Stress testing in patients with left bundle branch block or a paced ventricular rhythm

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Literature review current through: Jun 2022. | **This topic last updated:** Jul 22, 2019.

INTRODUCTION

Cardiac stress testing is an important diagnostic and prognostic tool in the evaluation and management of patients with known or suspected heart disease. While stress testing can be performed in a variety of ways, the most commonly used and widely available stress testing modalities are exercise electrocardiography (ECG; non-imaging) and exercise or pharmacologic stress combined with imaging (stress echocardiography or stress radionuclide myocardial perfusion imaging [rMPI]).

The choice of stress testing modality depends on many factors, including but not limited to:

- Ability to perform adequate exercise
- Resting ECG findings
- Clinical indication for performing the test
- Patient's body habitus
- History of prior coronary revascularization

While exercise ECG testing is generally recommended for patients who are able to exercise, the ability to accurately identify ischemic ECG changes during exercise requires the absence of baseline ECG abnormalities that could interfere with interpretation of the test. Two such abnormalities are complete left bundle branch block (LBBB) and a paced ventricular rhythm, which are also associated with a high rate of false positive or

uninterpretable tests in patients undergoing exercise stress. The 2002 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on exercise testing concluded that there is no level of ST segment change (depression or elevation) that confers diagnostic significance during exercise ECG testing in patients with LBBB [1,2]. Because of the lack of diagnostic ECG information in patients with LBBB or paced ventricular rhythm, stress testing in these patients requires an imaging modality. Coronary computed tomography angiography (CCTA) is another option for CAD diagnosis in patients with LBBB who are not likely to have significant coronary artery calcification or other artifacts that may obscure the ability to assess for coronary artery stenosis. (See "Cardiac imaging with computed tomography and magnetic resonance in the adult".)

The approach to stress testing in patients with LBBB or paced ventricular rhythm will be presented here. The approach to stress testing in patients without LBBB is discussed in detail separately. (See "Exercise ECG testing: Performing the test and interpreting the ECG results" and "Selecting the optimal cardiac stress test".)

INDICATIONS FOR STRESS TESTING

In patients with symptoms suggesting coronary artery disease (CAD), cardiac stress testing is most often indicated to aid in making the diagnosis of, and assessing risk related to, CAD. In some patients with known CAD and prior coronary revascularization or a change in clinical status, stress testing is indicated for the diagnosis of new or progressive disease and/or for risk stratification. In addition to symptomatic patients with known or suspected CAD, patients with heart failure, cardiomyopathy, valvular heart disease, or planned non-cardiac surgery may be candidates for stress testing. A full discussion of the indications for stress testing is presented separately. (See "Selecting the optimal cardiac stress test", section on 'Indications for stress testing'.)

LEFT BUNDLE BRANCH BLOCK

Stress radionuclide myocardial perfusion imaging (rMPI) and stress echocardiography both have significantly higher diagnostic accuracy than exercise ECG without imaging and should be used for patients with baseline LBBB who require a stress test for the diagnosis of known or suspected CHD, as well as for management and risk stratification in known CAD [3,4]. In symptomatic patients with LBBB, both imaging tests are considered appropriate for detection and risk assessment of CAD by the ACCF/AHA/ASE/ASNC /HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria [3].

A variety of stress testing modalities have been evaluated in patients with LBBB. Studies

have shown that exercise-induced ST segment depression is common in the presence of LBBB and has no association with ischemia [5,6]. In a study of 31 asymptomatic men with LBBB on their baseline ECG, the majority of patients exhibited ST segment change. All subjects underwent invasive coronary angiography, and only five were found to have significant CAD [5]. Based on these and other data, ST segment responses cannot be used to make diagnostic decisions on patients with LBBB, and the exercise ECG alone is always considered to be nondiagnostic for CAD in the setting of LBBB. Additionally, no prognostic data are available on exercise ECG in patients with LBBB. For these reasons, ACC/AHA guidelines do not recommend using exercise ECG alone for diagnosis of CAD in patients with LBBB [1,7].

Stress rMPI in LBBB — Because of a higher specificity for the diagnosis of CAD in patients with LBBB, we recommend vasodilator stress rMPI rather than exercise rMPI. This is true even for patients who can exercise and who would otherwise be candidates for exercise stress testing. The choice of vasodilator (dipyridamole, adenosine, or regadenoson) will depend upon local availability and expertise.

Proposed mechanisms of false positive exercise rMPI — Exercise rMPI in the setting of resting LBBB has lower specificity and positive predictive value compared with vasodilator stress rMPI. Compared with vasodilator rMPI, exercise rMPI has a higher rate of **false positive** reversible septal perfusion defects in the absence of an obstructive lesion in the left anterior descending coronary artery (LAD). The mechanism of false-positive septal perfusion defects during exercise rMPI in patients with LBBB is not completely understood, but several hypotheses have been proposed [8-12]:

- Septal contraction is delayed and occurs at the end of systole, leading to abnormal septal post-systolic motion and delayed ventricular relaxation, which then results in compression of the septal perforators, impairment of diastolic coronary blood flow, and septal hypoperfusion. This becomes more prominent with tachycardia.

- The impairment in diastolic coronary blood flow may lead to reduced septal endothelial function and reduced coronary flow reserve, resulting in microvascular dysfunction, again manifesting as septal hypoperfusion, and also worsened by tachycardia.

- The septum contracts late in systole at a time when the remaining walls of the left ventricle (LV) have already completed their contraction. When the septum contracts against less outflow resistance, septal perfusion is reduced due to coronary autoregulation. With exercise induced tachycardia and a shortened diastole, the septal hypoperfusion becomes more apparent.

- Increased relative contribution of the lateral wall to global LV contraction compared to the septum with a more pronounced exercise-related hyperemic response of the lateral wall resulting in an apparent underperfused septum.

Vasodilator stress rMPI — Vasodilator stress rMPI, using dipyridamole, adenosine, or regadenoson, should be used rather than exercise rMPI for patients with LBBB.

Unlike exercise stress, vasodilator stress agents do not rely on achieving a pre-specified maximal heart rate but instead produce coronary vasodilation, thereby increasing coronary blood flow up to four to five times above baseline levels in normal coronary arteries and producing relative hypoperfusion distal to any flow-limiting coronary stenosis. Two commonly used vasodilator stress agents in rMPI, dipyridamole and adenosine, generally will increase the heart rate by only 10 to 20 percent as compared with baseline measurements. As a result of the lower stress heart rate with these two vasodilator stress agents, the incidence of false positive results with vasodilator stress rMPI appears to be lower than that of exercise rMPI. Vasodilator stress is, therefore, more specific for the diagnosis of coronary artery disease than exercise rMPI [8,13-17].

Although randomized studies have not been performed, a meta-analysis of published studies using either dipyridamole or adenosine vasodilator stress with rMPI in the setting of LBBB reported a specificity of approximately 80 percent for the detection of angiographic disease in the LAD coronary artery, significantly higher than the specificity of 47 percent for exercise rMPI [4]. Unlike specificity in rMPI, sensitivity was high for both exercise (92.9 percent) and pharmacological stress (88.5 percent) in the presence of LBBB. The higher specificity of vasodilator stress rMPI compared with exercise rMPI in LBBB has resulted in the recommendation to perform vasodilator stress with either dipyridamole or adenosine with rMPI, rather than performing exercise rMPI, even if the patient is able to exercise [7,9].

Regadenoson, a more selective A2A adenosine receptor agonist with fewer side effects than dipyridamole or adenosine, is now the preferred vasodilator stress agent in many stress labs worldwide [9]. Regadenoson can be given as a bolus injection rather than an infusion as required by the older agents. Regadenoson generally increases the stress heart rate by as much as 40 percent compared with baseline, which has raised concerns regarding its use in LBBB. In a single study published in 2013, in which 64 patients with LBBB underwent regadenoson (47 patients) and adenosine (17 patients) stress rMPI, respectively, the relative increase in heart rate during vasodilator stress was significantly higher in the regadenoson group (37.8 percent) compared with the adenosine group (23.2 percent), but there was no increase in septal or LAD perfusion defects or in total perfusion by quantitative analysis with regadenoson as compared with adenosine [18].

In a single-center study of 101 consecutive patients with an LBBB without known CAD who underwent rest-stress regadenoson positron emission tomography (PET) rMPI, none had LBBB perfusion artifacts. Among 10 patients with both regadenoson SPECT and PET rMPI, three patients had exhibited LBBB artifacts on SPECT but no defects on subsequent PET [19].

Adding low-level exercise to vasodilator stress rMPI has been shown to decrease side effects and improve image quality. However, given the greater increase in heart rate with the addition of exercise to any vasodilator stress and the potential to increase false positive results in LBBB, concomitant low-level exercise in patients with LBBB is not recommended [9]. (See "Overview of stress radionuclide myocardial perfusion imaging", section on 'Combined exercise and vasodilator stress'.)

The prognostic value of vasodilator rMPI has been demonstrated in patients with an LBBB [20,21]. In a study of 544 patients with an LBBB (50.7 percent) or ventricular pacing who underwent regadenoson SPECT rMPI and who were followed for an average of 2.5 years, 39 patients (7 percent) had a major adverse cardiac event (MACE, defined as cardiac death or myocardial infarction). The annualized MACE rate in patients with normal MPI was 0.9 percent (LBBB, 0.8 percent; ventricular pacing, 1.0 percent). There was a significant stepwise increase in MACE rates with increasing burdens of perfusion abnormality and myocardial ischemia [21].

Dobutamine stress rMPI — In the 2016 American Society of Nuclear Cardiology (ASNC) imaging guideline for rMPI, LBBB is listed as a relative contraindication to the use of dobutamine stress rMPI; this relates to safety concerns (ie, inability to monitor for ischemia at higher heart rates with dobutamine) as well as concerns regarding diagnostic accuracy [9]. However, in a study of 383 patients with LBBB who underwent stress rMPI (exercise in 206, adenosine in 127, and dobutamine in 50 patients) and coronary angiography (154 patients), the false positive rate for septal perfusion defects was 46 percent during exercise, 11 percent with adenosine, and 8 percent with dobutamine (non-significant difference compared to adenosine) [13]. The study reported no major adverse effects in the dobutamine group. Based on these data and clinical experience, we feel that dobutamine can be used safely, and may be preferred over exercise stress testing, in patients with LBBB undergoing rMPI who have contraindications to vasodilator stress. (See "Overview of stress radionuclide myocardial perfusion imaging", section on 'Contraindications'.)

Stress echocardiography — Because of a higher diagnostic accuracy for the diagnosis of CAD, stress echocardiography is also preferred over exercise ECG testing in patients with LBBB [3,10]. Moreover, as an added benefit, other non-ischemic cardiac conditions

associated with LBBB, including valvular heart disease, hypertensive heart disease, and cardiomyopathy, can be readily recognized during baseline imaging.

The diagnostic accuracy of stress echocardiography in patients with LBBB, using exercise or dobutamine-atropine, has been examined in small series of patients.

- In a study of 35 patients with LBBB and suspected CAD, in which all patients underwent exercise echocardiography (without an echocardiographic contrast agent) and coronary angiography, exercise-induced wall motion abnormalities had an overall sensitivity of 76 percent, specificity of 83 percent, and accuracy of 84 percent for the diagnosis of obstructive CAD [11].

- In a study of 64 patients with LBBB and suspected CAD who underwent dobutamine-atropine stress echocardiography (without an echocardiographic contrast agent) and coronary angiography, stress-induced new or worsening wall motion abnormalities had a sensitivity of 68 percent, specificity of 91 percent, and diagnostic accuracy 84 percent for diagnosis of obstructive CAD [22].

Importantly, these studies included patients with limited exercise capacity and limited acoustic windows and did not use contrast echocardiography to optimize imaging, both of which could have led to an underestimation of the diagnostic accuracy of the test.

Stress echocardiography (exercise echocardiography, and pharmacologic dobutamine stress echocardiography [DSE] or dipyridamole) provides important prognostic information in patients with known or suspected CAD who had LBBB at rest. Patients undergoing stress echocardiography (exercise or pharmacologic) who had stress inducible wall motion abnormalities (ie, myocardial ischemia) had significantly greater mortality and more adverse cardiac outcomes compared with patients without inducible ischemia [23,24]. Importantly, stress echocardiographic results provided incremental value over clinical, resting echocardiographic, and treadmill exercise data for the prediction of mortality and major cardiac events [24]. A more in-depth discussion of the role of stress echocardiography in determining prognosis in patients with CAD is presented separately. (See "Prognostic features of stress testing in patients with known or suspected coronary disease", section on 'Stress echocardiography'.)

Stress cardiac magnetic resonance imaging — Stress cardiac magnetic resonance imaging (CMR) is another option for the evaluation of obstructive CAD in patients with an LBBB. While pharmacologic stress CMR can be useful and is considered "appropriate" for patients with intermediate to high pretest probability of CAD and LBBB, this test is only available in a limited number of centers who have expertise in performing and interpreting the test [7].

There are limited data on stress CMR in patients with LBBB, although in one study that compared dobutamine stress CMR (with assessment of both first-pass perfusion and late gadolinium enhancement [LGE]) with contrast-enhanced DSE in 82 patients who also underwent invasive coronary angiography, there was similar sensitivity (72 percent), with a higher specificity and diagnostic accuracy for dobutamine stress CMR [25]. While there are limited data on the utility of stress CMR in patients with LBBB, this stress imaging modality has excellent spatial resolution and can incorporate assessment of stress wall motion, first-pass perfusion, and LGE.

PACED VENTRICULAR RHYTHM

A variety of stress testing modalities have been evaluated in patients with a paced ventricular rhythm. Exercise ECG without imaging is not recommended in patients with right ventricular (RV) pacing, given the inability to detect ischemic ECG changes on the exercise ECG in these patients [1]. As such, stress testing in patients with a paced ventricular rhythm should incorporate imaging (eg, stress radionuclide myocardial perfusion imaging [rMPI] or stress echocardiography) to improve the diagnostic capacity of the test [3]. Stress CMR has not been evaluated in patients with a pacemaker due to limitations on performing magnetic resonance imaging in patients with a metallic pacemaker in situ.

Most patients with a paced ventricular rhythm are paced via a transvenous RV endocardial lead; such pacing generally produces the appearance of LBBB on the ECG. Like LBBB, RV pacing during exercise rMPI is associated with false positive reversible perfusion defects in the absence of an obstructive coronary artery lesion [26-28]. The postulated mechanisms are similar to those of false positive perfusion defects in LBBB. (See 'Vasodilator stress rMPI' above.)

In patients with RV pacing, the inferior, inferoseptal, and apical walls are the most common sites of false positive perfusion defects during exercise rMPI [26,29]. The false positive perfusion defects associated with a paced ventricular rhythm may result from delayed and asynchronous activation of the LV, although impaired microvascular flow may also contribute to these defects [29]. The site of RV pacing may have a role in the frequency of perfusion defects with RV apical pacing having a higher incidence of myocardial perfusion defects compared with RV outflow tract pacing [30,31]

Adenosine or dipyridamole rMPI is recommended by professional society guidelines for the diagnosis of suspected CAD in patients with a paced ventricular rhythm [32]. However, data are very limited on the diagnostic performance of rMPI in patients with an RV paced rhythm. In a single study comparing adenosine and regadenoson rMPI in patients with RV

paced rhythm, there was no significant difference in ischemia between the two agents, suggesting that regadenoson is an acceptable vasodilator stress agent in this group of patients [18].

Adenosine or dipyridamole rMPI is also recommended by the ACC/AHA guidelines for the risk stratification of known or suspected CAD in patients with a paced ventricular rhythm [32]. Data regarding prognostic testing in this setting are even more limited than data regarding diagnosis. In one study of 108 patients with single or dual chamber pacemakers, exercise rMPI was able discriminate between those at low and high risk [33]. At five years, patients with high-risk scans had a significantly higher rate of cardiac death or myocardial infarction than those with low-risk scans (19 versus 7 percent). There are no published prognostic data on the use of regadenoson in this population.

As with LBBB, exercise or dobutamine stress echocardiography may be used to detect ischemia in patients with a paced ventricular rhythm. If the heart rate does not increase with dobutamine and atropine in a patient with a permanent pacemaker, stress echocardiography can be achieved by increasing the pacing rate until the target heart rate is achieved [34].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Multimodality cardiovascular imaging appropriate use criteria" and "Society guideline links: Stress testing and cardiopulmonary exercise testing".)

SUMMARY AND RECOMMENDATIONS

- Because of the inability to adequately detect ischemic electrocardiography (ECG) changes in the setting of a baseline left bundle branch block (LBBB) or paced ventricular rhythm, exercise ECG alone is nondiagnostic for coronary artery disease (CAD). As such, exercise ECG stress without imaging should not be performed for the diagnosis of CAD. (See 'Proposed mechanisms of false positive exercise rMPI' above.)

- Stress radionuclide myocardial perfusion imaging (rMPI) and stress echocardiography both have significantly higher diagnostic accuracy than exercise ECG without imaging and should be used for patients with baseline LBBB or paced ventricular rhythm who require a stress test for the diagnosis and management of known or suspected CAD, and for risk stratification. (See 'Left bundle branch block'

above and 'Paced ventricular rhythm' above.)

- Vasodilator rMPI is preferred over exercise rMPI in patients with an LBBB or paced ventricular rhythm secondary to the higher rate of false positive perfusion defects in the absence of obstructive coronary artery disease. (See 'Vasodilator stress rMPI' above.)

- Though few comparative data are available, exercise and dobutamine-atropine stress echocardiography are likely overall similar in patients with an LBBB or paced ventricular rhythm with slightly higher sensitivity for exercise stress and slightly higher specificity for dobutamine-atropine stress echocardiography. (See 'Stress rMPI in LBBB' above and 'Stress echocardiography' above.)

- The choice of which stress imaging modality (rMPI, stress echocardiography, or stress cardiac magnetic resonance imaging in patients with an LBBB; rMPI or stress echocardiography in patients with a paced ventricular rhythm) should be dictated by local expertise given the limited comparative studies of these imaging techniques in this patient subset. (See "Selecting the optimal cardiac stress test".)

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Topic 5312 Version 19.0

Contributor Disclosures

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