

## Editorial



# A Small Animal Model of Diabetic Heart Failure With Reduced Ejection Fraction

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► See the article “Development of a Zebrafish Larvae Model for Diabetic Heart Failure With Reduced Ejection Fraction” in volume 53 on page 34.

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### Conflict of Interest

The authors have no financial conflicts of interest.

Diabetes mellitus (DM) is a chronic and progressive metabolic disorder characterized by elevated blood glucose levels in the body, currently affecting more than 500 million people worldwide. DM has been classified into four major types: type 1, type 2, gestational diabetes mellitus (GDM), and specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and chemical-induced diabetes.<sup>1,2)</sup>

DM significantly increases the risk of cardiovascular disease (CVD), which remains a leading cause of morbidity and mortality in types 1 and 2 DM (T1DM and T2DM). Heart failure (HF), the most frequent first presentation of CVD, has been recognized as a common complication of DM, with a prevalence of up to 22% in individuals with diabetes and increasing incidence rates. Despite recent medical advances in treatment and improvement in the 5-year survival rate, the overall mortality remains about 50%.<sup>3-5)</sup>

Animal models are effective tools to understand the pathogenesis of many diseases, including experimental DM and HF. These two diseases are most often modeled in rodents using a variety of strategies, such as induction of genetic modifications, specific diet regimens, and exposure to chemical agents as well as surgical manipulation.<sup>6)</sup> Even though laboratory rodents are still the most widely used animal model for human pathology, in the last decade the number of zebrafish models in biomedical studies has explosively increased. Zebrafish have several advantages including *ex vivo* fertilization and embryogenesis, optical transparency of embryos and larvae, rapid embryonic development, low housing costs, and genetic similarity with mammals.<sup>7)</sup> Thus, zebrafish has great potential as a complementary model for human pathophysiology.

In this issue of *Korean Circulation Journal*, Kim et al.<sup>8)</sup> introduce a chemical-induced larval zebrafish model for DM which also presents HF and reduced ejection fraction. In previous work, the authors had established a different zebrafish model of HF induced by short treatment with terfenadine (TER), an antihistamine, which is a known cardiotoxic agent.<sup>9)</sup> The larvae exhibited a reduction in heart beating and dilated cardiomyopathy by atrioventricular dyssynchrony, as well as impaired cardiac contraction, which are all pathologic features found in human patients with HF.

**Data Sharing Statement**

The data generated in this study are available from the corresponding author upon reasonable request.

**Author Contributions**

Conceptualization: Jung SH, Kim HT;  
Supervision: Kim HT; Writing - original draft: Jung SH, Kim HT; Writing - review & editing: Jung SH, Kim HT.

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To establish the DM-HF model, the authors first exposed zebrafish larvae to a combination of D-glucose (GLU) and streptozotocin (STZ) to induce a diabetic condition characterized by hyperglycemia and impaired glucose homeostasis, without an effect on animal viability. Although STZ can induce hypoinsulinemia and hyperglycemia due to damage to pancreatic islet cells ( $\beta$ -cells), in the reported DM model insulin expression was decreased without affecting the morphology and maturation of pancreatic  $\beta$ -cells, similar to the established pathogenic course of T2DM. In a second step, starting from this DM model, the authors established the larval zebrafish model of DM-HF by treatment with TER. The resulting DM-HF model shows reduced cardiac contractility and increased irregular cardiac contraction, as well as reduced motility and survival rate compared to the DM model. These phenotypes are reminiscent of results from clinical studies in which patients with DM-HF have increased morbidity and mortality as compared with only DM.

As DM-HF is a progressive chronic disease, the chemical-induced zebrafish DM-HF model presented here has several advantages that will benefit research into this disease. The diabetic and cardiac phenotypes manifest upon administering a simple drug combination, and the induction time is short. In addition, this model can be easily deployed for targeted or large-scale drug testing which could yield pharmacologically relevant candidate compounds for human use. Nonetheless, even though the zebrafish DM-HF model can recapitulate important pathogenic features of human DM-HF, as a non-mammalian species zebrafish has a different cardiac structure and circulatory system compared to rodents and humans. Therefore, the chemical strategy used here in the zebrafish should be further tested and verified in laboratory rodents and human-derived *in vitro* systems. Nevertheless, the zebrafish DM-HF larval model will be useful to enable further investigation into the pathophysiology and therapeutic approaches for this disease.

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