Predicting Cardiac and All-Cause Death in Asymptomatic Patients on Hemodialysis
– Importance of Training in Interpretation of $\beta$-Methyl Iodophenyl-Pentadecanoic Acid Single-Photon Emission Computed Tomography (BMIPP SPECT) Imaging –

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The prevalence and incidence of end-stage kidney disease (ESKD) have continued to increase worldwide, and Japan is known to have the highest prevalence of ESKD in the world. In 2009, there were 67,000 predialysis chronic kidney disease stage G5 patients, 37,365 patients introduced to dialysis therapy, and 101 patients who received pre-emptive renal transplantation. In total, there were 37,466 patients who newly required renal replacement therapy in 2009. Cardiovascular disease accounts for almost half of the total mortality in patients with ESRD. In comparison with subjects of similar age without ESRD, patients on maintenance dialysis have a marked increase in cardiovascular morbidity and mortality. Recently, Kumada et al reported in a large series of maintenance dialysis patients (997 cases) that the survival rate in the CABG and PCI groups was similar during the overall 10-year follow-up period; however, PCI had the advantage within the 6 post-procedure months and CABG had the advantage only thereafter on landmark analysis. Therefore, risk stratification in patients on maintenance dialysis has been needed to identify and treat subclinical myocardial ischemia.

Nishimura et al demonstrated the deleterious effect of altered metabolism in relationship to ischemia among patients with ESRD with a report of a significant association between abnormal $\beta$-methyl iodophenyl-pentadecanoic acid (BMIPP) uptake and subsequent cardiac death among asymptomatic dialysis patients without history of prior myocardial infarction. Recently, a multicenter prospective cohort study in Japan, the B-SAFE (BMIPP single-photon emission computed tomography [SPECT] Analysis for Decreasing Cardiac Events) study, was conducted to assess the prevalence and incidence of ESKD in Japan and to identify risk factors for cardiac death among asymptomatic dialysis patients. The study demonstrated that BMIPP SPECT imaging can predict cardiac death in asymptomatic dialysis patients.

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in Hemodialysis Patients) showed that the severity of impaired fatty acid utilization in the myocardium found by BMIPP SPECT can predict cardiac and all-cause death in asymptomatic patients on hemodialysis with one or more cardiovascular risk factors. The 3-year cardiac-derived death-free survival rate was 95.7%, 90.6%, and 78.8% when the BMIPP summed score was ≤3, 4–8, and ≥9, respectively (Figure). BMIPP summed score (≥4) also was a predictor of all-cause death (HR, 1.63; 95% CI 1.13–2.33, P=0.009).

In this issue of the Journal, Kiriyama et al demonstrate that considerable variability in the visual interpretation of BMIPP SPECT images between experts at the nuclear core laboratory and non-experts at clinical centers was observed, and it had a substantial effect on the prognostic value of BMIPP SPECT in asymptomatic hemodialysis patients in the multicenter prospective cohort B-SAFE study. SPECT images were interpreted by experts at the nuclear core laboratory and by readers with various skill levels at clinical centers (48 hospitals in Japan) based on the standard 17-segment model and 5-point scoring systems. Readers and the environment of image interpretation were quite different at each clinical center. Of the 48 readers involved with image interpretation in clinical centers, 4 were as experienced as the experts at the core laboratory; 15 were familiar with myocardial perfusion SPECT but had only several years of experience interpreting BMIPP SPECT; 13 had 2–3 years of experience in reading myocardial perfusion SPECT but were inexperienced in BMIPP imaging; and the remaining 14 readers were novices in nuclear cardiac imaging. The κ values only reached fair agreement for overall impression (κ=0.298, normal vs. abnormal) and for categorical impression (κ=0.244, normal vs. mildly abnormal vs. severely abnormal). The normalcy rate was lower in readers at the clinical centers (412/677 [60.9%]) than in experts (473/677 [69.9%]). Furthermore, a Kaplan-Meier analysis based on the interpretation by readers at the clinical centers failed to distinguish the risk of events in patients with normal scans from that of patients with mildly abnormal scans.

These results have important investigative implications. If the interpretation of BMIPP studies lacks reproducibility, the test may not provide consistently useful information for clinical practice and the effect on patient management. BMIPP studies should be equally well analyzed at each of the participating clinical centers. Results in the current study echo prior findings and suggest that trainees tended to report more abnormal results than experienced readers in the interpretive variability of myocardial perfusion SPECT (MPS), and that the normalcy rate in clinical centers was lower than that in the core laboratory, and the κ value reached only fair agreement for the overall impression (normal vs. abnormal MPS) in the visual interpretation of 201Tl planar myocardial perfusion imaging in a large multicenter trial. In the present study, the authors showed the discrepancy of BMIPP uptake score in each myocardial segment between the clinical centers and the core laboratory. Readers at clinical centers were inclined to give higher segmental uptake scores, particularly in basal and septal segments, and apex. This might be explained by normal thinning of the basal membranous septum and apex, and attenuation in basal segments. As the authors mentioned, several resolutions to improve the interpretive variability of BMIPP SPECT and the use of automatic quantitative analysis compared with a normal database may improve the reproducibility of image interpretation. Second, training in interpretation and an increase in the number of experts in BMIPP SPECT are necessary. Third, usage of 201Tl and 123I-BMIPP dual isotope SPECT might increase reproducibility of interpretation by referring MPS images.

In the future, large clinical trials will provide further insight into the potential strengths of this metabolic agent as a target for ischemic memory and expand our ability to diagnose and treat subclinical myocardial ischemia. Reproducible interpretation of BMIPP images in all clinical centers can be achieved by using a uniformly accepted method of quantitative image processing, reference to a normal database and objective interpretative criteria and training on interpretation.

References