9-14-2018

Left Ventricular Mechanical Dyssynchrony for CAD Diagnosis: Does It Have Incremental Clinical Values?

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Gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been widely practiced to assess left ventricular (LV) function after stress and at rest, which has in turn improved the diagnosis of coronary artery disease (CAD). The visualization of wall motion and thickening has greatly improved the identification of attenuation artefacts(1, 2) and allows the recognition of stress-induced abnormalities in the case of post-ischemic stunning which helps with multi-vessel CAD detection(3).

Recently, the phase analysis technique has become a major innovation in nuclear cardiology and greatly boosted the clinical values of MPI scans. It measures the LV mechanical dyssynchrony (LVMD) and wall thickening from the regional LV count changes throughout the cardiac cycle (4, 5). Previous studies identified LVMD as an independent predictor for a favorable response to cardiac resynchronization therapy (6) and for all-cause death in patients with dilated cardiomyopathy and narrow QRS (7).

LVMD has also demonstrated its clinical values in CAD diagnosis. As reported by Uebleis et al (8), the occurrence of LVMD is mainly influenced by reduced myocardial contractility as expressed by the summed thickening score (STS). In a recent study, STS and the proportion of segments with reduced wall thickening in segments with normal perfusion were the independent risk factors of LV remodeling in myocardial infarction patients(9). Thus it is not a surprise to see that LVMD is related with stress-induced myocardial ischemia (10-13). Chen et al (11) firstly demonstrated different LVMD changes in ischemic, infarcted and normal myocardium using gated thallium-201 SPECT MPI, which was acquired at 5–10 minutes after stress. Other researchers have also found the evidence of stress-induced LVMD when acquisitions were performed earlier than one hour post stress with technetium-99m sestamibi (14-16). Our research showed that, in patients with moderate to severe myocardial ischemia, LVMD changes were also related to myocardial stunning even when the acquisition was 60 minutes after stress(17).

Furthermore, the direct comparison with coronary angiography has suggested that LVMD can help with multi-vessel CAD detection. Hida et al (14) reported that in the detection of 128 patients with multi-vessel CAD, a summed stress score (SSS) of ≥9 showed a sensitivity of 84% and a specificity of 53%, while after exercise an increase in phase standard deviation (PSD) of ≥4.4° and phase bandwidth (PBW) of ≥14° had sensitivities of 74% and 68%, and specificities of 84% and 91%, respectively. Huang et al (18) demonstrated that patients with severe multi-vessel CAD had more significantly global and territorial LVMD. Gimelli et al (19) reported that in patients with suspected or known CAD, the presence and severity of LVMD was correlated with the extent of CAD, and that it was significantly more prevalent in patients with multi-vessel CAD.

In the current issue of the journal, Lin et al (20) investigated the diagnosis value of LVMD in patients with less severe CAD (coronary artery stenosis ≥ 50%). A total of 476 patients without known CAD who underwent dipyridamole gated SPECT MPI and coronary angiography within 6 months were enrolled. Depending on the duration and severity of ischemia, myocardial stunning lasts from minutes to days. Thus immediate

acquisition after stress is better for the detection of this phenomenon (21). In this study, with thallium-201 and cadmium-zinc-telluride detectors, the acquisition time was possible during 5 minutes after radiotracer injection. They concluded that perfusion abnormalities like SSS and summed difference score (SDS) were still the best diagnostic tools in detecting CAD, although less LVMD was observed post-stress in the CAD group compared to the non-CAD group. Regarding this study, we have following comments:

Firstly, it is a good attempt to use 50% as a definition for CAD, which tested the sensitivity of LVMD for CAD diagnosis. In prior studies, coronary artery stenosis of 70% - 75% was mostly used (14, 18, 19) and myocardial ischemia is usually related with more severe coronary stenosis (≥ 70%). The current study found that only SDS, age, hypertension and smoking were related with CAD. Though the results were negative, it still contributes to the knowledge that LVMD from gated SPECT MPI have limitations for the diagnosis of mild CAD.

Secondly, both global and regional LV function parameters have been used to detect myocardial stunning, such as reduced LV ejection fraction (21), enlarged end diastolic volume or end systolic volume (14), and decreased wall motion (22-24) or wall thickening (24). Whether the addition of LVMD and wall thickening can yield increased diagnostic value beyond these variables, especially STS, is unknown. Hida et al(14) found that the combination of post-stress increases in PSD, PBW, transient ischemic dilation (TID) ratio and SSS best identified multi-vessel CAD (sensitivity 77%, specificity 88%), compared with TID ratio and SSS only (sensitivity 70%, specificity 76%). In another study(25), patients with systolic dysfunction were evaluated. SDS, SSS and changes in PSD and PBW with stress were greater in 26 patients with CAD than those in 15 patients without CAD. In the multivariate analysis a PSD of >14° and a SSS of >17 best differentiated LV dysfunction of ischemic and non-ischemic etiologies, with a sensitivity of 89% and a specificity of 87%, compared with SDS only (sensitivity, 46%; specificity, 87%).

Last, it is noteworthy that a total of 476 patients and over 27 clinical variables were included in the patient baseline, univariate and multivariate, and subgroup analysis. Variable interaction may be an issue in the statistical analysis, for example, it has been demonstrated by Ludwig et al that PSD may be spuriously increased by scar(26). These may challenge the traditional linear analysis. Algorithms for the non-linear model with a big number of inter-correlated variables may further improve the accuracy of the prediction. Machine learning may be a good choice. In a recent multi-center study with 10,030 patients with suspected CAD, Motwani et al used machine learning to predict 5-year all-cause mortality and achieved an AUC of 0.79(27). In their method, the information gain algorithm was employed to select important variables from 25 clinical and 44 coronary CTA parameters and the LogitBoost algorithm was employed to build the prediction model.

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