Energy States in Mitochondrial Cardiomyopathy – In Vivo Functional Imaging and L-Arginine Therapy –

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Mitochondrial cardiomyopathy is one of the main features in patients with mitochondrial diseases caused by mitochondrial DNA (mtDNA) mutations, and it determines the prognosis, as well as encephalopathy.^{1–3} In particular, an A-to-G transition mutation at nucleotide position 3243 (A3243G) in mtDNA, which was originally discovered in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS),¹ is the most common cause of mitochondrial cardiomyopathy.^{2,3} Accumulated abnormal mitochondria and increased mutant mtDNA in the myocardium of patients with mitochondrial cardiomyopathy have been demonstrated in pathological studies.^{3,4} Although in vitro biological studies using cultured cells have demonstrated that increased mutant mtDNA provokes respiratory chain failure, which leads to decreased ATP production and enhanced oxidative stress,⁵ the pathogenesis of mitochondrial cardiomyopathy in living patients remains obscure. Recent in vivo functional imaging studies demonstrated the energy states in the myocardium of living patients.

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Arakawa et al investigated myocardial oxygen consumption using positron emission tomography (PET) with ¹¹C-acetate in patients with mitochondrial cardiomyopathy carrying A3243G.⁶ The ¹¹C-acetate-PET was used to non-invasively evaluate the metabolic rate of the tricarboxylic acid (TCA) cycle, myocardial efficiency and myocardial blood flow (MBF) (Figure).^{7,8} As reported in this issue of the Journal, they found suppressed TCA-cycle kinetics and, paradoxically, increased myocardial efficiency at baseline in their patient group compared with the control group.⁶ The TCA cycle generates NADH, which is converted to ATP in normal mitochondrial respiratory chains (ie, aerobic metabolism), from glycolysis and fatty acid metabolism (Figure). Deteriorated TCA-cycle activity indicates impaired respiratory chains and enhanced anaerobic metabolism in patients with mitochondrial cardiomyopathy.

We previously investigated the activity of mitochondrial respiratory chains and oxidative metabolism in the myocardium using single-photon emission tomography (SPECT) with technetium 99m methoxyisobutyl isonitrile (^{99m}Tc-MIBI) and iodine-123-labeled 15-4-iodophenyl-3-(R,S)-methyl-pentadec-

anoic acid (¹²³I-BMIPP) in patients with mitochondrial cardiomyopathy carrying A3243G.⁹ ^{99m}Tc-MIBI is retained in the mitochondria of myocardial cells depending on the mitochondrial membrane potential ($\Delta\psi_m$) created in the respiratory chain,¹⁰ whereas the uptake of ¹²³I-BMIPP reflects the enhanced triglyceride-pool because of suppressed fatty acid metabolism with enhanced glucose utilization in mitochondrial dysfunction (Figure).¹¹ Our study demonstrated an increased washout rate and decreased uptake of ^{99m}Tc-MIBI, and increased uptake of ¹²³I-BMIPP (ie, ¹²³I-BMIPP/^{99m}Tc-MIBI mismatch) in patients with severe cardiac involvement.⁹ These findings indicated that respiratory chain failure and suppressed oxidative metabolism lead to cardiac dysfunction in patients with mitochondrial cardiomyopathy.

PET imaging with ¹⁸F-fluorodeoxyglucose and proton magnetic resonance spectroscopy are also useful techniques for evaluating glucose metabolism and lactate concentration in patients with mitochondrial dysfunction (Figure). Although these techniques have not yet been applied to mitochondrial cardiomyopathy, we previously demonstrated enhanced glucose metabolism and increased lactate concentration in the brain lesions of stroke-like episodes in patients with MELAS.^{12,13}

Taken together, these functional imaging methods clearly demonstrate that impaired respiratory chains inhibit TCA-cycle activity and enhance anaerobic glycolysis in the pathogenesis of mitochondrial cardiomyopathy (Figure).

Although there are no radical therapeutic strategies focusing on either MELAS or mitochondrial cardiomyopathy, Koga et al have recently demonstrated the therapeutic effects of L-arginine (L-Arg) for stroke-like episodes.^{14,15} L-Arg presumably has 2 effective mechanisms: (a) L-Arg transforms into nitric oxide, and may provoke vasodilatation and relieve ischemic damage (ie, effects for angiopathy) and (b) L-Arg undergoes conversion to 2-oxoglutarate, and has the potential to improve TCA-cycle metabolism (ie, effects for cytopathy). For stroke-like episodes, L-Arg is assumed to have therapeutic effects related to correction of cerebral blood flow (mechanism (a)).^{14,15}

In the current issue of the Journal, Arakawa et al also demonstrate, using ¹¹C-acetate-PET, that L-Arg administration rescues the impaired TCA-cycle metabolism without a correlation to MBF in patients with mitochondrial cardiomyopathy carrying A3243G (mechanism (b)).⁶ Although further

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longitudinal studies will be necessary to confirm their results, these findings suggest that L-Arg improves myocardial oxidative metabolism, as well as inducing vasodilatation in patients with mitochondrial cardiomyopathy. Thus, L-Arg may be a beneficial therapy for mitochondrial cardiomyopathy.

Functional imaging using PET and SPECT facilitates the evaluation of energy states and respiratory chain function in patients with mitochondrial cardiomyopathy. Furthermore, these imaging techniques demonstrate the therapeutic potential of L-Arg for these patients.

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