

Sodium-Glucose Cotransporter 2 Inhibitors for Heart Failure

Hidekatsu Yanai

In this issue (P94), Kutoh reports type 2 diabetic patients who showed changes in cardiac function which is concomitant with changes in ketone bodies by using one of sodium glucose cotransporter 2 inhibitors (SGLT2i), tofogliflozin [1], proposing a possible mechanism for SGLT2i-mediated prevention of heart failure. EMPA-REG OUTCOME trial showed a striking relative risk reduction in hospitalization for heart failure (35%) [2]. Further, the CVD-REAL Study, the large multinational study, concluded that treatment with SGLT2i was associated with a lower risk of hospitalization for heart failure and death as compared with other glucose lowering drugs, suggesting that the benefits seen in empagliflozin in a randomized trial may be a class effect applicable to a broad population of type 2 diabetic patients in real-world practice [3]. Such attractive studies urge clinicians and scientists to study to elucidate SGLT2i-mediated cardioprotective mechanisms.

Dapagliflozin successfully prevented the development of hypertrophic cardiomyopathy in a diabetic lipodystrophic mouse model [4]. Left ventricular hypertrophy and cardiac diastolic function in a female rodent model of diabetes were improved by empagliflozin [5]. Various factors such as weight loss, blood pressure lowering and sodium depletion, renal hemodynamic effects, effects on myocardial energetics and neurohormonal effects have been suggested to contribute to cardioprotective mechanisms of SGLT2i [6].

SGLT2i may induce relative glucose deficiency, and then may trigger increased lipolysis and fatty acid oxidation which increase hepatic ketone body production [7]. SGLT2 is expressed in pancreatic α cells, and SGLT2i promote glucagon secretion [8]. Increased glucagon secretion due to SGLT2i may be also associated with elevation of hepatic ketone body production.

The report by Kutoh focused on the contribution of change in ketone bodies due to SGLT2i to cardioprotection [1]. Ferrannini et al hypothesized that under conditions of persistent mild hyperketonemia during treatment with SGLT2i, β -hydroxybutyrate is freely taken up by the heart and oxidized in preference to fatty acids, and this fuel selection improves the transduction of oxygen consumption into work efficiency at the mitochondrial level as a “Thrifty Substrate Hypoth-

esis” [9]. Martens et al also suggested that SGLT2i might improve the efficiency of myocardial energetics by offering β -hydroxybutyrate as an attractive fuel for oxidation [10]. Mudaliar et al postulated that the cardiorenal benefits of SGLT2i are due to a shift in myocardial and renal fuel metabolism away from fat and glucose oxidation, which are energy inefficient in diabetic heart and kidney, toward an energy-efficient super fuel like ketone bodies, which improve myocardial/renal work efficiency and function as a “Unifying Hypothesis” [11]. These findings were supported by changes in cardiac function which is concomitant with changes in ketone bodies by SGLT2i observed in the report by Kutoh [1].

Bedi et al reported increased ketone utilization in the severely failing human heart independent of diabetes, supporting that ketone body is an alternative fuel due to a crucial adaptation in the failing heart [12]. Nagao et al showed that β -hydroxybutyrate attenuated reactive oxygen species production and alleviated apoptosis induced by oxidative stress in cardiomyocytes, suggesting that the accumulation of β -hydroxybutyrate occurs as a compensatory response against oxidative stress in failing heart [13]. Very recently, ketone body infusion with 3-hydroxybutyrate has been reported to reduce myocardial glucose uptake and increase myocardial blood flow in healthy humans, suggesting that ketone bodies are important cardiac fuels and vasodilators, which may have therapeutic potentials [14]. However, further well-planned studies, preferably by using a greater number of subjects, should be performed to understand an association between ketone body metabolism and heart failure.

Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this article.

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Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, 1-7-1 Kohnodai, Ichikawa, Chiba 272-8516, Japan.
Email: dyanai@hospk.ncgm.go.jp

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