Sex difference in cardiac metabolism in nonischemic heart failure: Insight for prognostic value of altered cardiac metabolism

Hyung-Jun Im, MD, PhD,[a,b] and Gi Jeong Cheon, MD, PhD[a,c]

[a] Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea
[b] Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, Korea
[c] Institute of Radiation Medicine, Seoul National University College of Medicine, Seoul, Korea

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Heart has the highest metabolic demands than any other organs. To maintain contractile function of the heart, constant and rapid production of adenosine triphosphate (ATP) is needed. Fatty acid (FA) and glucose are the main fuels for production of the ATPs by mitochondrial oxidative phosphorylation. In normal condition, 60% to 90% of total ATP is made from FA and the other from glucose or lactate. In a failing heart, cardiac metabolism is profoundly altered, and majority of the studies suggest that FA metabolism decreases. However, it is not clear and still in controversy whether the alteration in cardiac metabolism in a failing heart is an adaptation or maladaptation.[1–3]

In this issue of the Journal, Kadkhodayan et al compared myocardial blood flow (MBF), FA metabolism, and glucose metabolism between men and women with nonischemic HF, and found that MBF and FA metabolism were higher in women than men, which were independent of age, obesity, and insulin resistance. Although higher MBF and FA metabolism in women are well known,[4] this study firstly showed that the sex difference of MBF and FA metabolism still stands true in subjects with nonischemic HF. Also the authors found that high MBF was associated with the prognosis. Although, FA metabolism did not show significant association with survival in this study, there has been a hypothesis that decreased FA metabolism in nonischemic HF is a maladaptation. In particular, recent mouse studies indicate that lower FA metabolism can exacerbate nonischemic heart failure.[5,6] Also, 'obesity paradox' is supporting the hypothesis, which is the observation that obese heart failure patients have better prognosis than nonobese heart failure patients even though obesity is risk factor for heart failure.[7] In this study, it is hard to conclude the association between high FA metabolism and prognosis, because the size of this study was too small and potential confounding factors including perfusion reserve were not evaluated. Thus, the hypothesis on association between FA metabolism and prognosis in nonischemic HF should be confirmed in a larger study with adjustment of other prognostic markers especially sex and perfusion reserve.

In young and healthy subjects, women have lower glucose extraction fraction and utilization than men,[8] in contrast, sex difference of glucose metabolism was not found in patients with nonischemic HF in this study. This result could reinforce the previous finding that FA and glucose metabolism are not always counterbalanced in HF.[6,9] Previous studies on glucose metabolism in HF are less consistent,[1] and the consequence of shifting toward high glucose metabolism in HF is also in controversy.[3] In several studies using mice, increased glucose utilization showed favorable cardiac outcome.[10,11] In contrast, one recent prospective clinical study showed that high FDG uptake in right ventricle predicted worse outcome in patients with pulmonary arterial hypertension. Meanwhile, FDG PET/CT or MR can also be utilized to assess inflammatory activity in

Reprint requests: Gi Jeong Cheon, MD, PhD, Department of Nuclear Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Korea; *larrycheon@gmail.com*
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Table 1. Radiotracers for evaluation of FA metabolism

Radionuclide	Half-life	Compound	Use
SPECT			
^{123}I	13.3 hours	IPPA	FA uptake, oxidation, and storage
		BMIPP	FA storage
PET			
^{11}C	20.4 minutes	Palmitate	FA uptake, oxidation, and storage
^{18}F	110 minutes	FTHA	FA uptake and oxidation
		FTP	FA uptake and oxidation
		FCPHA	FA uptake and oxidation

pericardial fat or visceral fat which could be associated with the risk of heart diseases.[12–15] Thus, prognostic value of the integrated information from FDG PET/CT or PET/MR is worth to be tested in future studies.

Multiple tracers have been developed to assess cardiac FA metabolism (Table 1). FAs enter to myocardium by either passive diffusion or by protein-mediated transport, and activated to fatty acyl-coenzyme A (CoA) by fatty acyl-CoA synthase (FACS) in cytoplasm. Fatty acyl-CoA is either stored to triglyceride or converted to long-chain acylcarnitine. Long-chain acylcarnitine is transported to mitochondria, and processed by beta oxidation. Radiolabeled single-branch FAs such as ^{123}I-15-(p-iodophenyl)-pentadecanoic acid (IPPA) or ^{11}C-palmitate follows the steps of normal FA metabolism, thus we can evaluate FA uptake, storage, and beta oxidation with the tracers. The branched FAs such as ^{123}I-beta-methyl-p-iodophenylpentadecanoic acid (BMIPP) can only be used for evaluation of FA storage, since alkyl branching of the tracers inhibits beta oxidation. Several modified FA tracers with ^{18}F labeling such as 14(R,S)-[18F]-fluoro-6-thiaheptadecanoic acid (FTHA),[16] 16-^{18}F-fluoro-4-thia-palmitate (FTP),[17] Trans-9(RS)-^{18}F-fluoro-3,4(RS,RS) methyleneheptadecanoic acid (FCPHA)[18] are trapped during beta oxidation, therefore can be used in evaluation of FA uptake and beta oxidation partially. ^{11}C labeled palmitate (^{11}C-palmitate) is the most commonly used tracer for FA metabolism assessment and mathematical modeling to assess FA uptake, oxidation, and storage using ^{11}C-palmitate are well established.[19] The main advantages of ^{11}C-palmitate is that the kinetics of the tracer is the same with the unlabeled palmitate which is a long-chain saturated FA. On the other hand, rapid clearance and short half-life of ^{11}C-palmitate results in relatively poor image quality. Also, kinetic analysis is easier in tracers which are stored or trapped in myocardium than ones undergo beta oxidation and wash out. Accordingly, above-mentioned ^{18}F labeled tracers have advantages over ^{11}C-palmitate regarding ease of kinetic modeling, longer physical half-life, and better image quality. Selection of appropriate tracer would be of importance for prospective trial for evaluation of prognostic value of cardiac metabolism and therapeutic trials. For example, for an initial exploratory study, a tracer with wide range of applications such as ^{11}C-Palmitate could be the tracer of choice, while ^{18}F labeled tracers will be better choices for a study to evaluate difference in FA uptake and beta oxidation, for ease of analysis and better image quality.

Modulation of cardiac metabolism could be an early treatment target for failing heart and already has been attempted in several clinical trials. However, controversies remained whether increasing FA, decreasing FA, increasing glucose, or decreasing glucose metabolism is more beneficial to prevent progression of HF. Prior to test efficacy of drugs which alter cardiac metabolism in HF, larger case study should be done to validate the association between prognosis and cardiac FA/glucose metabolism. Also, appropriate FA metabolism tracer should be carefully selected for the future clinical trials.

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