Coronary artery disease detection - limitations of stress testing in left ventricular dysfunction

Ritin Bomb, Senthil Kumar, Anand Chockalingam

(LVD) is common in clinical practice. The prevalence of asymptomatic LVD (Ejection Fraction, EF < 50%) is 6.0% in men and 0.8% in women and is twice as common as symptomatic LVD. The timely and definitive exclusion of an ischemic etiology is central to optimizing care and reducing mortality in LVD. Advances in cardiovascular imaging provide many options for imaging of patients with left ventricular dysfunction. Clinician experience, patient endurance, imaging modality characteristics, cost and safety determine the choice of testing. In this review, we have compared the diagnostic utility of established tests - nuclear and echocardiographic stress testing with newer techniques like coronary computerized tomography and cardiac magnetic resonance imaging and highlight their inherent limitations in patients with underlying left ventricular dysfunction.

Key words: Coronary artery disease; Stress testing; Left ventricular dysfunction; Myocardial perfusion imaging; Dobutamine stress echocardiography

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Core tip: Left ventricular systolic dysfunction is common in clinical practice and may be detected in asymptomatic patients. The timely and definitive exclusion of an ischemic etiology is central to optimizing care and reducing mortality. Clinician experience, imaging modality characteristics, cost and safety determine the choice of testing. We compare the diagnostic utility of established tests like nuclear and echocardiographic stress testing with newer techniques like coronary computerized tomography and cardiac magnetic resonance imaging. Due to limitations inherent to each non-invasive modality, oftentimes cardiac catheterization remains the definitive method to exclude coronary artery disease in patients with underlying left ventricular dysfunction.

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INTRODUCTION

Incidental diagnosis of left ventricular systolic dysfunction (LVD) is common in clinical practice. The prevalence of asymptomatic LVD (ejection fraction, EF < 50%) is 6.0% in men and 0.8% in women[1]. Asymptomatic LVD is at least twice as common as symptomatic LVD[2]. The diagnosis of LVD is usually made by demonstration of reduced systolic contractility and low EF by echocardiography. To determine whether LVD is due to coronary artery disease (CAD) is critical in the management of these patients as coronary revascularization has been shown to substantially reduce mortality in ischemic LVD. Modalities available for CAD diagnosis are either invasive coronary angiography (CA) or various non-invasive techniques such as dobutamine stress echocardiography (DSE), myocardial perfusion imaging (MPI) or single photon emission computerized tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance imaging (CMR) and coronary computerized tomography (CCT). Clinician experience, patient endurance, imaging modality characteristics, cost, safety and local availability determine the choice of testing.

ACC/AHA in 2005 recommended CA for patients with heart failure who have angina or significant ischemia; CA was felt to be reasonable in patients with chest pain that may or may not be cardiac in origin in whom coronary anatomy is not known, those with known or suspected CAD as well as patients with myocardial viability on noninvasive tests[3]. The 2013 revised guidelines finds it reasonable (class IIa) to pursue either non-invasive imaging or CA in revascularization eligible patients[4]. CA is an invasive procedure with potentially serious complications such as atheroembolism, bleeding, renal failure, myocardial infarction, ventricular tachyarrhythmias, stroke and death. The low yield of CA in the setting of LVD further highlights the unfavorable risk benefit ratio. Therefore, a noninvasive method that can identify ischemic myocardial scar or coronary luminal narrowing would be ideal in this setting. This would reduce the number of unwanted CA in patients with a truly non-ischemic cardiomyopathy. On the other hand, importantly, an ischemic etiology for cardiomyopathy can be missed when relying solely on non-invasive tests. In patients undergoing cardiac transplantation, severe CAD was found in all patients with a pretransplant diagnosis of ischemic cardiomyopathy (57 percent of a total 112 patients); unexpectedly at the time of transplant, severe CAD was also found in 9 of 38 patients previously thought to have idiopathic dilated cardiomyopathy (DCM) and 3 of 4 with presumptive alcoholic cardiomyopathy[5].

DSE and MPI are commonly used modalities for evaluation of CAD. Both have proven to be clinically useful in large series, are widely available and provide prognostic information as well. Despite the high sensitivity and specificity reported with these tests over the last 2 decades, clinicians still have to deal with ambiguous test results when evaluating systolic heart failure patients. Available literature suggests that the sensitivity and specificity of non-invasive methods ranges between 80%-95%; this implies that the etiology of cardiomyopathy may be misdiagnosed in approximately 1 out of every 10 patients. Myocardial perfusion using newer imaging modalities like CMR and PET provide physiological data similar to DSE and SPECT while CCT predominantly provides anatomical information along the lines of invasive angiography. In this review, we will focus specifically on CAD detection in patients with LVD; role of imaging in LVD associated with myocarditis or specific cardiomyopathies like tachycardia induced cardiomyopathy, peripartum cardiomyopathy and stress cardiomyopathy are beyond the scope of this review.

LITERATURE SEARCH

We performed a search of MEDLINE, PUBMED, SCOPUS, Clinical trials.gov and The Cochrane Library from January 1975 through Dec 2015. We set no geographic or language restrictions. To increase yield, we also searched the references of all the retrieved manuscripts and review article. MeSH terms used were Coronary Artery Disease; Ventricular Dysfunction, Left; Magnetic Resonance ImagingCine; Computerized Tomogram, Echocardiography, Stress; Dobutamine; Positron-Emission Tomography; Tomography, X-Ray Computed; and Tomography, Emission-Computed, Single-Photon.

After extensive review it was noted that though modalities like DSE, SPECT, PET and magnetic resonance imaging (MRI) have been extensively studied and written about as regards to assessment of viability in patients with cardiomyopathy, recent published literature is scant specifically with diagnosis of CAD in these patients. A few recent reviews extensively discuss specific technical aspects[6][7]. We present our review highlighting the limited literature specifically pertaining to diagnostic accuracy of various cardiac imaging modalities in left ventricular (LV) systolic dysfunction.

DISCUSSION

SPECT

SPECT allows direct assessment of myocardial perfusion. Parameters that factor into SPECT reporting are myocardial perfusion, wall motion abnormalities and LV ejection fraction. An inducible perfusion abnormality indicates impaired perfusion reserve which in turn corresponds to epicardial coronary obstruction.

Various studies have evaluated the utility of SPECT in detection of CAD. Bulkley et al[8] in 1977 reported that SPECT could reliably differentiate between ischemic and idiopathic cardiomyopathy obviating the need for cardiac catheterization. A similar conclusion was made by Tauberg et al[9] in 1993; based on the size of perfusion...
deficit, they showed that large defects have 97% predictive value for ischemic cardiomyopathy and 94% predictive value for idiopathic cardiomyopathy, and could reliably differentiate the two entities\textsuperscript{19}. In contrast, Dunn \textit{et al}\textsuperscript{18} in 1982 reported lower accuracy (80%) for SPECT in differentiating between the two entities. Moreover, only complete perfusion defects indicated CAD in this study; partial perfusion defects as well as reversible defects were seen both in CAD as well as DCM. A study by Wu \textit{et al}\textsuperscript{11} in 2003 reported that SPECT was only of modest value to distinguish between ischemic and idiopathic cardiomyopathy and concluded that SPECT cannot be relied upon in an individual patient to differentiate the two entities. Overall, the existing literature points to a high sensitivity for SPECT in CAD detection (nearly 100% in some published studies) while specificity on average is only about 40%-50% in LVD patients\textsuperscript{12-15}.

**Limitations of SPECT**

Although individual studies report high diagnostic accuracy for detecting CAD, SPECT has limitations specific to prior LVD that impact reliability. Regional wall motion abnormalities may point to CAD if located in particular coronary distributions. However, in a study of 50 DCM patients, 64% had regional wall motion abnormalities\textsuperscript{16}; other studies report the presence of regional wall motion abnormalities in 30%-50% of patients with DCM\textsuperscript{17-19}. Thus, regional wall motion abnormalities do not automatically imply an ischemic etiology for the cardiomyopathy.

Reversible myocardial perfusion defects are traditionally considered specific for ischemia. However reversible perfusion defects can occur in dilated cardiomyopathy as well. In one study, complete perfusion defects in thallium redistribution studies appeared to imply an ischemic etiology but was seen in only a few patients\textsuperscript{11}; the key finding in this study was that partially reversible defects occur in both DCM and ischemic cardiomyopathy when the LVD is severe (EF in the 25% range). In most instances, there is overlap of perfusion abnormalities between DCM and ischemic cardiomyopathy (even when large or reversible perfusion defects are present), thereby limiting the role of SPECT in the setting of LVD.

There are several possible reasons for the presence of perfusion defects in DCM. Structural changes in the myocardium of DCM patients like fibrosis and scarring could account for fixed perfusion defects\textsuperscript{19}. Dilatation of ventricle and abnormal cell membrane permeability could lead to variable radioactive tracer uptake and redistribution. Stress testing induced LV geometry changes are also known to cause reversible defects in DCM\textsuperscript{20}. Exercise induced coronary spasm\textsuperscript{21}, mitral valve prolapse\textsuperscript{22}, and aortic stenosis\textsuperscript{23} have been associated with SPECT abnormalities. Clinicians should consider the role of these confounders while interpreting SPECT results.

In a given patient with LVD, DCM is likely if SPECT shows normal perfusion and global (\textit{i.e.}, non-regional) systolic dysfunction. However, if reversible defects are detected, especially in coronary territories, possibility of CAD remains high\textsuperscript{24}. Another important concern in patients with severe LVD is balanced ischemia. Severe left main or triple vessel disease could cause equal reduction in tracer uptake in all major segments. As SPECT does not involve absolute quantification of tracer uptake, this matched perfusion defect in multiple territories appears as “normal” in this qualitative comparison of segments relative to each other\textsuperscript{25}. In patients with balanced ischemia, diffuse ST depression during stress, subtle perfusion defects and transient cavity dilatation (TID) may be the only clues for underlying severe CAD.

**DSE**

In contemporary clinical practice, DSE and exercise stress echocardiography play a major role in detection of CAD and risk stratification. A graded dobutamine infusion starting at 5 mg/kg per minute and increasing at 3-min intervals to 10, 20, 30 and 40 mg/kg per minute is the standard for dobutamine stress testing\textsuperscript{26}. If LVD is known to be of ischemic etiology, presence of myocardial viability and the probability of recovery after revascularization can be reliably predicted based on demonstrating contractile reserve with low dose dobutamine stress testing. There is a paucity of literature for exercise stress echocardiography in LVD.

Geleijnse \textit{et al}\textsuperscript{27} reported the sensitivity, specificity and accuracy of DSE for detection of CAD to be 80%, 84% and 81% respectively. In a study by Marcovitz \textit{et al}\textsuperscript{28}, DSE had 96% sensitivity and 66% specificity for detection of CAD based on resting or inducible wall motion abnormalities. Similarly, in a study evaluating chest pain, Hennesse \textit{et al}\textsuperscript{29} showed that the overall sensitivity and specificity of DSE were 82% and 65% respectively: Positive and negative predictive values were 89% and 51% respectively. In a recent meta-analysis of 32 studies, DSE had a higher sensitivity (94% vs 75%, \textit{P} < 0.001) and lower negative likelihood ratio (0.21 vs 0.47, \textit{P} < 0.001) compared to SPECT for detection of left main or triple vessel disease\textsuperscript{30}. These studies were performed predominantly in patients with preserved cardiac function.

Few DSE studies have been specifically performed in patients with LVD. One study by Jong \textit{et al}\textsuperscript{31} showed that most of the patients with DCM were found to have an abnormal regional myocardial contractile response to dobutamine. Cohen \textit{et al}\textsuperscript{32} reported in a study that although dobutamine had a reasonable specificity and positive predictive value, it lacked sensitivity in diagnosis of CAD in DCM patients. Sharp \textit{et al}\textsuperscript{33} reported that using the change in global wall motion score index from low to peak dose, DSE had a sensitivity of 83% and a specificity of 71% for detection of CAD. In one study, changes in left ventricular geometry as seen in patients with DCM can lead to false positive and false negative results in approximately 22% patients, hence reducing the accuracy of DSE\textsuperscript{34}. Vigna \textit{et al}\textsuperscript{35} showed that
although DSE has a specificity of 96% it has a lower sensitivity of 80% in diagnosis of CAD in patients with DCM.

Limitations of DSE
Similar to SPECT, the reliability of DSE for CAD detection remains a challenge in the setting of LVD. Coronary territory specific hypokinesia, characteristic thinning and scar related hyperechoic signals would help confirm an ischemic etiology. When baseline LVD is significant with predominantly global hypokinesia, lack of response to dobutamine could mean a poor contractile reserve and not necessarily ischemia. On the other hand, some regional variability in improved contractility may be due to endothelial dysfunction, microvascular abnormalities or focal fibrosis. These factors together with increased wall stress may lead to a reduced myocardial perfusion reserve and wall motion abnormalities in the absence of CAD. Segmental wall motion abnormalities and abnormal contractile response that could be interpreted as ischemia or hibernation are common in patients with DCM despite the absence of CAD[36]. Finally, DSE is an observer and patient dependent procedure, the accuracy of which depends on the experience of the interpreter as well the acoustic windows available during stress testing.

Not much data is available comparing the accuracy of SPECT and DSE in detection of ischemia in patients with prior LVD. There are multiple studies comparing these modalities in patients with preserved cardiac function and a pooled analysis concluded that MPI was more sensitive compared to DSE (84% vs 80%) but DSE was more specific (86% vs 77%)[37]. The accuracy for both modalities is likely to be significantly lower in patients with LVD and dilated hearts.

CCT
Many new techniques are clinically useful in LVD providing information about etiology, ischemia and prognosis. Prominent among them are coronary computed tomography (CT) and cardiac magnetic resonance imaging (MRI). Currently 64-slice CT is considered the minimum standard for evaluation of coronary stenosis. In a study using 64-slice CT, the accuracy, sensitivity, specificity, positive and negative predictive value were found to be 95%, 90%, 97%, 93% and 95% respectively for identifying ischemic cardiomyopathy[38]. Another new study also using 64-slice CT showed sensitivity, specificity, positive and negative predictive values of 96%, 99%, 94%, and 100% respectively for detection of > 70% coronary stenosis in patients with cardiomyopathy of unknown etiology[39]. Compared to CA, CT technology has advanced rapidly with 256- and 320-slice CT becoming available in many centers; it is likely that these newer scanners will provide better results. Thus, CCT is a non-invasive alternative to CA in patients with LVD for detection of CAD; however, CCT in its current state cannot overcome the inherent limitation of luminography, i.e., ability to provide only coronary anatomic information. Detection of atherosclerosis or stenotic lesions may not prove causality in LVD. Active research is underway to test the feasibility of ischemia detection simultaneously using myocardial perfusion CT.

CMR
In evaluation of patients with LVD, CMR has distinct advantages over other modalities. Delayed enhancement CMR is the only technique that is able to directly visualize myocardial infarction in vivo. Subendocardial and transmural hyperenhancement corresponding to coronary perfusion territories is observed in CAD compared to mid-myocardial and epicardial hyperenhancement that may be found in non-ischemic cardiomyopathies[40]. Delayed enhancement CMR has 40 times higher spatial resolution compared to nuclear imaging[41]; it can detect small subendocardial infarcts that are likely to be missed by nuclear imaging[42]. CMR can also help in identifying the specific etiology of DCM[40].

CMR is now considered as an effective alternative to CA for CAD diagnosis in patients with heart failure (Figure 1, illustrative images). In one study, delayed enhancement CMR was shown to have sensitivity and specificity comparable to CA in differentiation between ischemic and non-ischemic cardiomyopathy[43]. In a recent study, it was named as a noninvasive gatekeeper to CA due to its accuracy and cost-effectiveness; delayed enhancement CMR had a sensitivity of 100%, specificity of 96%, and diagnostic accuracy of 97% for CAD detection, which were equivalent to CA[44,45]. One study clearly showed that the absence of CAD type hyperenhancement can reliably exclude myocardial infarction or severe CAD in patients with LVD and may obviate the need for CA[46]. With high sensitivity and specificity, CMR is now considered the gold standard for differentiation of ischemic and non-ischemic cardiomyopathy[47].

PET
PET imaging can help determine if CAD is the etiology of LVD based on sequential Perfusion-Metabolic scan using flow tracer N-13 Ammonia (N-13 NH3) followed by metabolic tracer F-18 2 fluorodeoxyglucose (FDG). Two techniques have traditionally been used for reading PET scans: Visual analysis and Circumferential Profile Analysis[48]. On Visual analysis it was observed that patients with DCM had a homogenous distribution of blood flow on the N-13 NH3 and glucose metabolism on FDG in contrast to patients with CAD who exhibited LV segments with discrete blood flow reduction and enhanced or concordantly reduced glucose utilization. On Circumferential Profile Analysis ICMP patients had a regional reduction in N-13 NH3 Myocardial uptake[49]. DCM patients with left bundle branch block demonstrate selective uptake of FDG in the septum resulting in false positive results. PET imaging has limitations, including assumption of uniformity of myocardial thickness and decreased spatial resolution. Patchy fibrosis in DCM can falsely resemble a CAD pattern. The most important
of undetermined etiology have a low to intermediate probability of CAD; here various imaging modalities may serve as the gatekeeper for CA. In our opinion, the wide availability of DSE or SPECT makes these modalities reasonable in those with low likelihood of CAD. CCT is also appropriate in low to intermediate risk groups.

Our algorithm for evaluation of LVD patients is outlined in Figure 2. CMR, if available, would arguably be the ideal test in the setting of LVD to identify CAD scar pattern; at the same time, CMR may establish the specific etiology in several non-ischemic cardiomyopathies (Table 2). Finally, even in patients with CA proven CAD, the CMR scar pattern will help differentiate true ischemic cardiomyopathy (embolic or recanalized coronary lesions) from coincidental CAD.

CONCLUSION
Incidental LVD is not uncommon in clinical practice. Numerous imaging modalities are available to help establish the etiology and guide management in this population. When the suspicion of CAD is high, proceeding directly to CA would be of highest clinical value eliminating the need for noninvasive testing. In other settings where noninvasive testing would be appropriate, an algorithmic

limiting factor is cost and availability. In most centers, PET is thus used for viability assessment in LVD patients to determine revascularization suitability after CA quantifies CAD burden. Combined PET-CT imaging has shown promise in low risk patients and in the future may provide the combined functional and anatomic information to obviate the need for invasive CA.

Recommendations
Identifying the etiology in patients with LVD is critical. The imaging modalities differ in their accuracy for CAD detection (Table 1). In patients with ischemic cardiomyopathy, adequate revascularization, especially if done early, significantly improves outcome. To achieve favorable risk-benefit ratio as well as cost effectiveness, we suggest a stepwise algorithm that incorporates patient demographics, clinical presentation and probability of CAD to determine the imaging approach for CAD detection. In patients with LVD and high index of suspicion for CAD, proceeding directly to CA would be prudent (Figure 2). When a reversible etiology such as stress cardiomyopathy or tachycardiomyopathy is likely, supportive treatment and repeat imaging in few weeks may obviate the need for invasive CA.

A sizeable proportion of patients with cardiomyopathy of undetermined etiology have a low to intermediate probability of CAD; here various imaging modalities may serve as the gatekeeper for CA. In our opinion, the wide availability of DSE or SPECT makes these modalities reasonable in those with low likelihood of CAD. CCT is also appropriate in low to intermediate risk groups.

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Table 1  Comparative analysis of the sensitivity, specificity and diagnostic accuracy for coronary artery disease detection using various imaging modalities

| Modality | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Diagnostic accuracy |
|----------|-------------|-------------|---------------------------|---------------------------|-------------------|
| SPECT    | 80%-100%    | 40%-50%     | 90%-95%                   | 90%-95%                   | 75%-80%           |
| DSE      | 80%-85%     | 60%-80%     | 80%-90%                   | 45%-60%                   | 75%-80%           |
| PET      | 85%-90%     | 80%-85%     | 85%-90%                   | 80%-95%                   | 80%-85%           |
| CCT      | 70%-90%     | 85%-90%     | 90%-95%                   | 90%-95%                   | 90%-95%           |
| CMR      | 95%-100%    | 90%-95%     | 90%-95%                   | 95%-100%                  | 95%-100%          |

This data is limited as it includes both patients with and without left ventricular dysfunction. DSE: Dobutamine stress echocardiography; SPECT: Single photon emission computerized tomography; PET: Positron emission tomography; CCT: Coronary computerized tomography; CMR: Cardiac magnetic resonance imaging.

Figure 1  Two patients underwent cardiac stress magnetic resonance imaging for evaluation of significant left ventricular dysfunction systolic dysfunction. Patient 1 with Idiopathic dilated cardiomyopathy, EF 30%. Panel A shows post gadolinium contrast images with absence of delayed enhancement in the left ventricular myocardium and Panel B shows lack of perfusion defect with adenosine stress imaging. Patient 2 with Ischemic cardiomyopathy, EF 15%. Panel C shows subendocardial delayed enhancement in the inferolateral wall (arrow) and Panel D shows stress perfusion defect in the anteroseptum (red arrow) consistent with ischemia and another matched perfusion defect caused by the inferolateral infarction (arrow).
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