Strain, perfusion, and fat in the diabetic heart

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Abstract
Clinical and experimental studies indicate an association between diabetes mellitus and myocardial dysfunction, eventually leading to congestive heart failure irrespective of the presence or absence of arterial hypertension and coronary artery disease. However, myocardial dysfunction due to diabetes mellitus, referred to as “diabetic cardiomyopathy,” is not generally accepted as a distinct clinical entity. Because patients with myocardial dysfunction due to diabetes are at substantially higher risk for life-threatening arrhythmias and death, their early identification is crucial. This review aims to present distinct aspects of diabetic cardiomyopathy and their identification by cardiac magnetic resonance (CMR) techniques. Such noninvasive imaging techniques can aid in the early detection of myocardial dysfunction in diabetes and possibly shed light on the underlying pathophysiologic mechanisms. In this regard, echocardiography is the most widely available and frequently used imaging technique for the assessment of myocardial function in patients with diabetes. However, the diagnostic performance of echocardiography depends on the experience of the operator and the echogenic window of the patients. By contrast, the versatility of CMR allows the assessment of myocardial function, deformation, perfusion, viability, and, if required, metabolism within a single examination and without radiation exposure for the patients. For this reason, CMR represents an attractive alternative for the detection of subtle alterations of myocardial function in diabetic cardiomyopathy, particularly in overweight patients with poor echogenic windows. ■ Heart Metab. 2015;68:15-19

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The prevalence of diabetes mellitus has dramatically increased within the last decades in industrial countries and is expected to further increase in the coming years. In 2013, 381 million people were estimated to suffer from diabetes, and by 2030, this number may nearly double.1 Reasons for this phenomenon are aging populations and lifestyle changes in industrial countries, linked to reduced physical activity and increasing rates of obesity. Diabetes mellitus is associated with a multitude of organ-related complications affecting renal, vascular, brain, retinal, and cardiac functions.

Congestive heart failure as a consequence of diabetes mellitus in the absence of arterial hypertension and coronary artery disease (CAD) is referred to as “diabetic cardiomyopathy.” However, this pathologic condition is not widely accepted as a distinct entity. Rubler et al already described this disease pattern back in 1972. Since then, experimental and clinical data supporting the hypothesis that diabetes can affect myocardial function independently of ischemic heart disease have become available.2 In this regard,
A high proportion of patients with type 2 diabetes mellitus were found to have diastolic dysfunction and heart failure with preserved ejection fraction and without clinically evident CAD. However, the underlying pathophysiologic mechanisms are not yet fully understood. It remains unclear whether diastolic dysfunction is an intrinsic metabolic myocardial disorder with diabetes or whether it is related to impaired microvascular integrity.

Previous observational studies demonstrated that 33% of men and 45% of women with diabetes develop heart failure within 5.5 years of follow-up, independently of CAD and arterial hypertension. Once heart failure is clinically evident in such patients, they exhibit a substantially higher mortality rate compared with patients without diabetes, independent of CAD. Due to the poor prognosis of patients with heart failure and diabetes, it becomes clear that the early diagnosis of subtle myocardial dysfunction is crucial. This becomes even more important since a high number of patients with impaired systolic function and diabetes may not report specific symptoms due to physical inactivity.

Cardiac magnetic resonance for the assessment of myocardial dysfunction with diabetes

Myocardial function and deformation

Altered cardiac function with diabetes is characterized by an initial increase in left ventricular (LV) stiffness and subclinical diastolic dysfunction (for a review, see references 13 and 14). In one of the first cardiac magnetic resonance (CMR) studies, investigating the presence of subclinical myocardial dysfunction in patients with diabetes, Fonseca et al described the presence of impaired systolic and diastolic function by tagged CMR in patients with type 2 diabetes mellitus and preserved LV function. In subsequent clinical studies, patients with type 2 diabetes mellitus exhibited decreased circumferential, radial, and longitudinal systolic strain by CMR displacement encoding with stimulated echoes (DENSE), compared with age-matched control subjects. Recently, these findings were confirmed using strain-encoded (SENC) magnetic resonance imaging, which demonstrated the presence of diastolic dysfunction in patients with diabetes and preserved ejection fraction, independent of impaired myocardial perfusion reserve. Along that line, diastolic dysfunction was present in young patients with type 2 diabetes mellitus, and was associated with diabetes duration and aortic distensibility. Two other studies described paradoxically increased LV torsion in patients with type 1 and type 2 diabetes mellitus, which in both cases was attributed to small-vessel disease and impaired microvascular integrity.

An example of a patient with decreased circumferential systolic strain by CMR tagging is shown in Figure 1. In another patient, SENC demonstrates the presence of normal peak systolic strain, but reduced diastolic strain rate, in a young patient with type 2 diabetes mellitus and preserved ejection fraction (Figure 2). Higher spatial resolution allowing more accurate assessment of diastolic function can be appreciated using SENC.

Myocardial perfusion and fibrosis (LGE and T1 mapping)

A number of studies have demonstrated the presence of reduced myocardial perfusion reserve (MPR) during
adenosine-stress CMR in patients with type 2 and long-term (>10 years) type 1 diabetes mellitus.\(^{17,20-22}\) Along that line, decreased MPR was previously reported in patients with type 1 diabetes mellitus and autonomic neuropathy.\(^{23}\) However, two further studies failed to demonstrate reduced MPR in asymptomatic patients with diabetes mellitus,\(^{18,24}\) indicating that microvascular dysfunction may be a relatively late phenomenon and may therefore not be the primary underlying mechanism for the development of diastolic dysfunction, which obviously occurs earlier in the disease.

An example of an asymptomatic patient with type 2 diabetes mellitus and decreased MPR during adenosine stress is shown in Figure 3.

Late gadolinium enhancement (LGE) has been reported to identify occult myocardial scarring indicative of previous infarction in patients with diabetes mellitus and without clinically evident CAD.\(^{17,20-22}\) The identification of such occult scarring was a strong independent predictor of adverse cardiac events. Along that line, infarct-related LGE was described in patients with diabetes and unrecognized CAD, being a robust predictor of cardiac death and myocardial infarction.\(^{25}\)

Limited data exist, on the other hand, about the presence of non-CAD–related LGE in patients with diabetes mellitus and without CAD. Recently, Khan and colleagues demonstrated the presence of non-CAD–related mid-wall LGE in patients with diabetes mellitus.\(^{18}\) An example of a patient with a prominent non-CAD–related mid-wall LGE and type 2 diabetes mellitus and preserved LV function is shown in Figure 3. The prognostic significance of such findings in patients with diabetes remains to be evaluated in future clinical studies.

In contrast to LGE, which is helpful for the detection of regional myocardial fibrosis, modern \(T_1\)-mapping techniques can detect and quantify diffuse myocardial fibrosis, with the \(T_1\) time being inversely related to the degree of myocardial fibrosis by histologic vali-
In this regard, an association between diffuse myocardial fibrosis by T₁ mapping and diastolic dysfunction was demonstrated in asymptomatic type 2 diabetes mellitus patients. Along that line, diffuse fibrosis was reported to be an early sign of cardiomyopathy in patients with type 2 diabetes mellitus in the absence of CAD or regional myocardial scarring, eventually contributing to subclinical diastolic myocardial dysfunction.

**Myocardial triglyceride content**

Increased myocardial triglyceride content, referred to as “myocardial steatosis,” can be noninvasively assessed by cardiac resonance spectroscopy. Several clinical studies have reported the presence of myocardial steatosis in patients with diabetes mellitus. However, the presence of LV dysfunction has been rated differently in these studies. In this regard, McGavock et al reported myocardial steatosis in patients with impaired glucose tolerance and diabetes mellitus in the absence of systolic dysfunction and heart failure symptoms. Conversely, myocardial steatosis was reported to be associated with reduced longitudinal strain and strain rate in men with uncomplicated type 2 diabetes mellitus. Rijzewijk et al, on the other hand, demonstrated diastolic dysfunction in a group of patients with uncomplicated diabetes with myocardial steatosis compared with control subjects. The latter findings are in line with recent observations by our group, which demonstrated an association between myocardial steatosis and diastolic dysfunction by SENC. Cardiac steatosis and diastolic dysfunction seem to develop independently of impaired MPR in an early stage of diabetic disease, while ischemia may aggravate myocardial dysfunction in later stages, as described by Poulsen et al. Subsequently, subclinical diabetic heart disease may advance to systolic dysfunction, and ultimately progress to overt congestive heart failure, arrhythmias, and myocardial infarction. An overview of the mechanisms involved in diabetic heart disease is provided in Figure 5.

**Summary and conclusions**

Diabetes leads to structural changes in the myocardium, which may be described as diabetic heart disease. Diabetic heart disease is characterized by myocardial steatosis and impaired diastolic function in the early stages, and may be accompanied by impaired microvascular integrity and reduced systolic function in later stages of the disease. Despite the fact that impaired diastolic function may be an early marker of myocardial dysfunction with diabetes, the effect of early diagnosis on clinical outcomes still merits further investigation, in light of rather limited options for the effective treatment of such heart failure patients with preserved ejection fraction. In addition, it should be noted that perfusion abnormalities may develop in such patients, independently of the presence or absence of diabetic cardiomyopathy. During clinical manifestation, macrovascular disease and arterial hypertension are also frequently present, so that the relative contribution of myocardial versus vascular disease to the clinical phenotype cannot be discerned. CMR can enable better understanding of diabetic heart disease, through detection of alterations in myocardial function, including increased triglyceride content and impaired relaxation in early stages and...
red}uced myocardial deformation and micro- as well as macrovascular abnormalities in later stages of the disease.

**REFERENCES**


