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Coronary microvascular dysfunction in overt diabetic cardiomyopathy☆,☆☆,★,★★

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ABSTRACT

Background: Diabetic cardiomyopathy is characterized by microvascular disease and interstitial fibrosis, which lead to progressive heart failure; however, its pathogenesis remains uncertain. Perfusion cardiac magnetic resonance (CMR) has been proven efficient to detect subclinical myocardial perfusion reserve abnormalities in context of diabetes type 1 in the absence of epicardial coronary artery disease.
Objective: To evaluate myocardial perfusion reserve in patients with advanced cardiomyopathy and type 2 diabetes mellitus but without obstructive coronary artery disease (DM2). We hypothesized that impaired myocardial perfusion reserve deteriorates as systolic dysfunction progresses.
Method and results: Mean myocardial perfusion relative upslope at rest and during hyperaemia (adenosine 140 mg/kg/min) and mean perfusion reserve index (MPRI), were examined in 11 clinically stable DM2 patients (mean (SD) age 67 (8.4) years, range of 54–83 years; NYHA I–II; EF: 37.4 (11.3) %) using perfusion cardiac magnetic resonance (CMR). They were compared against 16 patients with idiopathic cardiomyopathy (mean age: 62 (14.0) years, range of 37–82 years; NYHA I–II; mean EF: 46 (12.3) %) and 10 healthy volunteers with normal ECG and no evidence of cardiac disease (mean age 35 (11.2) years, range of 27–66 years; mean EF: 65 (5.1) %).
DM2 patients had lower hyperemic perfusion relative upslope (0.2 (0.07) v. 0.31 (0.04) $p = 0.001$) and MPRI (0.736 (0.233) v. 2.35 (0.284), $p = 0.001$) compared to healthy subjects. Results of DM2 and DCM patients were similar. MPRI in DM2 patents with moderate LV dysfunction was not different from patients with severe dysfunction.
Conclusion: In patients with DM2 myocardial perfusion reserve is markedly decreased, suggestive of microvascular disease. In this small cohort MPRI impairment did not correlate to the LV EF deterioration.

1. Introduction

Diabetic cardiomyopathy describes the presence of impaired function in the absence of CAD or hypertension, in patients with a background of diabetes. It represents a complex cardiac disorder with involvement of myocardial, interstitial, coronary and neural alterations [1]. Previous studies have shown that subclinical abnormalities of functional indices of diastolic dysfunction and myocardial thickening and more rarely of systolic dysfunction of both cardiac ventricles in diabetes occur in the early stages of the disease [2,3].

Impaired myocardial perfusion reserve in diabetic heart disease, suggestive of microvascular dysfunction, has been previously described. Microvascular dysfunction in diabetes is a multifactorial phenomenon, related to anatomical but also functional properties alterations of the myocardium. Animal and human experimental studies have identified

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★★ Author contributions: KB wrote the manuscript and researched data. NC participated in the design of the study and performed the statistical analysis. JT, JN, KA, IF, CS, AC, EN and SM conceived of the study, and participated in its design and coordination and reviewed/edited the manuscript. All authors read and approved the final manuscript.
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Table 1
Clinical and CMR characteristics of patients and controls.

Parameters	DM2 (n = 11)	DCM (n = 16)	Normal (n = 10)
Age, years (SD)	67 (8.4)	62 (14.0)	35 (11.2)
Gender, male (%)	7 (64)	11 (69)	5 (50)
NYHA (I/II/III/IV)	6/5/0/0	11/5/0/0	–
Angiography (any coronary lesion)	0	0	0
Hypertension	0	0	0
Type 2 diabetes mellitus	11/11	0	0
Microalbuminuria	6/11	5/16	0
Treatment			
Beta-blocker	11/11	16/16	0
ACE/ARB	11/11	16/16	0
MR antagonist	3/11	3/16	0
Ivabradine	0	0	0
Oral hypoglycemic	10/11	0	0
Insulin	1/11	0	0
Function			
LVEF (%)	37.4 (11.3)	46 (12.3)	65 (5.1)*
LVEDV (ml)	207.3 (56.5)	195 (47.7)	135 (18.0)*
LVESV (ml)	133 (51.2)	110 (44.1)	50 (10)*
RVEF (%)	53.4 (14.0)	45.7 (14.8)	64 (11.7)
RVEDV (ml)	122.3 (45.1)	139.2 (40.1)	169.4 (80.1)
RVESV (ml)	55.8 (22.1)	51.4 (23.8)	93.0 (54.0)
LV mass	137.4 (35.7)	135 (44.0)	93 (6)*
Myocardial perfusion			
Inducible visual defect	0	0	0
Stress relative upslope	0.19 (0.03)	0.18 (0.07)	0.31 (0.04)**
Rest relative upslope	0.27 (0.10)	0.26 (0.17)	0.14 (0.03)$
MPRI	0.736 (0.233)	0.844 (0.354)	2.35 (0.284)**
LGE+	0	0	0

Data are expressed as mean (SD) unless otherwise specified.
ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CMR: cardiac magnetic resonance, DM2: type 2 diabetic cardiomyopathy, DCM: idiopathic dilated cardiomyopathy, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic function, LGE: late gadolinium enhancement, MPRI: mean perfusion reserve index, MR: mineralocorticoid receptor, NYHA: New York Heart Association Classification, RVEF: right ventricular ejection fraction, RVEDV: right ventricular end diastolic function, RVESV: right ventricular end systolic function, and SD: standard deviation.
$ $p < 0.1$.
* $p < 0.05$.
** $p < 0.01$.

changes consistent with diabetic cardiomyopathy including perivascular and interstitial fibrosis [4], myocardial hypertrophy [5] and endothelial proliferation with fibrosis in small coronary arteries and subsequent impaired perfusion reserve [6]. Impaired myocardial perfusion reserve in diabetes has been related to the level of autonomic neuropathy [7,8] and diastolic dysfunction [9]. Current evidence on the perfusion pattern of the diabetic myocardium in the advanced stages of the disease, where overt global systolic function has been established, is poor.

We aimed to evaluate myocardial perfusion patterns in a cohort of type 2 diabetic cardiomyopathy patients with overt systolic dysfunction with the use of adenosine perfusion CMR and compare them against normal controls and patients with idiopathic dilated cardiomyopathy, defining a control group with known microvascular dysfunction and absence of comorbidities. We hypothesized that impaired myocardial perfusion reserve deteriorates as systolic dysfunction progresses. To our knowledge, this is the first study to examine myocardial perfusion pattern in the advanced stages of the disease.

2. Methods

2.1. Patients and controls

The study was conducted between September 2009 and December 2012 at Hippokration Hospital, Athens and St Thomas' Hospital, London. Consecutive patients meeting the WHO criteria for type 2 diabetes mellitus [10] and AHA echocardiographic criteria for LV systolic dysfunction (left ventricle end diastolic diameter (LVEDV) >31 mm/m^2 in men, >32 mm/m^2 in women or LEFV < 45%) [11], without history of hypertension, valvular disease or epicardial CAD (defined by a normal angiogram, less than 1 month prior to CMR exam) were invited to participate. Despite the rather stringent criteria for a population of severely diseased diabetic patients, participants with microalbuminuria (but normal renal function) were included in the study. Exclusion criteria were known contraindications for CMR or adenosine administration. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Informed consent was obtained from each patient.

2.2. CMR protocol

All patients and controls underwent CMR at 1.5-T field strength using electrocardiographic gating and a 32-channel phased-array coil. ECG-gated 2D steady-state free precession sequences were applied to assess function in 2-chamber, 3-chamber, 4-chamber and short-axis views. Turbo fast low-angle shot sequences (in-plane spatial resolution: 2.5 * 2.5 * 10 mm) were used to evaluate myocardial first-pass perfusion in 3 short-axis slices during intravenous contrast medium infusion (gadolinium at a dose of 0.1 mmol/kg body weight) with adenosine (140 mg/kg/h), and at rest, after a 15-minute interval. After 10 min, inversion recovery turbo fast low-angle shot was performed in 2-chamber, 3-chamber, 4-chamber, and short-axis views to assess fibrosis. Arterial blood pressure was recorded by an automatic cuff sphygmomanometer at one-minute intervals and the ECG was monitored continuously throughout the adenosine infusion period. The mean duration of the examination was 60 min.

2.3. CMR image analysis

CMR studies were analyzed by 2 cardiologists, who were blinded to the patient details (KB, SM). The standard cine SSFP short axis was used