The role of non-invasive imaging in the diagnosis of cardiac allograft vasculopathy

Miller; Non-invasive assessment of cardiac allograft vasculopathy

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Introduction

Cardiac allograft vasculopathy (CAV) is common, with a prevalence of 52% at 10-years post-transplantation, and represents a leading cause of death beyond the first year, responsible for approximately 15% of deaths annually.\(^1\) It is characterised by diffuse and concentric intimal proliferation, typically involving the intramural, as well as epicardial coronary arteries. Its diagnosis is difficult to establish clinically due to denervation of the transplanted heart. Consequently it presents late with silent myocardial infarction, progressive heart failure or arrhythmic sudden death.\(^2\) Screening is therefore required for its early detection.

Whilst coronary intravascular ultrasound (IVUS) is considered the 'gold-standard' technique for detecting the anatomical features of CAV (Table 1), its broad clinical use in this context is limited by cost and lack of widespread expertise, and its evaluation is limited to epicardial vessels.\(^3\) Coronary angiography, performed annually or biannually, remains the most common clinical screening method.\(^4\) However due to the diffuse nature of CAV with a lack of ‘normal reference’ segments and the relatively late occurring luminal narrowing, the sensitivity of angiography is as low as 30% when compared to IVUS (Figure 1).\(^5\) As a result, complications frequently occur before disease is evident angiographically.\(^6\) Furthermore, angiography is associated with significant, albeit uncommon complications (overall complication rate 7.4/1000 procedures, including rates of 0.65/1000, 1.6/1000 and 0.72/1000 for cerebrovascular accidents, vascular complications and death respectively), is disliked by transplant recipients, is costly and repeated studies are associated with an important cumulative radiation dose.\(^7\)

Non-invasive screening would conceivably be safer, more tolerable and cheaper and as such is highly desirable. Echocardiography and single photon emission computed tomography (SPECT) are the most extensively investigated, but neither has become widely
accepted as an alternative to invasive screening. Preliminary data regarding positron emission tomography (PET), cardiovascular magnetic resonance (CMR) and coronary computed tomography angiography (CTA) suggests these modalities may prove to be more effective.

The evaluation of imaging modalities faces two particular challenges. First, invasive coronary physiological assessment demonstrates that the functional significance of CAV represents a complex interplay between epicardial and microvascular coronary compartments.\(^8\) Both must be taken into account for accurate diagnosis. Second, as described, the clinical standard for detecting CAV (i.e. angiography) has limited sensitivity. Therefore studies using this as the sole comparator are inherently limited in the information they provide. Furthermore angiographic coronary stenoses of 50% or 70%, often used as the significance threshold in such studies, represent advanced disease. Adverse events frequently occur well before this degree of luminal narrowing is reached.

The pathophysiology, invasive diagnostic assessment and treatment of CAV have been extensively reviewed in a recent article by Schmauss \textit{et al.}\(^4\) This review will focus on the non-invasive imaging approaches for the diagnosis of CAV.

\textbf{Echocardiography}

The sensitivity of resting left ventricular ejection fraction and regional wall motion for detecting CAV is low at less than 50% across multiple studies, although the specificity of regional dysfunction is much higher (more than 80%) and should prompt further investigation.\(^9\) Tissue Doppler imaging may improve sensitivity, indeed a study using pulsed-wave tissue Doppler obtained at the basal left ventricular inferolateral wall in nearly 300 transplant recipients found a peak systolic wall motion velocity \(\leq 10\text{cm/s}\) had a 97% positive
predictive value for CAV, whereas a value of >11cm/s had a 90% negative predictive value. The comparator was angiography and IVUS (those without angiographic evidence of CAV also underwent IVUS) (Figure 2).

Stress echocardiography is the most widely investigated functional imaging technique for detecting CAV, although published studies are relatively small with heterogeneous design and varying results (Table 2). Dobutamine-stress appears more sensitive than exercise, most likely because allograft denervation results in a blunted heart-rate response to exercise. The largest study, which included 109 patients, found Dobutamine stress echocardiography (DSE) to have a sensitivity and specificity of 72% and 88% respectively for the diagnosis of CAV, defined as approximately Stanford Class III or IV on IVUS (Table 1) or any luminal irregularities on angiography.

Quantitative DSE analysis using regional deformation parameters may improve sensitivity. In a study of 42 patients undergoing DSE with colour myocardial Doppler imaging, a peak systolic longitudinal strain rate of <0.5/second had a sensitivity of 88% for detecting any angiographic abnormalities including minor diffuse irregularities, compared to 63% for conventional DSE analysis. Mitral annular systolic, early diastolic and late diastolic velocities at peak Dobutamine-stress are also reduced in transplant recipients despite no demonstrable abnormality in regional systolic function.

The value of myocardial contrast echocardiography (MCE) to assess myocardial perfusion remains to be established in CAV. In a study of 33 patients undergoing Dobutamine-stress, semi-quantitative MCE (ratio of stress and rest myocardial signal-intensity upslopes) had a sensitivity and specificity of only 58% and 67% respectively for detecting significant CAV, defined as a combination of >50% stenosis on angiography or significant wall irregularities on IVUS and an associated reversible perfusion defect on SPECT. However when MCE
analysis was combined with conventional DSE analysis, sensitivity and specificity improved to 86% and 91% respectively, compared to 71% and 83% respectively for conventional DSE analysis alone. In another study, qualitative Dobutamine-stress MCE performed in 35 patients had a sensitivity and specificity of 70% and 96% respectively for detecting angiographic stenoses >50%. Correlation with coronary territory was poor except for the left anterior descending artery (LAD), and it failed identify disease extent.\textsuperscript{15}

Direct measurement of coronary blood flow velocity at rest and during adenosine-stress in the distal LAD using contrast-enhanced transthoracic Doppler echocardiography to calculate coronary flow reserve (CFR) has also been used to assess for CAV. In a study of 22 patients, a CFR of less than 2.9 had sensitivity, specificity and negative predictive value of 80%, 100% and 89% respectively for detecting a maximal intimal thickness of \( \geq 0.5 \text{mm} \) on IVUS.\textsuperscript{16}

Both resting and stress echocardiography provide useful prognostic information with DSE in particular having a high negative predictive value for adverse cardiac events.\textsuperscript{11, 17} In the largest prognostic study, 1 of 159 normal DSEs (0.6%) were followed by an adverse cardiac event during a mean 2.5-year follow-up.\textsuperscript{11}

\textbf{Nuclear imaging}

As with the DSE literature, there is considerable variation in methodology and results of studies assessing the accuracy of SPECT for detecting CAV. Of note, SPECT has only been assessed in relation to angiography, most commonly using luminal narrowing of \( \geq 50\% \) (Table 3). In the largest study, Dipyridamole-stress Sestamibi SPECT had a sensitivity and specificity of 92% and 86% respectively when compared to luminal narrowing of \( \geq 50\% \), but a
sensitivity of only 56% when compared to any angiographic abnormalities including minor luminal irregularities.\textsuperscript{18}

Like DSE, Dobutamine-stress SPECT provides important prognostic information. In two studies of 77 and 166 patients followed-up for 22- and 30-months respectively, 12-month negative predictive values for major cardiac events were 98% and 95%.\textsuperscript{19, 20} The prognostic value of Dipyridamole-stress SPECT may be lower (negative predictive value of 86% in a study of 78 patients), although this has only been assessed in a single study with a substantially longer follow-up (mean 78-months).\textsuperscript{18}

The ability of positron emission tomography (PET) to readily quantify myocardial blood flow (MBF) has provided insight into coronary artery function in CAV, indeed there is data, albeit limited at present, to suggest that this ability may allow PET to be more sensitive for detecting CAV than other non-invasive techniques.

Studies using PET have shown that resting MBF is higher in transplant recipients than in healthy controls, thought to be due to the increased resting heart rate secondary to allograft vagal denervation.\textsuperscript{21-23} PET has also been used to demonstrate impaired endothelial function in CAV, with an abnormal MBF response to cold-pressor testing due to impairment of vasodilatory capacity.\textsuperscript{22, 23} Furthermore, PET data has shown that MBF is homogeneous across coronary territories, in keeping with the diffuse nature of the CAV.\textsuperscript{21} This finding may explain in part the limited sensitivity of conventional functional imaging techniques that rely on the development heterogeneity in myocardial blood flow or contractility (Figure 3).

In 2 studies using $^{13}$N-ammonia PET, myocardial perfusion ratio (MPR, ratio of absolute MBF during stress and rest) correlated significantly with IVUS measures of CAV severity, albeit with modest correlation coefficients. In the first study, using adenosine-stress in 27
patients with normal angiographic appearances, MPR showed a significant inverse correlation with plaque volume index, defined as total plaque volume divided by total vessel volume x100 (r=-0.40; p<0.05). In the second study using Dipyridamole-stress in 32 patients, MPR showed a significant inverse correlation with mean maximal intimal thickness and intimal index, defined as intimal area divided by intimal plus luminal area (r=-0.61; p<0.005 and r=-0.52; p<0.05 respectively). Further highlighting the advantage of absolute MBF, 20% of subjects regarded as normal by semi-quantitative PET analysis (summed stress and rest scores) had a significantly abnormal MPR. In another study in which Dipyridamole-stress $^{13}$N-ammonia PET and IVUS were performed in 17 patients at 18-months post-transplant, MPR predicted the changes in total vessel area and luminal diameter seen on repeat IVUS 15-months later.

A limitation of nuclear imaging as a screening tool is the associated radiation dose, particularly with serial studies. PET also remains expensive with limited availability.

**CMR**

The versatility and safety profile of CMR make it attractive as a screening modality for CAV but evidence is limited at present.

In a study of 69 transplant recipients with no evidence of acute rejection, mean diastolic strain rate (mean strain rate from peak systole to 50% of diastole) measured using CMR ‘tagging’ at 1.5Tesla, was significantly reduced in patients with ‘severe’ CAV (angiographic luminal narrowing >50%) and with ‘minor’ CAV (lumen irregularities or focal stenoses <50%), compared to age-matched healthy controls. Mean diastolic strain rate also allowed differentiation between transplant recipients with ‘severe’ CAV, ‘minor’ CAV and normal angiographic appearances. Systolic parameters were less sensitive (Figure 4).
The prevalence of infarct-typical late-gadolinium enhancement (LGE) and mean infarct mass per-patient on CMR imaging in a study of 53 transplant recipients, correlated significantly with the degree of CAV visible at angiography. The majority of infarcts were found in the mid and apical segments, with no correlation to coronary territory. Interestingly, nearly a quarter of patients with ‘mild’ angiographic CAV (minor irregularities causing <30% stenosis) had infarct-typical LGE. The authors suggested this was due to ‘silent’ myocardial infarction occurring in the presence of non-significant angiographic disease and may provide further evidence of prognostically significant CAV occurring in the absence of significant angiographic changes. However patients were not scanned at baseline (i.e. shortly after transplant) and therefore unrecognised infarct in the donor heart or peri-operative infarction could not be excluded as the cause. The study also described the presence of infarct-atypical LGE patterns unrelated to angiographic severity, the cause and significance of which are not clear.

In a study of 69 transplant recipients undergoing adenosine-stress perfusion CMR, semi-quantitative MPR (ratio of stress and rest signal intensity upslopes) was significantly reduced in transplant recipients with ‘severe’ CAV (angiographic luminal narrowing ≥50%), ‘minor’ CAV (irregularities causing <50% stenosis) and even those with angiographically normal arteries compared with aged-matched healthy volunteers. MPR also allowed differentiation between grades of CAV. In another study that included 27 patients, those with ‘severe’ CAV (angiographic stenoses ≥50% in all major epicardial vessels) had a significantly lower MPR (ratio of stress and rest maximum signal intensity) and resting endocardial:epicardial maximal signal intensity ratio than patients without angiographically-evident disease. Interestingly in a subgroup of patients with normal angiographic appearances but with significantly reduced coronary flow reserve on invasive Doppler assessment, MPR and resting endocardial:epicardial ratio were significantly reduced. In a further study of 17
patients, resting absolute endocardial blood flow and resting endocardial:epicardial blood flow ratio were significantly lower in patients with ‘severe’ CAV (≥50% stenosis in all major epicardial vessels and an invasive coronary flow reserve of <2.5) than in patients with a normal invasive parameters (Figure 5).\(^{27}\)

Non-contrast, respiratory-navigated, 3-dimensional steady-state free precession CMR coronary angiography performed at 1.5 Tesla in 16 patients, had a sensitivity and specificity of 60% and 100% respectively for detecting CAV, defined as any irregularities on conventional angiography (‘per-segment’ analysis).\(^{28}\) Vessels with a diameter of less than 1.5 mm were excluded from analysis.

There is presently no published data on the prognostic value of CMR in CAV, although work is underway.

Nephrogenic systemic fibrosis (NSF) is an extremely rare but serious complication of Gadolinium contrast administration that causes fibrosis of the skin and other organs and can result in significant functional impairment and reduced life expectancy. It is particularly associated with advanced chronic kidney disease or severe acute renal failure. As renal dysfunction is common post-transplant, with approximately 4% and 10% of patients having an estimated glomerular filtration rate (eGFR) of less than 30 milliliters/minute/1.73m\(^2\) at 5- and 10-years following transplant respectively, NSF may limit the role of CMR in CAV screening.\(^{29}\) In one of the largest registries, overall incidence of NSF following a Gadolinium contrast-enhanced magnetic resonance examination was 0.02%.\(^{30}\) All cases occurred in patients with an eGFR of less than 30 milliliters/minute/1.73m\(^2\), particularly in those with an acute deterioration in renal function. Haemodialysis, especially when performed on the same day as imaging, was associated with a significant reduction in NSF incidence. Other risk factors for NSF include Gadolinium dose administration of greater than 0.1 mmol/Kg, severe
liver failure or liver transplant and pro-inflammatory events such as tissue injury secondary to surgical procedures.

Cardiac devices e.g. pacemakers, implantable cardioverter-defibrillators and retained wires also represent a potential limitation to CMR, although increasingly CMR-compatible devices are being manufactured.

**CTA**

The potential combination of non-invasive luminal and vessel wall assessment makes CTA attractive for CAV screening.

Sixty-four detector CTA has been assessed in a small number of studies (Table 4). Two studies have compared CTA with IVUS, both defining CAV as intimal thickening >0.5mm. In the first, which included 20 patients, sensitivity and specificity of CTA was 70% and 92% respectively (analysis performed ‘per-segment’). B-blockers were administered when resting heart-rate was above 65 beats-per-minute (bpm). Whilst this sensitivity may initially appear disappointing, the sensitivity of conventional angiography was only 11%. The considerably higher sensitivity of CTA was because it was able to visualise vessel wall changes and coronary plaque. Indeed other studies have found 30–50% of coronary segments classified as normal by conventional angiography have wall thickening visible on CTA (Figure 6, 7). In the second study, which included 30 patients, dual-source 64-detector CTA had a sensitivity and specificity of 85% and 84% respectively, including correct identification of all 17 patients with CAV. Heart-rate limiting medication was not used. The authors suggested the greater sensitivity of CTA in this study was due to the higher temporal resolution afforded by dual-source technology.
Temporal resolution remains a weakness of CTA, indeed motion artefact accounted for the majority of the 20-30% non-analysable coronary segments in the available studies. As such, the high resting heart-rate of transplant recipients (typically 80-110 bpm) together with a delayed and variable B-blocker response (mean heart-rate in the available studies was 77–86 bpm following pre-scan B-blocker and 79–87 bpm without) represent particular challenges. Newer technology may lead to significant improvements, indeed only 4% of segments were non-analysable in the described study utilising dual-source CTA, despite a mean heart-rate of 80 bpm.\textsuperscript{34} No studies have reported the use of I\textsubscript{1} channel blockers.

CTA also has limited ability to assess smaller vessels, particularly important given the nature of CAV. Many of the available studies excluded vessels <1.5 mm from analysis, including the study using dual-source CTA.\textsuperscript{35}

Another drawback of CTA as a potential screening technique is the associated radiation dose. Average dose per CTA in the available studies was 9.5–21.4 millisieverts compared to 2.0–6.0 millisieverts for conventional angiography. The latest CTA technology used in experienced centres for assessing native coronary artery disease is reported to be associated with much lower doses, although such technology often requires controlled heart-rates.

Furthermore, patients at risk of CAV are also at increased risk of contrast-induced nephropathy (CIN). High iodine-concentration contrast is usually required for CTA in similar or greater volumes than for conventional angiography. Mean eGFR in patients 5-years post-transplant is approximately 55 milliliters/minute/1.73 m\textsuperscript{2} and the incidence of CIN is known to increase when eGFR is <60 milliliters/minute/1.73 m\textsuperscript{2}.\textsuperscript{29} Indeed up to a quarter of potential patients were excluded from the available studies due to renal impairment.
Coronary calcium scoring is of limited value in CAV as calcification is often absent even in severe disease. There is no prognostic data for CTA in the context of CAV yet.

**Adenosine supersensitivity**

Enhanced sensitivity of the denervated sinus and atrioventricular nodes to adenosine is well recognised in transplant recipients and therefore high vigilance is required for any functional imaging technique using this stressor agent. In a study of 102 transplant recipients undergoing SPECT, adenosine infusion at a dose of 140 micrograms/kilogram/minute over 6-minutes was associated with significantly higher rates of sinus pauses (4.9% vs. 0%), second (11.8% vs. 4.9%) and third degree (2.9% vs. 0%) atrioventricular block compared to age and sex-matched non-transplant patients, resulting in early termination of 1.9% of studies although there were no significant immediate or long-term sequelae.

**Guidelines**

The 2010 International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Recipients assign DSE and SPECT a Class IIa recommendation, Level of Evidence B; stating that they “may be useful for the detection of CAV in transplant recipients unable to undergo invasive evaluation”. CTA is assigned a Class IIb recommendation, Level of Evidence C; with the description “CTA shows promise in the evaluation of CAV although higher resting heart rates in these patients limit the technical quality”. PET and CMR are not included in the guidelines. Annual or biannual invasive coronary angiography is given a Class I recommendation, Level of Evidence C. CAV screening is not included in the respective Appropriate Use Criteria for the imaging techniques described.

**Conclusions**
The development of accurate non-invasive imaging techniques for CAV screening is important given the impact of the disease and the significant limitations of the current clinical surveillance technique. Echocardiography and SPECT are the most extensively investigated however most published studies are small with markedly differing methodologies and often discrepant results and as such, neither technique as found widespread acceptance for CAV screening. Newer techniques allowing quantification of myocardial deformation, visualisation of myocardial injury, absolute MBF quantification and arterial wall imaging hold potentially greater promise however supporting data is limited at present. Further investigation is needed in appropriately powered studies with evaluation against ‘gold-standard’ methods for characterising the anatomical and physiological manifestations of CAV.

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**Disclosures**

None
References


Figure legends

Figure 1. Invasive assessment of CAV in a patient with severe disease, highlighting the limited sensitivity of conventional coronary angiography. Whilst no LAD flow-limiting stenoses are seen on angiography (A), IVUS (B) shows significant intimal thickening, measuring up to 0.9mm (dashed line) and fractional flow reserve (FFR, C) is markedly reduced at 0.61 indicating significant epicardial disease. No discrete ‘step-down’ is seen on FFR pull-back along the LAD (D) in keeping with the diffuse nature of CAV. In this case, index of microcirculatory function (IMR, C) was 11.6 indicting normal microvascular function.

Figure 2. Mid-ventricular radial strain derived from 2-dimensional speckle tracking echocardiography in 2 transplant recipients at rest. In the first patient (A-C) with minimal CAV seen at IVUS (C, intimal thickness 0.2mm (dashed line)), global peak systolic strain was 51% (A, B). In the second patient (D-F) with severe CAV (F, intimal thickness 0.9mm), global peak systolic strain was reduced at 10% and peak strain was seen to occur following aortic valve closure (AVC). In both patients, left ventricular ejection fraction was normal.

Figure 3. Adenosine-stress Rubidium-82 PET in a patient 20-years post-transplant. Screening angiography was not possible due to lack of vascular access. Relative perfusion analysis was normal (A, mid-ventricular short-axis; B, vertical long-axis; C, horizontal long-axis stress images with corresponding rest images, B, D, F respectively). However given the high likelihood of significant disease at this late stage post-transplant and the modest sensitivity of semi-quantitative perfusion analysis in CAV, it was unclear whether this result was correct or whether there was homogenous reduction in perfusion secondary to diffuse disease which semi-quantitative analysis was unable to detect. Quantitative perfusion analysis (G, stress; H, rest; I, reserve; J, myocardial blood flow values) confirmed normal myocardial blood flow in all three coronary territories.
**Figure 4.** Mid-ventricular short-axis circumferential strain and strain rate derived from ‘tagged’ CMR images in patients in minimal (A-D) and severe (E-H) CAV. Strain maps (B and F), derived from tagged CMR images (A and E respectively), use colour to display degree of strain. Strain and strain rate (peak systolic and diastolic) were reduced in the patient with severe disease (G and H) compared to the patient with minimal disease (C and D). Left ventricular ejection fraction was normal in both patients.

**Figure 5.** Quantitative adenosine-stress perfusion CMR in 2 transplant recipients; one with minimal (A-H) and one with severe CAV (I-P). Absolute MBF is calculated from arterial input function (AIF) and myocardial time-signal intensity curves (B and J) through a process of model-independent deconvolution and displayed as perfusion maps (C-H and K-P), where pixel colour corresponds to blood flow in milliliters/gram/minute. The patient with minimal disease (intimal thickness 0.2mm on IVUS, A) showed normal stress (C, basal; D, mid-ventricular; E, apical short axis; global median MBF 2.92milliliters/gram/minute) and rest perfusion (F-H; MBF 1.30milliliters/gram/minute) and normal perfusion reserve (2.2). In the patient with severe disease (intimal thickness 0.9mm, I) stress perfusion was reduced (K-M; MBF 1.44milliliters/gram/minute) and rest perfusion was normal (N-P; MBF 1.34milliliters/gram/minute) resulting in a reduced perfusion reserve (1.1). In both patients blood flow was homogeneous across coronary territories.

**Figure 6.** CTA of a patient 5-years post-transplant showing diffuse concentric thickening of the wall of the mid-LAD (A, arrows) best seen in curved multi-planar reformatted (B, arrows) and short axis images (C, arrow heads) but difficult to appreciate on invasive angiography (D, arrows).
**Figure 7.** CTA of a patient 12-years post-transplant showing mixed plaque in the LAD after the second diagonal (A, arrow) causing greater than 50% luminal stenosis, confirmed with invasive angiography (B, arrow). However, mixed plaque seen more proximally on CTA (arrow heads) is difficult to appreciate on invasive angiography.
Table 1. Stanford Classification of CAV severity on IVUS

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Table 2. Studies evaluating the accuracy of stress echocardiography for the diagnosis of CAV

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Weighted average 53 88

*Coronary stenosis>40%, †Stanford classification>Grade III, ‡any angiographic abnormalities including luminal irregularities, §coronary stenosis>50%, | | approximating to Stanford classification grade III-IV, #angiographic luminal irregularities or IVUS severity approximating to Stanford classification grade III-IV, **conventional regional wall motion analysis, ††regional peak systolic strain rate analysis.
Table 3. Studies evaluating the accuracy of SPECT for the diagnosis of CAV

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<td>Angiography†</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>Ciliberto et al., 2001&lt;sup&gt;19&lt;/sup&gt;</td>
<td>78</td>
<td>99mTc sestamibi</td>
<td>Dipyridamole</td>
<td>Angiography†</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>Elhendy et al., 2000&lt;sup&gt;53&lt;/sup&gt;</td>
<td>50</td>
<td>99mTc tetrofosmin</td>
<td>Dobutamine</td>
<td>Angiography†</td>
<td>90</td>
<td>55</td>
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<tr>
<td>Hacker et al., 2005&lt;sup&gt;19&lt;/sup&gt;</td>
<td>63</td>
<td>99mTc sestamibi</td>
<td>Dobutamine</td>
<td>Angiography†</td>
<td>82</td>
<td>87</td>
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<tr>
<td>Wu et al., 2005&lt;sup&gt;54&lt;/sup&gt;</td>
<td>47</td>
<td>Thallium-201</td>
<td>Dobutamine</td>
<td>Angiography†</td>
<td>89</td>
<td>71</td>
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<tr>
<td><strong>Weighted average</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68</td>
<td>87</td>
</tr>
</tbody>
</table>

* discrete stenoses or diffuse concentric coronary narrowing, † coronary stenosis >50%, ‡ any angiographic abnormalities including luminal irregularities.
Table 4. Studies evaluating the accuracy of 64-detector CTA for the diagnosis of CAV

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>CAV diagnosis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
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<tbody>
<tr>
<td>Gregory et al., 2006**</td>
<td>20</td>
<td>IVUS*</td>
<td>70**</td>
<td>92**</td>
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<tr>
<td>Iyengar et al., 2006†</td>
<td>19</td>
<td>Angiography†</td>
<td>100</td>
<td>67</td>
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<tr>
<td>Pichler et al., 2008‡</td>
<td>60</td>
<td>Angiography‡</td>
<td>88</td>
<td>97</td>
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<tr>
<td>Von Ziegler et al., 2008§</td>
<td>26</td>
<td>Angiography§</td>
<td>100</td>
<td>81</td>
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<tr>
<td>Schepis et al., 2009**</td>
<td>30</td>
<td>IVUS*</td>
<td>85**</td>
<td>84**</td>
</tr>
<tr>
<td>Nunoda et al., 2010</td>
<td></td>
<td>10</td>
<td>Angiography</td>
<td></td>
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<tr>
<td><strong>Weighted average</strong></td>
<td>81</td>
<td></td>
<td>81</td>
<td>91</td>
</tr>
</tbody>
</table>

*Intimal thickness>0.5mm, †coronary stenosis<50% or minor luminal irregularities, ‡coronary stenosis>70%, §coronary stenosis>50%, | |any angiographic abnormalities including luminal irregularities, **analysis by coronary segment.