Cardiomyopathy in Type 2 Diabetes
Update on Pathophysiological Mechanisms

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Abstract
Type 2 diabetes mellitus (DM) is associated with increased risk for developing heart failure (HF) and worse outcomes once HF is present. While the exact mechanisms underpinning these observations remain poorly understood, several metabolic perturbations associated with DM have been implicated as contributors to the HF risk, including alterations of cardiomyocyte metabolic substrate switching between free fatty acid (FFA) and glucose metabolism; increased FFA exposure and cellular accumulation; and alterations in peroxisome proliferator-activated receptor-(PPAR-)α activity, among others. The commonly coincident conditions of left ventricular hypertrophy and ischemic heart disease likely confound the metabolic derangements further increasing HF risk. Continued investigation into these mechanistic connections is necessary to better understand the pathophysiology and ideally inform the pursuit of novel therapeutic targets and strategies to intervene on the HF associated with DM.

Introduction
Patients with type 2 diabetes mellitus (DM) are at two- to fivefold higher risk for developing heart failure (HF) compared with age-matched patients without DM [1–3]. The epidemiologic evidence supporting this connection and its clinical relevance are reviewed elsewhere in this issue by Pfister & Erdmann [4]. While the exact etiologic underpinnings of the observed associations between DM and HF risk remain poorly understood, the potential contributory role of a number of specific metabolic perturbations occurring in the setting of DM due to hyperglycemia, insulin resistance, dysregulation of lipid metabolism, or a combination of these and other metabolic insults continue to be the focus of much scientific investigation [5].

Myocardial Energy Metabolism
The cardiac myocyte can metabolize numerous substrates for energy generation, including free fatty acids (FFA), glucose, and, to a lesser extent, lactate [6]. While the fetal heart primarily uses glucose for energetic requirements, the rise of serum levels of FFA after birth is associated with a metabolic switch within the cardiomyocyte to the preferential metabolism of FFA [7]. This is in contrast to most other cell lines that use glucose as their principal source of energy generation [8, 9]. In unstressed conditions in cardiomyocytes, FFA metabolism is preferred due to its higher energy yield per molecule metabolized [10]. However, under stressed conditions such as ischemia or hypertrophy where oxygen supply is compromised, the cardiomyocyte reverts to utilization of glucose (Figure 1). This metabolic switch is useful because of the increased metabolic efficiency of glucose versus FFA metabolism based on the amount of adenosine triphosphate (ATP) generated per mole of oxygen consumed [11]. Thus, substrate availability (oxygen) impacts the preferred mode of cardiomyocyte metabolism (glucose vs. FFA) [7]. As will be discussed later, perturbations...
in the setting of DM impact the ability to convert from FFA to glucose metabolism, and this inflexibility likely contributes to diabetic myocardial dysfunction.

The preferential cardiac metabolism of FFA or glucose is reciprocally regulated at the cellular level such that the upregulation of gene expression and enzyme activation for the metabolism of one substrate is associated with coordinate downregulation and inhibition of the other [12]. These changes are mediated by complex alterations in gene expression and activation of various enzymes involved in FFA and glucose metabolism [6, 7, 11].

Increased FFA metabolism in the cardiomyocyte inhibits glucose metabolism [13], through peroxisome proliferator-activated receptor-PPAR-α transcriptional regulation and via direct inhibitory effects of intermediates of FFA metabolism [6]. While FFA metabolism inhibits glucose metabolism, the converse is true as well. That is, increased glucose metabolism inhibits FFA metabolism, particularly by inhibition of carnitine palmitoyltransferase-(CPT-)1 impeding FFA transport into the mitochondrion [14, 15]. Glucose-mediated inhibition of FFA metabolism is a key adaptation to various stressors (e.g., ischemia, hypertrophy) that is accomplished at least in part by downregulation of PPAR-α [16]. The reciprocal inhibitory effects exerted between FFA and glucose metabolism are balanced in the normal cardiomyocyte by substrate availability and transcriptional control by PPAR-α, a key regulator of this process as will now be reviewed.

PPAR-α and Coordinate Regulation of Glucose and FFA Metabolism

PPAR-α is a ligand-activated nuclear transcriptional regulator playing a pivotal role in modulation of cellular lipid and glucose metabolism [17]. Initially identified in the late 1970s [18, 19], PPAR-α is predominately expressed in tissues with high rates of FFA oxidation such as liver and heart [16]. The uptake of FFA increases PPAR-α activity in the cardiomyocyte and contributes to the reliance on FFA metabolism both by transactivation of gene products involved in FFA metabolism, and by transrepression of those used for glucose metabolism (Figure 2).

PPAR-α regulates transcription of genes central to FFA uptake and oxidation including transport from the cytosol into the mitochondrion for further oxidation [16]. Transport into mitochondrion is mediated by CPT-1, which is highly regulated, and is increased by PPAR-α activation [20]. Each of the steps of FFA metabolism: FFA uptake; intracellular binding and esterification of FFA; and FFA transport into the mitochondria are regulated by transcriptional products of PPAR-α. Furthermore, in states of compensated caloric excess, surplus FFA are oxidized and then dissipated as heat through PPAR-α-dependent pathway [21, 22]. The normal cardiomyocyte is thus protected from intramyocellular FFA deposition through PPAR-α control over fatty acid metabolism.

Studies using animal models have elucidated the central role of PPAR-α downregulation to cardiac metabolic adaptation [23, 24]. Further, transgenic animals with constitutive PPAR-α overexpression develop a cardiomyopathy mimicking that observed in the human diabetic condition [17]. Interestingly, restriction of dietary fat in animals overexpressing PPAR-α prevents the cardiomyopathy, implicating serum FFA as a potential requisite mediator of the cardiac maladaptation as opposed to direct pernicious effects of PPAR-α per se [23]. Chronic exposure to excess circulating fatty acids (such as occurs in insulin resistance and DM) appears to paradoxically downregulate PPAR-α in the cardiomyocyte. This PPAR-α downregulation may result in further myocardial damage (a “second hit”) by inhibiting cellular FFA oxidation in the setting of excess circulating and intracellular FFA [25, 26].

Figure 1. Schematic summary of cardiac adaptive and maladaptive metabolic modifications occurring in response to diabetes with or without superimposed ischemia and/or hypertension, culminating in overt cardiomyopathy. FFA: free fatty acid; PPAR-α: peroxisome proliferator-activated receptor-α.

Abbildung 1. Schematische Zusammenfassung der kardialen adaptiven und maladaptiven metabolischen Veränderungen bei Diabetes mit oder ohne überlagerte Ischämie und/oder Hypertrophie, die schließlich zur manifesten Kardiomyopathie führen. FFA: freie Fettsäure; PPAR-α: „peroxisome proliferator-activated receptor-α“.