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Non-ischemic diabetic cardiomyopathy may initially exhibit a transient subclinical phase of hyperdynamic myocardial performance

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ABSTRACT

Cardiovascular complications are the key cause for mortality in diabetes mellitus. Besides ischemia-related cardiac malfunction there is growing evidence for non-ischemic diabetes-associated heart failure in both type 1 and type 2 diabetes mellitus. The underlying pathophysiology of non-ischemic diabetic cardiomyopathy (NIDC) is poorly understood and data on myocardial mechanics in early stages of the disease are rare. However, several studies in both human and experimental animal settings have reported *prima facie* unexplained features indicating myocardial hyperdynamics early in the course of the disease.

The new hypothesis is that – other than previously thought – NIDC may be non-linear and initially feature an asymptomatic subclinical phase of myocardial hypercontractility that precedes the long-term development of diabetes-associated cardiac dysfunction and ultimately heart failure. Diabetes-induced metabolic imbalances may lead to a paradoxic inotropic increase and inefficient myocardial mechanics that finally result in a gradual deterioration of myocardial performance.

In conclusion, diabetic patients should be screened regularly and early in the course of the disease utilizing ultra-sensitive myocardial deformation imaging in order to identify patients at risk for diabetes-associated heart failure. Moreover, hyperdynamic myocardial deformation might help distinguish non-ischemic from ischemic diabetic cardiomyopathy. Further studies are needed to illuminate the underlying pathophysiological mechanisms, the exact spatiotemporal evolvement of diabetic cardiomyopathy and its long-term relation to clinical outcome parameters.

Introduction

Worldwide diabetes mellitus (DM) is ranging among the most common chronic disorders of both childhood [1] and adulthood [2] with ever-increasing incidence [3]. Cardiovascular dysfunction is the principle cause of morbidity and mortality in diabetic patients and the number one overall cause of death in the western world [4]. Unarguably, ischemia-associated events lead to the majority of DM-associated cardiovascular disease [5]. However, there is increasing evidence indicating a substantial role of non-ischemic diabetic cardiomyopathy (NIDC) that can ultimately result in full-blown heart failure [6]. While the clinical relevance of NIDC is still questioned by a number of experts in the field [7,8], several studies have observed both systolic and diastolic myocardial dysfunction in diabetic patients in the absence of other cardiovascular disorders such as structural heart disease, coronary artery disease, ischemia, or arterial hypertension [9–14]. Pathologic remodeling, altered intracellular signaling, impaired calcium homeostasis, suppressed glucose oxidation, and enhanced fatty acid metabolism have been described as possible pathomechanisms that lead to NIDC. However, the exact underlying mechanisms currently remain elusive. Furthermore, cardiac function in patients with NIDC is widely believed to remain normal until it gradually declines on the long run – even though the exact temporal evolvement of NIDC regarding myocardial dynamics, especially in the early course of the disease, has not been investigated well to date [15].

The hypothesis

Diabetes-associated non-ischemic cardiomyopathy initially presents with a transient phase of hyperdynamic myocardial performance

Hypothetically, diabetic cardiomyopathy develops in a non-linear fashion featuring an early asymptomatic phase of subclinical hyperdynamic myocardial contractility that precedes the long-term cardiac deterioration which ultimately results in heart failure

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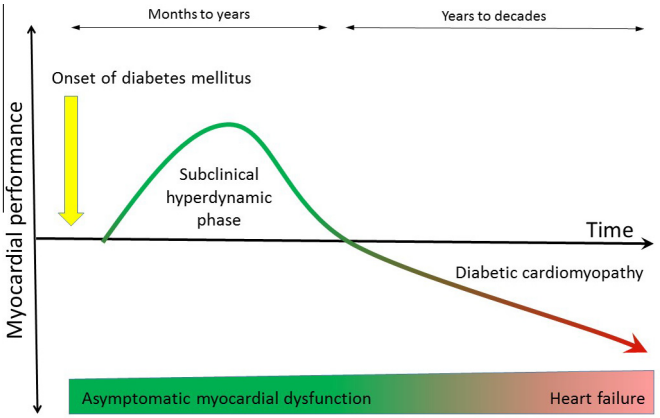

Fig. 1. Schematic time course model of the potential temporal evolvement of non-ischemic diabetic cardiomyopathy.

(see Fig. 1). Other than previously believed, DM-associated metabolic imbalances may cause the heart to initially exhibit increased positive inotropic activity and thus hyperdynamic myocardial deformation. These functional alterations remain widely unreported because firstly, they are clinically asymptomatic and secondly, they are too subtle to be detected by commonly used (non-ultra-sensitive) measures such as conventional echocardiography. Furthermore, this early phase of myocardial hyperdynamics in NIDC is transient in nature and since most studies on diabetic cardiomyopathy focus on late(r) stages of the disease, normal or depressed cardiac function have often been reported.

The concept of early cardiac hyperdynamics in NIDC is not *per se* in contrast to most previous studies but rather a complementary idea regarding an earlier phase in the evolvement of diabetic cardiomyopathy that has not been illuminated well to date.

This hypothesis is deduced from findings from a clinical study utilizing quantitative stress echocardiography on normotensive pediatric patients with uncomplicated type 1 DM and a short disease duration (4 ± 3.5 years; mean ± standard deviation) [16]. Children and adolescents with uncomplicated diabetes may serve as an ideal model to study the effects of diabetic metabolic conditions on myocardial contractility in the absence of potentially confounding ischemic events. Strikingly, type 1 DM patients exhibited overall increased longitudinal and circumferential left ventricular (LV) myocardial contractility both at rest and during stress testing when compared to sex- and age-matched healthy controls. This *prima facie* paradoxical hypercontractile phase may represent the DM-associated impaired mechanical efficiency long before the well-known long-term deterioration of myocardial function becomes evident. Several human and animal model studies spotlighting early stages of NIDC are in favor of this hypothesis.

Consequences of the hypothesis and discussion

Evidence for early cardiac dysfunction in diabetic metabolism

In an echocardiography-based study, Christiansen et al. found increased myocardial contractility in insulin-dependent DM patients with normoalbuminuria and a return to normal levels when microalbuminuria developed [17]. The study reports an inverse correlation of myocardial contractility and renal plasma flow in the diabetic cohort with a mean disease duration of 14 ± 4 years. Finally, the authors reason myocardial hypercontractility as a probable explanation for the development of diabetic nephropathy. This is in accordance with two echocardiographic studies by Grøtzsche et al. using M-mode and Doppler imaging to demonstrate increased LV contractility in diabetic children without nephropathy, arterial hypertension or ischemic heart disease [18,19]. In a tagged MRI study young adults with tightly controlled type 1 DM were found to have increased LV torsion despite preserved levels of ejection fraction and both longitudinal and circumferential shortening [20]. In a similar study using tagged MRI in young adults with uncomplicated type 1 DM, Shivu et al. reported hyperdynamic LV twist mechanics coexistent with altered myocardial perfusion [21]. Furthermore, utilizing stress MRI spectroscopy in young adults with uncomplicated type 1 DM, a reduced phosphocreatine/γ-ATP ratio independent of coronary microvascular function was found and interpreted as a sign of DM-induced altered myocardial energetics [22].

Diastolic function has been shown to be impaired in animal models [23–25] as well as in human MRI-based [26] and echocardiographic studies in children [27] and adult [22,28–31] patients with DM type 1 [22,27,31] and type 2 [28,29]. The clinical relevance and the underlying mechanisms of diabetes-associated LV diastolic impairment have yet to be determined in further studies.

The hypothesis of hyperdynamic myocardial contractility early in the course of DM is in agreement with findings from animal model studies in leptin receptor-deficient mice utilizing *in vivo* catheterization. Diabetes-associated LV hypercontractility was demonstrated and regarded as an indicator of altered myocardial substrate use and reduced myocardial efficiency in hyperglycemic metabolism. Similar to the above described finding of transient myocardial hypercontractility in pediatric patients with type 1 DM, the phenomenon occurred initially and slightly faded thereafter [32]. In addition, Van den Bergh et al. described increased preload and decreased afterload in association with increased ventriculo-arterial coupling and impaired mechanical efficiency in the same mouse model [33].

Moreover, several other animal model studies are in accordance with the observation of diabetes-associated alterations in myocardial performance. Probable underlying pathophysiologic mechanisms include impaired mitochondrial metabolism [34], activation of the renin-angiotensin system [35], formation of advanced glycosylation end products and impaired collagen cross-linking [36], loss of t-tubule structure [12], impaired calcium sequestration of the sarcoplasmatic reticulum [37], and various other metabolic disturbances [9,38].

In an experimental study utilizing isolated ventricular myocytes from type 1 diabetic OVE26 mice and from type 2 diabetic db/db mice, Kralik et al. reported significant impairment in contractility, a differentially reduced calcium decay rate (50% in type 1 and 20% in type 2 diabetic myocytes), and a decrease in cardiac content of the SERCA2a calcium pump in OVE26 diabetic myocytes. Furthermore, the reduction of SERCA2a in OVE26 myocytes was completely rescued by overexpression of the antioxidant protein metallothionein, rendering oxidative stress an important component of diabetic cardiomyopathy [39]. This explains why type 1 DM patients may feature altered myocardial contractility to a different extent and potentially earlier than individuals with type 2 DM.

Temporal evolvement of diabetic cardiomyopathy

Cardiac involvement in patients with DM is discrete early in the course of the disease. Since these subtle myocardial alterations are clinically silent and their accurate diagnostic detection is technically challenging, there is only limited data available regarding this issue. Most studies investigating myocardial performance in DM focus on late(r) stages of the disease and therefore paint a different picture of diabetes-associated myocardial mechanics. It is therefore not surprising that review of the literature – mainly speckle tracking echocardiography studies – largely yields intermediate