Annals of Nuclear Cardiology Vol. 5 No. 1 47–49

IMAGES IN NUCLEAR CARDIOLOGY

Increased Washout of ^{123}I-BMIPP in Triglyceride Deposit Cardiomyovasculopathy (TGCV) with Severe Coronary Stenosis: A Pitfall of Diagnosis for TGCV

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Received: July 22, 2019/Revised manuscript received: July 29, 2019/Accepted: July 30, 2019

Keywords: Diagnosis, Iodine-123-β-methyl iodophenyl-pentadecanoic acid, Ischemia, Pitfall, Triglyceride deposit cardiomyovasculopathy, Washout rate
Ann Nucl Cardiol 2019; 5 (1): 47–49

Triglyceride deposit cardiomyovasculopath (TGCV) is a novel cardiovascular disorder, discovered in Japan in 2008 (1, 2). A known cause for TGCV is the genetic or acquired dysfunction of adipose triglyceride lipase (ATGL). ATGL is a rate-limiting enzyme for the intracellular hydrolysis of triglyceride (TG) to provide long chain fatty acid (LCFA) as a major energy source in mitochondrial oxidation in normal heart. In TGCV, the defective hydrolysis of intracellular TG induced energy failure and TG deposition in affected cells. Patients with TGCV exhibit TG-deposit diffuse coronary atherosclerosis and cardiomyocyte steatosis, leading to severe coronary artery disease (CAD) and heart failure (1, 2).

In 2009, we launched the Japan TGCV study group to elucidate pathophysiology and develop diagnostic procedures. The latest version (version 4) of diagnostic criteria was posted in September 9, 2016 (http: //www. cnt-osaka. com/) (3). Iodine-123-β-methyl iodophenyl-pentadecanoic acid (^{123}I-BMIPP), a radioactive analogue for LCFA, is the important diagnostic tool for TGCV, because this tracer evaluates TG and LCFA metabolism in the entire (global) myocardium *in vivo*. As we found that the global washout rate (WOR) of ^{123}I-BMIPP was markedly decreased in patients with TGCV, WOR of ^{123}I-BMIPP is one of the major two items in the diagnostic criteria for TGCV (3).

The other major item for diagnosis is diffuse narrowing coronary artery. In TGCV, TG-deposition is observed in smooth muscle cells and endothelial cells (1, 2). Because these cells are the major cellular components of normal arterial wall, the TGCV-specific metabolic changes occur diffusely (2). This feature is contrast to the usual and classic atherosclerosis that cholesterol-deposition is observed in macrophages which migrate from blood stream by the response to injury and form atherosclerotic plaque focally. Therefore, for the diagnosis of TGCV, the presence and absence of significant stenosis or number of diseased branches is not considered. The latest diagnostic criteria obviously have facilitated the diagnosis of TGCV. The current patient number is approximately 200 in Japan, which is ten-fold of those in the first registered cohort (2). We have finished the third investigator-initiated clinical trial for TGCV (UMIN000035403).

Furthermore, we recommend that ^{123}I-BMIPP scintigraphy for the diagnosis of TGCV should be avoided in the ischemic condition (3), because washout of ^{123}I-BMIPP is increased in some patients with ischemic CAD (4). Here, we present nuclear and coronary images before and after percutaneous coronary intervention (PCI) in a TGCV patient with severe coronary stenosis.

A 70s-year-old woman, who had been treated with calcium antagonists for hypertension, complained atypical, prickly chest pain at rest. Coronary computed tomographic (CT)

doi: 10.17996/anc.19-00106

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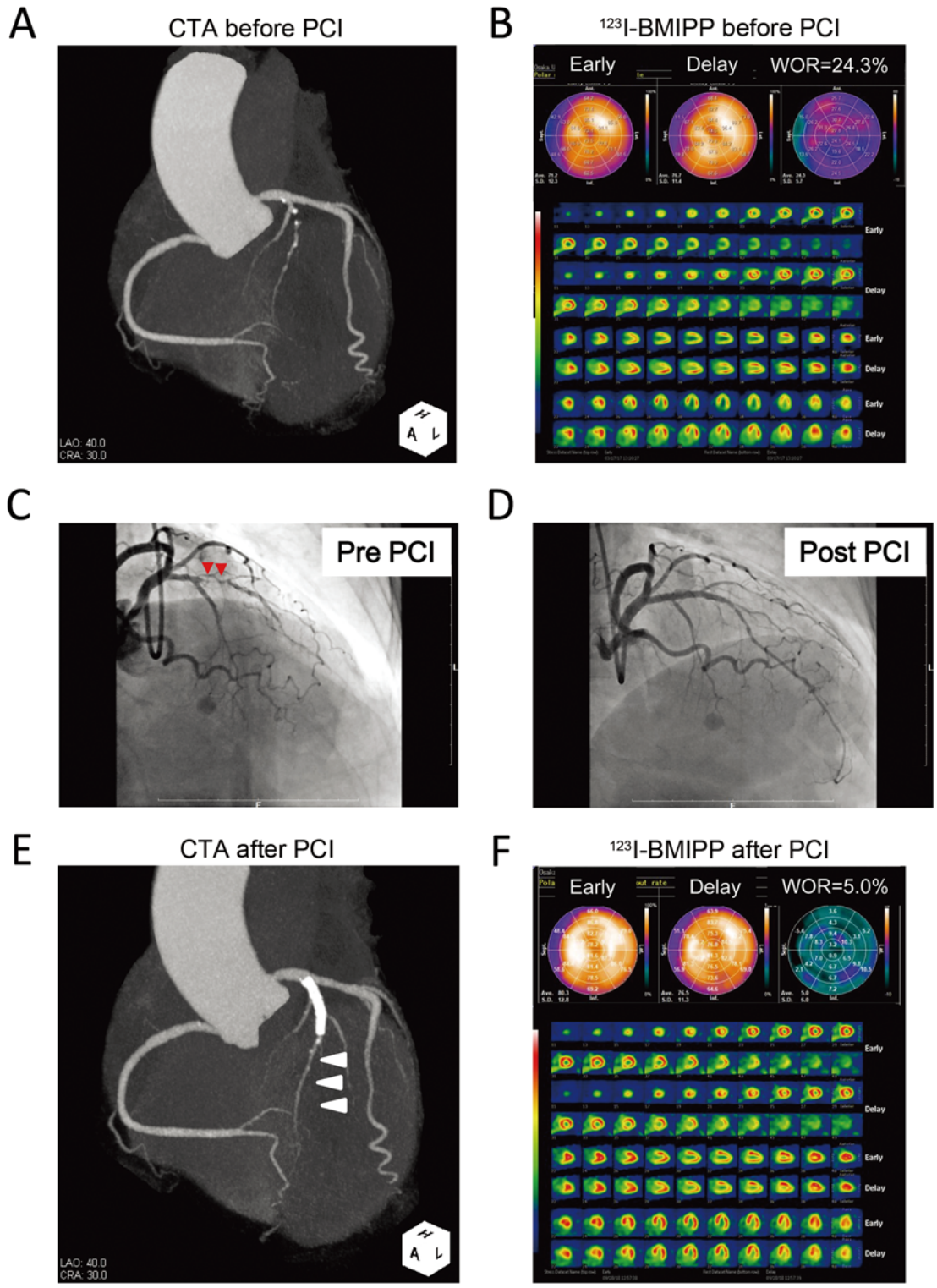

Figure 1　Computed tomographic (CT) angiograms, invasive coronary angiograms, and ^{123}I-BMIPP scintigraphy before and after percutaneous coronary intervention (PCI).

A: CT angiogram five months before PCI.

B: ^{123}I-BMIPP scintigraphy four months before PCI.
Increased WOR is prominent in the anteroapical region.

C: Invasive coronary angiogram one months before PCI.
Red arrowheads indicate the subtotal occlusion of the mid portion of left anterior descending coronary artery (LAD).

D: Invasive coronary angiogram at PCI.
Drug eluting stent (Xience Alpine 2.5×28 mm) was implanted, following plain old balloon angioplasty (NCB 3.0×15mm).

E: CT angiogram 20 months after PCI.
White arrowheads indicate diffuse narrowing in the periphery of LAD.

F: ^{123}I-BMIPP scintigraphy 14 months after PCI.

CTA: computed tomography angiography, PCI: percutaneous coronary intervention, WOR: washout rate

angiography demonstrated subtotal occlusion at the mid-portion and diffuse narrowing at the periphery of left anterior descending artery (LAD) (Panel A). Exercise scintigraphy with ^{99m}Tc tetrofosmin demonstrated mildly reduced uptake at exercise and filled-in observed at rest in the anteroapical region, suggesting ischemia in this region (data not shown). Because of atypical chest pain and diffuse narrowing coronary artery, myocardial scintigraphy with ^{123}I-BMIPP was conducted to suspect TGCV. The uptake of ^{123}I-BMIPP was almost normal. The increased washout was prominent in the anteroapical region and global WOR was 24.3% (Panel B). Coronary angiography revealed severe and diffuse stenosis in the LAD (#7, red arrowheads in Panel C) and stent was implanted successfully (Panel D). The intensive cholesterol lowering therapy was started. Twenty months after PCI, the stent was patent and the first diagonal branch, which was not imaged before PCI (Panel A), can be seen in Panel E. However, it is noted that diffuse narrowing remained observed in the periphery of LAD (white arrowheads in Panel E) even after PCI and that WOR of ^{123}I-BMIPP was decreased to 5.0 % (Panel F). In this patient, reduced WOR of ^{123}I-BMIPP (below 10%) (Panel F) and diffuse narrowing coronary arteries (Panels A and E) fulfilled with the two major items for the diagnostic criteria for TGCV, as mentioned above (3). We finally reached the diagnosis of TGCV. In addition, we measured ATGL activity in peripheral leucocytes, a surrogate biomarker for TGCV. The activity was low (32 nmol/h/mg, references 52 ± 13 nmol/h/mg), which was compatible with idiopathic type of TGCV (I-TGCV) (2, 5). Because in-stent restenosis and required multiple-round PCI were reported in some I-TGCV patients (2), we are carefully observing this patient.

^{123}I-BMIPP scintigraphy is the crucial nuclear imaging to provide information of myocardial metabolism of LCFA and TG in patients with several types of heart diseases. As mentioned the above, defective or decreased WOR of ^{123}I-BMIPP is essential for the diagnosis of TGCV. However, it should be noted that paradoxical increase, in other words, pseudonormalization of WOR can occur when patients with TGCV have severe coronary stenosis with myocardial ischemia, which could be a pitfall for the diagnosis of TGCV. We are preparing for revising the diagnostic criteria with the addition of new information during the last three years to facilitate the differential diagnosis for TGCV.

Author contribution

KH wrote the manuscript. MH analyzed CT angiogram and contributed to the discussion. AT and YI measured ATGL activity and contributed to the discussion. HM provided scientific suggestions for writing the manuscript. HM, YN, and TA contributed to the discussion. KH is the principal investigator for the Japan TGCV study group.

Sources of funding

This study was partially supported by research grants rare and intractable diseases from the Japan Agency of Medical Research and Development (AMED) (Grant No. 17ek0109092h0003).

Conflicts of interest

KH received grants from Nihon Medi-Physics Co. Ltd.

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