LETTER TO EDITOR

Diagnostic Principle with Washout Rate of ^{123}I-β-methyl-p-iodophenyl pentadecanoic Acid for Triglyceride Deposit Cardiomyovasculopathy

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Abstract

Triglyceride deposit cardiomyovasculopathy (TGCV) (Orphanet ORPHA code: 692305) is an emerging rare adult-onset cardiovascular disease, first identified in Japan. In TGCV, defective intracellular lipolysis of long-chain triglycerides results in cellular steatosis and energy failure, leading to intractable heart failure, diffuse coronary artery disease, and ventricular arrhythmia. A hallmark of TGCV diagnosis is the reduced washout rate (WR) of ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP), a well-established radiopharmaceutical of long-chain fatty acid (LCFA). Recently, the working group of the Japanese Society of Nuclear Cardiology published the practical guideline for measuring ^{123}I-BMIPP-WR. Here, we present the diagnostic principle of TGCV using ^{123}I-BMIPP-WR based upon basic and clinical studies in nuclear cardiology as well as current biochemical insights into TG and LCFA metabolism.

Keywords: BMIPP, Diagnostic principle, Heart failure, TGCV (Triglyceride deposit cardiomyovasculopathy
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Dear Editor,

Triglyceride deposit cardiomyovasculopathy (TGCV) (Orphanet ORPHA code: 692305) is a newly-recognized class of rare heart disease, first reported in Japanese patients carrying homozygous mutations of *PNPLA2* encoding adipose triglyceride lipase (ATGL) (1). This discovery highlighted the clinical significance of impaired intracellular lipolysis of long-chain triglycerides (LCTGs). In TGCV, defective LCTG lipolysis causes cellular lipid droplet accumulation and energy failure, leading to severe heart failure and diffuse coronary artery disease. We demonstrated that defective intracellular lipolysis of LCTGs can be assessed using the washout rate (WR) of ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP) (CARDIODINE®, Nihon Medi Physics, Tokyo, Japan) (2, 3) and subsequently established diagnostic criteria without genetic analysis (4, 5). As of October 2024, the cumulative number of diagnosed patients was 991, of which 145 cases had already died. Notably, TGCV has been shown to be treatable with supplemental intake of tricaprin, which improved cardiovascular symptoms and long-term prognosis accompanied by an increase in BMIPP-WR (5). Recently, the working group of the Japanese Society of Nuclear Cardiology published the practical guideline for ^{123}I-BMIPP imaging and calculation of ^{123}I-BMIPP-WR (6). The working group of the Japanese Circulation Society and Japanese Heart Failure Society has published the TGCV diagnostic criteria in their guideline on diagnosis and treatment of heart failure (7).

Here, we present the diagnostic principle with BMIPP-WR for TGCV (Figure 1). The figure is constructed based upon the pioneering basic studies (8-10), latest clinical findings of the intracellular ^{123}I-BMIPP metabolism in various cardiovascular disorders and established biochemical knowledge of TG and long-chain fatty acid (LCFA) metabolism. Intravenously administered ^{123}I-BMIPP is taken up via CD36 transporter. Approximately 90% of intracellular free (non-esterified) ^{123}I-BMIPP undergoes re-esterification and incorporation into the

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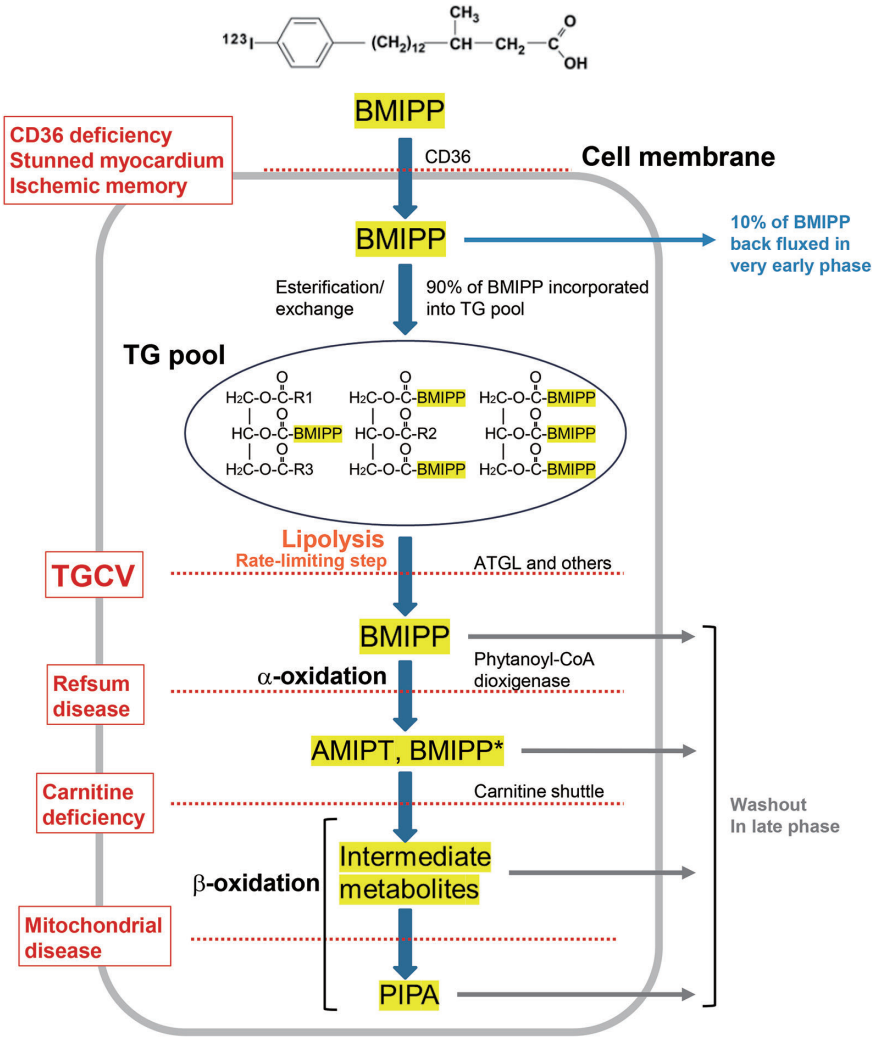

Figure 1　Intracellular metabolism and kinetics of ^{123}I-BMIPP and their relation to defect points in various cardiovascular and metabolic disorders.

Yellow shadings denote radioactivities.

*It was reported that BMIPP can enter into mitochondria without α-oxidation (14).

AMIPT, 14-(ρ-iodophenyl)-2(a)-R, S-methyltetradecanoic acid; ATGL, adipose triglyceride lipase; BMIPP, β-methyl-p-iodophenyl pentadecanoic acid; PIPA, 2-(ρ-iodophenyl) acetic acid; TG, triglyceride

triglyceride (TG) pool, as naturally existing LCFAs are toxic to the cells and quickly re-esterified and incorporated into the TG pool. ^{123}I-BMIPP-TGs in the TG pool are then hydrolysed by ATGL and other intracellular lipases. Lipolysis, the initial and rate-limiting step in this process, is crucial for the ^{123}I-BMIPP washout in the late phase. The released ^{123}I-BMIPP subsequently undergoes α- and β-oxidation to produce adenosine triphosphate. Since the ^{123}I-label is positioned at the terminal end of the BMIPP acyl chain, oxidised metabolites with shortened acyl chains remain radioactive (yellow shading) and are washed out from the cells (black arrows). This unique behaviour allows ^{123}I-BMIPP to serve as a tracer for evaluating both LCFA and TG metabolism.

The uptake of ^{123}I-BMIPP has been extensively studied and is useful for diagnosing and monitoring myocardial stunning in various pathological conditions, including Takotsubo syndrome, metabolic memory following transient ischemia, and metabolic changes in patients with malignancy. As mentioned above, we have reported the clinical utility of ^{123}I-BMIPP as a companion diagnostic tool for TGCV (5). Because the lipolysis is the rate-limiting and crucial step for the late-phase of washout of ^{123}I-BMIPP, a markedly reduced BMIPP-WR (<10%) is both essential and specific for TGCV diagnosis. While ^{123}I-BMIPP-WR may also be decreased in other metabolic disorders, the reduction is theoretically partial. This is because upstream metabolites of their defect points (red dotted lines) can still be washed out. Such conditions include Refsum disease α -oxidation deficiency), genetic or haemodialysis-associated carnitine deficiency (carnitine shuttle impairment) (11,12), and mitochondrial diseases (impaired β-oxidation).

In summary, ^{123}I-BMIPP-WR is essential for the diagnosis

of TGCV. A recent study reported a high prevalence of TGCV (approximately 30%) among patients with unexplained heart failure (13). In the current era of the heart failure pandemic, ^{123}I-BMIPP-WR serves as a valuable diagnostic tool to identify this treatable condition.

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Conflict of interests

KH holds the position of Joint Research Chair in collaboration with TOA EIYO LTD (Tokyo, Japan) since February 2021 and medical adviser for TOA EIYO LTD since December 2021. KH has a pending patent. KH has licenced and pending patents (PCT/JP2012/071594 and PCT/JP2021/008689, respectively). HM has a licensed patent (PCT/JP2023/032407). KN received funds for the endowed department (Functional Imaging and Artificial Intelligence, Kanazawa University) from Siemens Healthcare Japan, Nihon MediPhysics (Japan), and PDRadiopharma, Inc. (Japan), and has collaborated with Spectrum Dynamics Medical (Israel).

Data availability statement

Not applicable.

Author contribution statement

All authors provided critical feedback and contributed to the discussion.

Ethics

Not applicable.

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