] One hypothesis for this age effect relates to the immaturity of the immune system of the infant,[72] and the use of younger donors being associated with less CAV as identified in both the ISHLT and PHTS registries. The lack of recipient and donor cardiovascular risk factors for atherosclerosis may also influence the lower prevalence and rate of progression compared with adult heart transplant recipients.

Angiography remains the purported gold standard for the diagnosis of CAV, but as evidenced by pathologic examination and clinical outcomes, is well recognized to underestimate disease severity consistently across reports in the pediatric population. There are variable anatomic classifications/scoring systems with lack of consistency and prognostic value.[70,73–78] There was a relatively low incidence of any degree of angiographic abnormality in the reported multicenter cohort, ranging from 2.5% at 1 year and plateaus at less than 10% from 3 to 8 years after transplant in the patients evaluated.[70] Comparable with the adult experience but notably with a lower prevalence, the data suggest that moderate to severe CAV by angiography is associated with cardiac events, death, and retransplant. In data from the PHTS registry, however, just fewer than 50% of patients were reported to have undergone routine serial angiography for surveillance for CAV.[70] Reasons for this are likely multifactorial, most predominantly (1) technical challenges in infants, younger patients, and those with a history of complex congenital heart disease; (2) need for general anesthesia; and (3) perceived diagnostic yield and potential clinical impact from a procedural risk-benefit perspective.

There are distinct difficulties with the performance of invasive tests in children. In experienced hands, coronary angiography, including selective ostial injection, is technically feasible with a low complication rate. The highest risk is in the infant population, generally considered to have a weight of less than 10 kg. Femoral arterial thrombus formation is a risk, especially in smaller patients. Many pediatric centers perform coronary angiography under a general anesthetic in a significant proportion of their pediatric transplant patients. Technical expertise and facilities exist in all pediatric heart transplant centers.

IVUS, although reports are limited in the pediatric population, has been found to be more sensitive for the detection of intimal thickening as reported in adults, often in the face of normal angiography. The prevalence of any intimal thickening using IVUS data has been reported as high as 74% in 27 patients studied at more than 5 years after transplant.[74] In the largest pediatric IVUS study of 66 patients, severe CAV by IVUS did not portend the same poor prognosis as with angiography, nor did a lack of CAV correlate with absence of rapid development of CAV.[79] As in adult studies, IVUS provides data about the epicardial vasculature but does not necessarily reflect microvascular disease.

Technical expertise to perform IVUS and patient-related challenges, as outlined above, make IVUS less feasible in the pediatric population; hence, even the use of IVUS as an experimental tool to help investigators evaluate the outcome of various therapeutic conditions in this population is limited. In contrast to angiography, the technical limitations to IVUS in the pediatric population remain a challenge. The lower weight limit commented on in the literature ranges from 10 to 25 kg; however, the actual reported weight range in the limited pediatric transplant literature is 21 to 79 kg.

The complication rates of IVUS vary and are generally higher than angiography. IVUS has a steep learning curve. From a procedural perspective, technical expertise and equipment exist in the minority of pediatric heart transplant centers. Added time and cost are significant, including the need for a general anesthetic and recovery. Thus, clinical utility is limited, but IVUS may be used at any point in the transplant process for excluding significant disease when the angiogram appears ambiguous and may become part of future research endeavors as more centers adopt this tool.

Dobutamine stress echocardiography (DSE) has been correlated with angiography and outcomes in the pediatric heart transplant population. Most studies have found reasonable correlation (about 80%) with angiography findings,

with a reported sensitivity of 72% and specificity of 80%.[80] More consistently and more importantly, a negative DSE strongly supports the absence of angiographic CAV, whereas a positive study result predicts death or graft failure.[81,82] Graft loss has been reported to be 27% by 2 years after an abnormal DSE result compared with 4% with a normal DSE.[80] In addition, correlation has been shown between angiography and DSE, with an increasing probability of an abnormal DSE with an increasingly abnormal angiography.[83] Both remain limited indicators of CAV, however. A key advantage of DSE over angiography is the determination of the functional impact of CAV on graft function and the provocation of stress-related ischemia or arrhythmias, or both. There is very limited pathologic correlation in the literature with DSE except in the most severe cases.

DSE is non-invasive and can be performed awake or with mild sedation in most pediatric patients. From a technical and resource perspective, the pediatric echocardiography laboratory does require appropriate software, sonographer expertise in image acquisition, nursing and electrocardiogram interpretation support, and physician expertise in interpreting wall motion abnormalities. However, it remains less costly and less invasive than angiography or IVUS. As noted for the adult population, DSE can be used as a prognostic tool. A patient with a normal DSE study result is unlikely to have prognostically important CAV, and DSE is useful for risk stratification in monitoring patients who have mild angiographic coronary abnormalities.

Data looking at coronary flow reserve (CFR) in pediatric heart transplant recipients are very limited, and that which exist demonstrate minimal correlation with outcomes.[84,85] In small numbers, a reduction in CFR was seen in patients with microvasculopathy diagnosed by endomyocardial biopsy specimen.[85] A reduction was also demonstrated in patients with both epicardial and microvascular disease of equivalent magnitude using systemic or intracoronary adenosine administration. A similar reduction was not seen in isolated epicardial CAV. CFR has been performed in a small number of pediatric patients, is not validated, and normative pediatric data are lacking. Technical considerations are similar to those of IVUS (weight reported, 8.2–60 kg). Again, most pediatric heart transplant centers do not have the technical expertise and equipment, and time and cost in addition to the use of a general anesthetic must be taken into consideration.

Tissue Doppler imaging (TDI) has been studied in a single-center retrospective report that identified patients with CAV who were at risk for death or graft failure within a 6-month period after observed changes.[86] Right heart function was the best predictor of graft failure, with reduced tricuspid annulus velocities correlated with risk of death or retransplant. In addition, decrease in LVEF and increase in tricuspid regurgitation also predicted an increased likelihood of increased mortality. Use of TDI varies across centers but does not form the basis for routine surveillance and needs further study, especially with regards to diagnosis of CAV and prognostication.

Reported experience with MDCT imaging for CAV is limited to 8 patients in a single-center study, and significant technical limitations were observed.[87] There is no significant reported experience on the utility of positron emission tomography or magnetic resonance imaging. Reports of exercise stress testing in relation to diagnosis and/or outcomes of CAV in pediatric patients is limited to the observation of a deterioration in maximum oxygen consumption over time being associated with graft loss in a handful of patients.[88]

Histopathology examination for microvasculopathy within endomyocardial biopsy specimens was reported in the pediatric population in 2 studies but without correlation with outcomes.[75,85] Pathologic descriptions and grading systems varied between the 2 studies. Stenotic microvasculopathy as a prognostic factor for long-term survival after heart transplantation has been reported in the adult population, but patients younger than 18 years old were excluded.

Given all of the considerations discussed herein, an adult-derived nomenclature focusing on anatomic, physiologic, and histologic characteristics could generally be applied to the pediatric population.

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