Utility of myocardial blood flow assessment with dynamic CZT single photon emission computed tomography in patients with myocardial bridging: Is this 'wishful thinking' in this dynamic situation?

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INTRODUCTION AND BACKGROUND

Four decades ago single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) stress testing was introduced as a useful tool to detect myocardial ischemia.[1] Globally, SPECT MPI has remained the workhorse in the non-invasive assessment of myocardial ischemia.[1] However, use of relative perfusion assessment both qualitatively and quantitatively with SPECT MPI have inherent challenges in the assessment of myocardial ischemia especially in the assessment of left main or multivessel ischemia, balanced ischemia with reduced sensitivity and also the inherent attenuation artifacts resulting in reduced specificity.[1,2] Additionally, there have been other technologically advances in nuclear cardiovascular imaging with regards to the increased role of cardiac positron emission tomography (PET MPI) in the assessment of myocardial blood flow (MBF) quantification.[3,4] This has challenged the clinical utility of SPECT MPI and has led to new technological advances with the development of dynamic SPECT MPI with solid state cameras such as Cadmium Zinc Telluride (CZT) cameras. These newer CZT cameras have 7-fold higher count statistics when compared to the standard gamma camera SPECT cameras.[1] They also have an innovative simultaneous SPECT acquisition which has allowed the acquisition of dynamic SPECT MPI and quantification of MBF.[5] Although this has not been widely adopted in clinical practice, early and ongoing studies have shown good correlation of MBF assessment with dynamic SPECT MPI when compared with that of PET MPI especially with the use of spline fitted models.[6] Additionally, although PET MPI with MBF is the gold standard, worldwide only 6% of nuclear labs have the availability of PET MPI (in North America only 17% of nuclear labs have cardiac PET available)[7] and even fewer perform MBF assessment during PET MPI. Therefore, there remains a need to improve and advance dynamic SPECT MPI for assessment of MBF.

MYOCARDIAL BRIDGING

Myocardial bridging (MB) is defined as a coronary anomaly in which a segment of the epicardial coronary artery dips beneath the myocardium and courses through the myocardium for a portion of its course.[8] The portion of the muscle that overlies this segment of the artery is called a myocardial bridge and the intramyocardial portion of the vessel is called the tunneled artery.[8] Most often the left anterior descending coronary artery (LAD) is involved in 67-98% of the time and there is less common involvement of the right coronary artery (RCA) and the left circumflex coronary artery (LCx).[8] The prevalence of this anomaly from autopsy studies, which

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is considered the reference standard, is 33-42%.[8] MB is increasingly being diagnosed by coronary computed tomography (CCTA) which is considered more sensitive than invasive coronary angiography (ICA) and intravascular ultrasound (IVUS) in the diagnosis of this anomaly.[8] However, when performing ICA, IVUS may improve the detection of this condition by up to 23%.[8] MB is generally considered a benign finding since the majority (85%) of coronary blood flow occurs during diastole rather than in systole when the tunneled coronary artery is typically compressed during MB.[8] However, MB is symptomatic in a few patients and the true prevalence of symptomatic MB patients is not known. The 2 main factors that may increase the risk of ischemia in patients with MB are the depth of the tunneled artery, with < 2 mm depth thought to be superficial and a myocardial bridging depth of >2 mm associated with increased degree of systolic compression.[8] The length of the tunneled artery may also impact the occurrence of ischemia in patients with MB, particularly when the length is ≥ 2.5 cm.[8]

ASSESSMENT OF ISCHEMIA FROM MYOCARDIAL BRIDGING

The assessment of patients with MB is highly nuanced. Although most patients with MB are asymptomatic, patients who are symptomatic may present with angina or anginal equivalent. There are several noninvasive tests available for the assessment of symptomatic MB, but many of these tests have limited accuracy.

CCTA provides anatomic details about the depth and length of the tunneled coronary artery. However, there is no physiologic assessment on CCTA and depending only on the anatomic findings may lead to over detection of MB and greater downstream testing which may not be necessary in view of the fact that most patients with MB are asymptomatic. Noninvasive fractional flow reserve on CCTA (FFR-CT) can assess the physiologic significance of the tunneled artery in MB, with a FFR-CT of $\leq .75$ considered to be significant.[8] However, the FFR-CT assessment can only be done in the proximal portion of the epicardial coronary arteries.[8]

The majority of coronary flow normally occurs during the diastolic period rather than the systolic period and the obstruction of flow in MB is dynamic occurring primarily in systole. However, although compressive physiology in MB occurs primarily in systole, there can be a delay in the diastolic luminal expansion and the longer this delay the greater the risk of myocardial ischemia.[8] The diastolic delay in coronary expansion is affected by the heart rate, sympathetic tone, and the cardiac cycle.[8] This delay inhibits rapid diastolic hyperemia in the sub endocardium. Indeed, a recent invasive hemodynamic study of 20 patients[9]with left anterior descending MB found that instantaneous wave-free ratio (iFR), an invasive lesion specific diastolic index, was abnormal at rest in two thirds of the patients with MB, and worsened across the MB during pull back; iFR after dobutamine infusion, termed dobutamine-induced hyperemic wave–free period pressure ratio (HWPR), was worse. However, rest and dobutamine FFR were not significantly different. These findings support the presence of coronary microvascular dysfunction in MB.

Given the compressive pathophysiology of MB, in clinical practice, the primary mode of stress is exercise or inotropic stress (dobutamine) combined with myocardial perfusion imaging. Stress perfusion defects on PET and SPECT MPI, when present, can be helpful to clinch the diagnosis of ischemia in MB. However, they often underestimate the presence of ischemia from MB due to the lower spatial resolution in assessment of subendocardial ischemia.[8] Quantification of MBF may offer advantages to image subendocardial ischemia. However, quantification of MBF with exercise stress can be challenging due to motion artifact if supine bicycle exercise is used. The role of vasodilator stress MPI with MBF quantification to evaluate significance of MB is not well established. Whether dobutamine MBF quantification is superior in MB is not known.[9] A prior study has shown that the presence of impaired vasodilator stress PET MFR (defined as a MFR (stress MBF/rest MBF) of < 2.0) was increased in MB patients involving the LAD (LAD-MB) [70% ($n = 12$) vs. 30% ($n = 34$), $p = .01$]. However, the proportion of patients with an abnormal stress MBF (< 1.9) was similar in patients with and without LAD-MB [12% ($n = 2$) vs. 24% ($n = 27$), $p = .36$] suggesting the presence of coronary microvascular dysfunction.[10] However, data on quantification of MFR with CZT-SPECT in assessing microvascular dysfunction in patients with symptomatic MB are limited.

ASSESSMENT OF SYMPTOMATIC PATIENTS WITH MYOCARDIAL BRIDGING WITH THE USE OF DYNAMIC CZT SPECT

In this issue of the Journal of Nuclear Cardiology Dr. Xu and colleagues aimed to investigate the feasibility and diagnostic value of MFR assessed by MPI with dynamic SPECT in patients with MB. In this study, 49 patients with isolated MB of the left anterior descending artery (LAD)who underwent dynamic SPECT myocardial perfusion imaging and quantitative coronary angiography (QCA) were retrospectively analyzed. Systolic compression of intramyocardial arterial segment

≥ 50% diameter stenosis was considered as angiographically significant MB and was used as the reference standard. Semiquantitative indices of myocardial perfusion(summed stress scores, SSS) and quantitative parameters (MFR) were assessed. Impaired MFR was defined as a MFR of < 2.0.SPECT-derived LAD MFR showed a borderline significantly negative correlation with SSS ($r = -.261$, $p = .070$). A trend toward higher prevalence of impaired myocardial perfusion was detected by dynamic SPECT-derived global MFR than by semiquantitative analysis of MPI (42.9% vs. 26.5%; $p = .090$). The authors concluded that the use of SPECT MFR may be a useful parameter for the functional assessment of MB. They also postulated that the use of dynamic SPECT could be a potential method for hemodynamic assessment in patients with MB. Overall, the study is thought-provoking and outlines emerging data that may support the use of dynamic SPECT with MFR in assessing patients with MB. The study also adds incremental data to support the use of dynamic SPECT with MFR in the assessment of patients with MB.

The strength of these study findings is the novel application of new technology of dynamic. SPECT with MFR in the assessment of patients with MB. This novel application and data provided from the study could support the expanded role of this new technology in this patient population. The limitations of the study include the small study sample, the fact that it is a single center study as well as the fact that the results were not validated by the gold standard of cardiac PET-MPI with MFR. Additionally, use of diameter stenosis of the LAD ≥ 50% in QCA as a reference standard for MB is questionable given other more validated reference standards such as iFR ≤ .85.[9] Another limitation is that given the pathophysiology of MB, one would expect regionally reduced stress MBF and MFR in the territory of the LAD MB. However, there was poor correlation between MFR in the LAD territory and diameter stenosis of the LAD ≥ 50% in QCA. Notably, whether a vasodilator stress test, as opposed to inotropic stress, can accurately capture flow limitation from MB that is experienced by the patients in real life is not known and was not explored in this study.

CHALLENGES IN THE QUANTIFICATION OF MYOCARDIAL BLOOD FLOW WITH DYNAMIC CZT SPECT

Several studies have shown a fair correlation between MBF assessed with dynamic CZT SPECT compared to MBF assessed by PET MPI.[11] The limitations of MBF quantification with CZT SPECT includes not only lower accuracy but also lower reproducibility when compared to PET based MBF.[6] There are several reasons for these limitations (Table 1). The extraction fraction of technetium 99m perfusion radiotracers at high flows is lower than that of 13N-ammonia or 82-rubidium.[6,12] This results in decreased accuracy of MBF quantification when compared to PET and requires correction models.[6,12] Also, the typical doses of Tc-99m-radiotracers can result in count poor multi-frame dynamic images.[12] Additionally, although the spatial resolution of the solid state CZT camera is 2-fold higher compared with the Anger sodium iodide gamma cameras, it is still inferior to that of PET systems.[6] This is further limited by the fact that most available CZT cameras do not have attenuation correction. Dynamic SPECT processing is largely reliant on manual motion correction which can be a source of error and decreased reproducibility.[6] Prior studies have also shown significant heterogeneity of CZT SPECT based MBF values which is due to variations in radiotracer selection, radiotracer injected doses, reconstruction algorithms and kinetic models.[6] Addressing these limitations may improve the accuracy and reproducibility of CZT SPECT based MBF when compared to PET MPI based MBF.

FUTURE DIRECTIONS

There are increasingly useful clinical applications of MBF quantification in cardiology that extends beyond MB. MBF quantification is the key diagnostic tool in the assessment of coronary microvascular dysfunction.[13,14] MBF quantification can also be used to greatly improve the diagnostic accuracy of MPI especially in the setting of left main or multivessel coronary artery disease which may cause balanced ischemia.[3] MBF quantification has also been useful in cardio-oncology in the assessment of cardiotoxicity related to cancer therapy.[15] Surveillance of post-transplant patients and the assessment of cardiac allograft vasculopathy can be done with MBF quantification.[16] These clinical applications of MBF quantification are based on studies with PET-MPI. It is still unclear if MBF quantification with dynamic SPECT MPI can be applied to these clinical scenarios.

However, availability of cardiac PET MPI in the United States (US) remains limited due to increased cost.[7] As SPECT is more widely available, there is an increasing need to develop technology to improve the accuracy and reproducibility of MBF assessment with SPECT. A recent study showed that spatiotemporal spline fitting improved the correlation of MBF quantification on dynamic SPECT when compared to that performed on cardiac PET and improved the reproducibility of MBF quantification on dynamic SPECT.[6] Robust attenuation correction with low dose transmission scanning with CT may further improve accuracy

Table 1. Challenges in the quantification of myocardial blood flow with dynamic CZT-SPECT and potential solutions

Challenges	Potential solutions
Lower extraction fraction of Technetium 99m radiotracers at high flows compared with those used for Cardiac PET MPI[6, 12].	(a) Use of correction models may be used to address this limitation[6]
Decreased spatial resolution of solid state CZT SPECT cameras compared with Cardiac PET[6]. Most CZT cameras on the market lack attenuation correction with low dose transmission CT and depend on 2 position stress positioning[1].	(a) Increasing availability of hybrid CZT SPECT-CT cameras on the market with improved image quality with CT based attenuation correction. (b) Use of artificial intelligence in attenuation correction may improve image quality[17].
Dynamic SPECT processing is largely reliant on manual motion correction which can be a source of error and decreased reproducibility[6].	(a) This may be an area where artificial intelligence could be developed and applied to this technology for automated motion correction. This may improve accuracy and reproducibility.
Heterogeneity of CZT SPECT based MBF values which is due to variations in radiotracer selection, radiotracer injected doses, reconstruction algorithms and kinetic models[6].	(a) Standardization of radiotracer utilized with standard dosing[6]. (b) Standardization of reconstruction algorithms and kinetic models[6] (c) Spatiotemporal spline fitting[6]

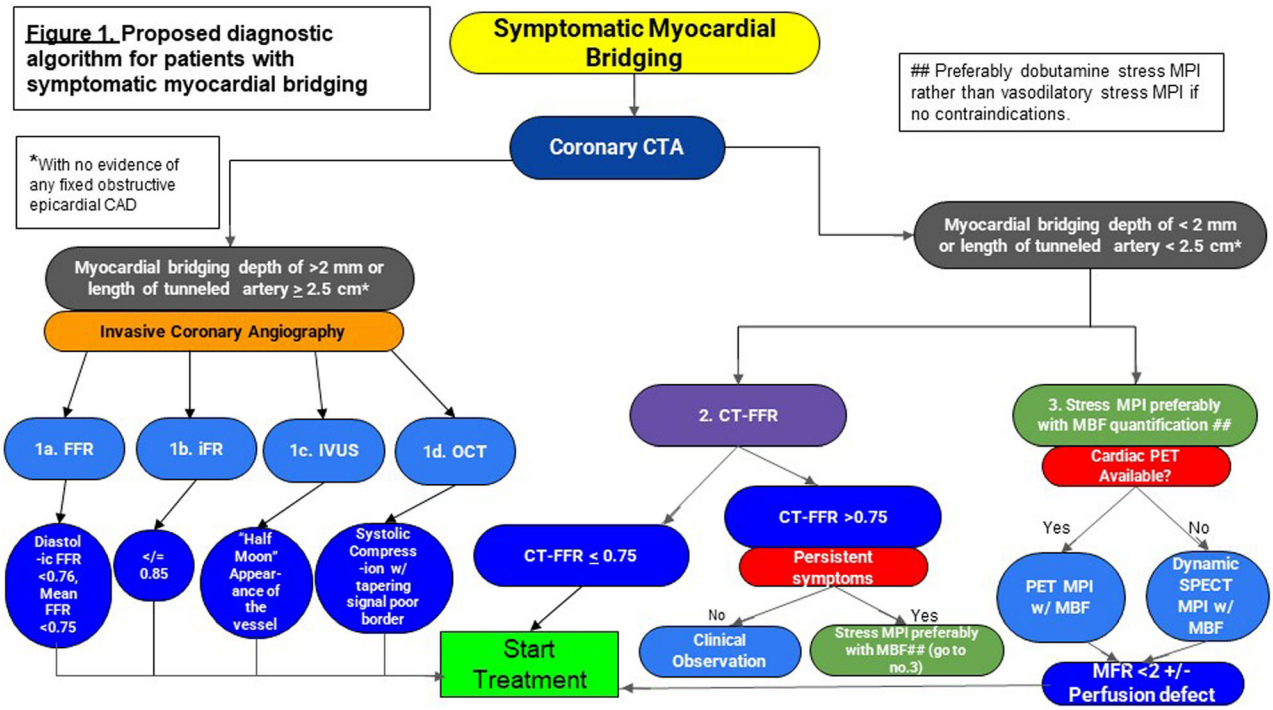

Figure 1. Proposed diagnostic algorithm for patients with symptomatic myocardial bridging. [8,9]. *CTA* computed tomographic angiography, *FFR* fractional flow reserve, *iFR*, instantaneous wave-free ratio; *IVUS*, intravascular ultrasound; *OCT*, optical coherence tomography; *CT*, computed tomography; *MPI*, myocardial perfusion imaging; *MBF*, myocardial blood flow; *PET*, positron emission tomography; *SPECT*, single photon emission computed tomography.

and reproducibility of MBF assessment with CZT SPECT. The emergence of artificial intelligence (AI) based attenuation correction of MPI from CZT SPECT has the added value of not requiring an additional CT scan.[17] Potentially AI could auto-correct for motion and improve accuracy in MBF assessment with dynamic CZT.

As the technology of MBF quantification with dynamic SPECT continues to evolve, it is hoped that this will result in greater accuracy of this technique. With improved accuracy it is conceivable that MBF quantification with dynamic SPECT may have wider clinical applications beyond MB. Diagnosing symptomatic MB remains challenging for reasons outlined earlier and there is a need to develop diagnostic tools such as MBF quantification with dynamic SPECT MPI when PET-MPI MBF is unavailable. A proposed diagnostic algorithm for MB incorporating MBF assessment is outlined in Figure 1.[8,9] Hopefully, with increased accuracy and reproducibility of dynamic CZT SPECT MBF, there will be greater adoption of this technology into routine clinical practice and not just 'wishful thinking'.

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