Elucidating the pathophysiology of left bundle branch block related perfusion defects

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Patients with left bundle branch block (LBBB) are well known to have perfusion defects in the anteroseptal wall seen on single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) often without having disease in the left anterior descending artery (LAD) (Figure 1). The prevalence of this perfusion abnormality with Tc-99m tracers has been reported to be over 50% and often occurs with exercise or dobutamine stress.^{1,2} Therefore, the guidelines for SPECT-MPI recommend performing pharmacologic vasodilator stress test for patients with LBBB.³ Several mechanisms have been proposed to explain this perfusion abnormality such as decreased blood flow in response to lower septal resting oxygen demand,^{1,4} diastolic compression of septal perforators,⁵ septal microvessel compression secondary to abnormal and delayed septal contraction/relaxation and redistribution of circumferential shortening.^{1,6} However, the relative contributions of these proposed mechanisms are not yet fully understood.

In this issue of the Journal, Hedeer and colleagues⁷ studied 23 patients with both SPECT and cardiovascular magnetic resonance (CMR) imaging available, in order to elucidate the etiology of LBBB-related perfusion defects. The typical LBBB perfusion defect pattern was visually defined as a nonreversible anteroseptal

perfusion defect without involvement of the apex. By SPECT-MPI, 13 patients were considered to have a typical LBBB defect pattern and 10 patients were not. The population of patients with LBBB assessed by noninvasive multimodality imaging including SPECT and CMR with cine, strain and late gadolinium enhancement (LGE) studied by Hedeer et al. is unique. This allowed for novel comparisons of myocardial fibrosis, wall motion, myocardial strain, and dyssynchrony between patients with and without typical LBBB perfusion defect patterns.

This study makes a few observations, which provide insight into the etiology of LBBB-related perfusion defects. First, lower myocardial radiotracer counts were present in the septal wall compared to the lateral wall in both groups of patients. Although the authors identified modest differences in wall thickness, it is unlikely to be the underlying mechanism for this finding. Sugihara et al. demonstrated that the lower septal count is more prominent at end-systole compared to end-diastole.⁸ In their study, the septal to lateral wall count ratio was lower in patients with LBBB compared to control patients on nongated images, while it was similar on end-diastolic images. In addition, in patients with LBBB the count increase from end-diastole to end-systole was smaller in the septal region compared to the lateral region.⁸ These findings suggest that the defect may be related to decreased wall thickening in the septal region.

LBBB activation leads to a distinct contraction pattern of wall motion.⁹ CMR imaging allows assessment of septal wall motion abnormality and LV mechanical deformation from cine and tagged images, using principles similar to those utilized in echocardiography, including radial, circumferential or longitudinal strain, timing of myocardial thickening and volume change.¹⁰ A related finding by Hedeer et al.⁷ was reduced radial strain in the septal wall in patients with a typical LBBB perfusion defect pattern compared to

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Figure 1. Case example with antero-septal perfusion defect on regadenoson stress and rest Tc-99m sestamibi D-SPECT-MPI in a 77-year-old female with left bundle branch block. SPECT-MPI showed a perfusion defect in antero-septal wall at stress and rest. Stress TPD (total perfusion deficit) derived by QPS software (Cedars-Sinai Medical Center, Los Angeles, CA)¹⁷ was 7% on upright and supine positions, and combined stress TPD was 2%. Rest TPD was 12% on upright position and 2% on supine position. LV wall motion demonstrated severe hypokinesis in the septal and apical walls. Invasive angiogram performed 2 weeks after the SPECT-MPI showed nonobstructive coronary artery disease.

those without, while there was no difference in the lateral wall between groups. This suggests that the extent and distribution of the perfusion defect in patients with LBBB might correlate with LV deformation. Vernooij et al. also demonstrated decreased septal circumferential shortening in a canine model with LBBB induced by radio frequency ablation.⁶ In addition, they demonstrated that myocardial blood flow decreased after induction of LBBB, suggesting that septal hypoperfusion may be contributory.

Few studies have investigated the prevalence of myocardial fibrosis in the antero-septal wall in patients with LBBB. In the present study, four patients with a

typical LBBB defect had any LGE, including two patients with LGE in the septum. Two patients without a typical LBBB defect had LGE in the lateral wall suggesting that it may have masked a relative septal defect. Grigoratos et al. examined the presence and extent of myocardial fibrosis by CMR in 196 patients with non-ischemic cardiomyopathy. LGE was observed more commonly in patients with LBBB ($n = 83$) compared to patients with normal intraventricular conduction ($n = 84$) and was more often located in the ventricular septum ($P < 0.001$).¹¹ The authors suggested that septal fibrosis on CMR might reflect the underlying anatomic interruption of the proximal His-bundle network and

identify patients who might benefit from pacing the distal portion of the His-bundle branches.¹² Mahmood et al. evaluated 55 asymptomatic patients with LBBB and demonstrated up to a third of patients with normal echocardiograms had abnormalities on CMR.¹³ The authors concluded that CMR detects sub-clinical cardiomyopathy in a third of asymptomatic patients with LBBB despite normal echocardiograms and provides clinically relevant information in patients with abnormal echocardiograms. Mahrholdt et al. evaluated LGE by CMR in 19 patients with LBBB, without any CAD on invasive coronary angiography, who had fixed perfusion defects.¹⁴ In their study, subendocardial or transmural LGE, representing myocardial infarction, was not found in any patient. Compared to the previous study, LGE was observed in the anterior or septal wall in two of 13 patients with typical LBBB perfusion defect and patients with significant CAD were not excluded in the present study. Given the spectrum of findings, the relative contribution of myocardial fibrosis to LBBB-related perfusion defects is most likely driven substantially by characteristics of the studied patient population.

Although the study by Hedeer et al.⁷ offers some important findings, there are some limitations to consider. The study population was small and had inherent selection bias due to including patients referred for both SPECT and CMR imaging. Although the mean LVEF was ~ 35%, there was little information available regarding the etiology of cardiomyopathy in most patients. Although a minority of patients had ischemic LGE, invasive coronary angiography results were not available to allow the authors to account for extent of coronary artery disease as a potential confounder. Alternative etiologies for LBBB to be considered include: chronic myocardial fibrosis related to hypertension, valvular heart disease, cardiomyopathies (such as sarcoidosis), endocarditis, or myocarditis.¹⁵ Importantly, all of those etiologies could potentially impact LV mechanics, perfusion, and fibrosis. Lastly, the authors could have more thoroughly addressed the role of fibrosis if contemporary CMR sequences, such as T1 mapping or extracellular volume estimates, were available.

Overall, the study by Hedeer et al.⁷ suggests that the typical perfusion abnormality seen on SPECT-MPI is related to differences in wall thickening and myocardial deformation. In this selected population, ischemic myocardial fibrosis was not a major contributor. However, it may still be prudent for clinicians to exclude significant CAD using adjunctive modalities such as CMR or computed tomographic attenuation maps. Recently artificial intelligence technique has been developed to greatly improve the detection of disease or prediction of outcome in medical imaging field.¹⁶ In the

future, artificial intelligence techniques could help clinicians to differentiate typical LBBB perfusion defect pattern automatically from CAD-related perfusion defects, but those algorithms will likely be informed by studies like this.

Disclosure

Dr. Piotr J. Slomka received royalties for nuclear cardiology software from Cedars Sinai. Drs. Yuka Otaki, and Robert J. H. Miller have nothing to disclose.

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