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**Editorial**

# Aquaporin 7: the glycerol aquaeductus in the heart

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**This editorial refers to 'The heart requires glycerol as an energy substrate through aquaporin 7, a glycerol facilitator' by T. Hibuse *et al.*,[15] pp. 34–41, this issue.**

Deprivation of available energy has been postulated to play a major role in the genesis of heart failure,[1–3] and accumulating evidence points to the premise that changes in gene expression that alter energy metabolism weaken the heart muscle,[4,5] reinforcing the logic of ameliorating energy substrates, and/or metabolism as a heart failure therapeutic. Reduced cardiac energy levels, in turn, influence a plethora of cardiac events, including free radical defense mechanisms which lower cardiomyocyte survivability,[6] cardiac contractility,[7] adverse remodelling and arrhythmogenic susceptibility.[8]

The heart is able to produce energy from a wide range of substrates and shifts continuously between sources, according to supply availability as controlled by exercise, nutritional status, or pathophysiological conditions. Therefore, the immediate cardiac capacity to produce energy and to adapt its metabolism to requirement changes is a crucial cardiac functional parameter. ATP is the direct source of energy for all energy-consuming reactions in the heart (pump function, $Ca^{2+}$ re-uptake into the sarcoplasmic reticulum and maintenance of the sarcolemmal ion gradients). In the healthy adult heart, more than 70% of the energy required is covered by fatty acid oxidation in mitochondria, with the remaining 30% being accounted for by carbohydrate oxidation, mainly using glucose and ketone bodies as exogenous substrates.[9–11] Under conditions of high ATP demand relative to ATP availability, the myocyte is able to recruit additional pathways or depend more heavily on alternative pathways for ATP synthesis (e.g. glycolysis and phosphotransferase reactions). The efficiency of ATP generation differs depending on the oxidized substrates, with fatty acid oxidation generating more ATP, on a molar basis, than glucose utilization.[12]

Accumulating evidence indicates that glycerol could be an as of yet largely overlooked metabolic cardiac substrate.[13–15] In cardiomyocytes, glycerol controls several steps of lipid metabolism by forming a backbone for complex lipid synthesis (phospholipids and triacylglycerols).[16,17] In cultured rat cardiac cells, glycerol was shown to be phosphorylated to yield glycerol-3-phosphate, contributing dose-dependently to energy production through oxidation, to membrane homeostasis via phospholipid synthesis, and to lipid storage as triacylglycerol, and thus regulating energy balance.[13] Further, glycerol metabolism in the heart seems to be regulated by energy demand. This has been addressed in a model of isolated working rat heart where both glycerol supply and energy demand levels resulted in increased glycerol uptake and suppressed fatty acid oxidation.[14] At low glycerol levels, higher energy demand by increased heart rate did not affect glycerol uptake; however, this was augmented once the available glycerol concentrations were also elevated. Furthermore, increasing energy demand requires higher amounts of phospholipids[13] and thus improved phospholipid turnover, which may be dependent on the available concentrations of glycerol in the cell. Although the metabolic pathways for ATP production from glycerol do theoretically exist in the heart, their functionality has not been elucidated thus far.

The study by Hibuse *et al.*[15] in this issue of the journal opens a novel perspective by demonstrating that glycerol, as an energetic substrate, is dispensable under physiological conditions but becomes important in the stressed heart. Under pressure and/or volume overload-induced cardiac stress situations, a reduction in fatty acid oxidation, caused in part by downregulation of fatty acid oxidation enzyme expression, is paralleled by a shift to higher dependency on glucose oxidation.[1–3] Glucose entry in myocytes is followed either by its storage as glycogen or by glycolysis, which converts it into pyruvate, which is converted into acetyl CoA by pyruvate dehydrogenase in the mitochondria. Similarly, myocyte glycerol uptake also leads to pyruvate formation. Hibuse *et al.*[15] now demonstrate that under low fatty acid oxidation conditions, the heart favours glycerol over glucose consumption, which points to a compensatory effect of glycerol metabolism under adverse cardiac conditions. On its own, this groundbreaking finding forces us to drastically revise our conceptualization of cardiac energy metabolism.

The authors then go further to identify aquaporin 7 (AQP7) as the main cardiac glycerol uptake channel. Although first identified as water uptake facilitators that increase

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membrane water permeability (reviewed by King *et al.*[18]), some members of the aquaporin superfamily have also been demonstrated to facilitate permeation of small neutral solutes, such as glycerol (aquaglyceroporins). To date, evidence suggests that AQP7 is the only aquaglyceroporin expressed in the heart. Through the generation of a AQP7-somatic null allele in the mouse, Hibuse *et al.*[15] were able to reduce cardiac glycerol and ATP content, which was followed by significant deterioration of glycerol consumption. Surprisingly, under basal conditions, AQP7 knockout mice did not develop discernable, spontaneous cardiac phenotypes. However, AQP7-deficient mice did exhibit impaired myocardial adaptation to pressure overload as shown by development of excessive cardiac hypertrophy and, subsequently, higher mortality compared with pressure overload-subjected wild-type counterparts.

Many questions now arise from this first thorough study of AQP7 function in cardiac glycerol metabolism and its impact on heart pathophysiology. First, is AQP7 the unique facilitator of glycerol in the myocardium and, more specifically, in cardiac muscle? Traces of glycerol processing remained under AQP7-deficient conditions, suggesting the existence of additional mechanisms of cellular glycerol uptake. Second, since Hibuse *et al.*[15] take advantage of a somatic AQP7 knockout mouse model, the specific contribution of glycerol uptake in cardiomyocytes remains unclear, since, in theory, compensatory mechanisms may have evolved to cope in a life without AQP7. More sophisticated approaches allowing temporal and heart muscle-restricted deletion[19] or gain-of-function for AQP7 could help in clarifying these relevant issues. Knockdown of AQP7 in the H9c2 cell line, an *in vitro* cellular model used for both skeletal and cardiac muscle studies, suggests that it may result in decreased glycerol uptake and, possibly, fibre-type switching in skeletal muscle.[15] And finally, thus far, the few existing studies concerning cardiac glycerol metabolism were performed either on cell lines or mouse models. It would be of great interest to access this issue in human subjects. Is AQP7 the only glycerol facilitator in the human heart? Is AQP7 expression increased in human heart failure?

In specific clinical situations where there is an excessive consumption of fatty acids and a high fatty acid/glucose ratio such as metabolic diseases (diabetes) and ischaemic heart disease, the control of fatty acid/glucose balance is of great importance. Many efforts have been made to shift the balance for ATP production away from utilization of glucose towards utilization of fatty acids. Although many issues remain unclear, based on numerous *in vitro* and *in vivo* studies one can accept glycerol as a vital cardiac substrate for energy that becomes crucial upon cardiac stress where its increased uptake suppresses fatty acid oxidation. In the future, molecular modulation of cardiac energy substrates and glycerol facilitators such as AQP7 in the heart may well enter the therapeutic arena in our fight against heart failure.

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