Cardiac perfusion, structure, and function in type 2 diabetes mellitus with and without diabetic complications

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Title: Cardiac perfusion, structure and function in type 2 diabetes mellitus with and without diabetic complications

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Abstract:

Aims: Coronary microvascular disease (CMD) is a known complication in type 2 diabetes (T2DM). We examined the relationship between diabetic complications, left ventricular (LV) function and structure and myocardial perfusion reserve (MPR) as indicators of CMD in patients with T2DM and control subjects.

Methods and results: This was a cross-sectional study of 193 patients with T2DM and 25 controls subjects. Patients were grouped as uncomplicated diabetes (n=71) and diabetes with complications (albuminuria, retinopathy, autonomic neuropathy). LV structure, function, adenosine stress and rest myocardial perfusion were evaluated by cardiovascular magnetic resonance. Echocardiography was used to evaluate diastolic function. Patients with uncomplicated T2DM did not have significantly different LV mass and E/e* but decreased MPR (3.8±1.0 vs 5.1±1.5, P<0.05) compared to controls. T2DM patients with albuminuria and retinopathy had decreased MPR (albuminuria: 2.4±0.9 and retinopathy 2.6±0.7 vs. 3.8±1.0, P<0.05 for both) compared to uncomplicated T2DM patients, along with significantly higher LV mass (149±39 and 147±40 vs 126±33g, P<0.05) and E/e* (8.3±2.8 and 8.1±2.2 vs. 7.0±2.5, P<0.05). When entered in a multiple regression model, reduced MPR was associated with increasing E/e* and albuminuria and retinopathy were associated with reduced MPR.

Conclusions: Patients with uncomplicated T2DM have reduced MPR compared to control subjects, despite equivalent LV mass and E/e*. T2DM patients with albuminuria or retinopathy have reduced MPR and increased LV mass and E/e* compared to patients with uncomplicated T2DM. E/e* and MPR are significantly associated after adjustment for age, hypertension and LV mass, suggesting a link between CMD and cardiac diastolic function.

Key words: Diabetes, myocardial perfusion reserve, albuminuria, retinopathy, cardiovascular magnetic resonance imaging, diastolic dysfunction

Clinical trial registration: https://www.clinicaltrials.org. Unique identifier: NCT02684331
**Introduction**

In patients with type 2 diabetes mellitus (T2DM) the risk of heart disease is twice as high at any age compared to those without T2DM and the risk of death from cardiovascular causes is increased two- to six-fold\(^1\). Furthermore, the risk of developing heart failure is increased two-fold in men and five-fold in women with T2DM\(^2\). This increased risk of heart failure can in part be explained by the increased prevalence of coronary artery disease (CAD) in T2DM\(^3\). However, the incidence of non-ischemic heart failure is also greatly increased in T2DM which suggests the existence of a specific diabetic cardiomyopathy characterized by left ventricular hypertrophy and diastolic dysfunction\(^4,5\). Many theories of the mechanism responsible for this diabetic cardiomyopathy and how T2DM can lead to heart failure in the absence of CAD exist, but so far the exact mechanism remains unclear. Among the hypotheses is intramyocardial microangiopathy causing reduced coronary blood flow and impaired myocardial perfusion\(^6,7\). Reduced myocardial perfusion has previously been described in diabetic patients\(^8\) and is linked to the presence of endothelial dysfunction\(^9\). Endothelial dysfunction, often seen early in individuals who develop atherosclerosis\(^10\) is also associated with the diabetic complications retinopathy and microalbuminuria\(^10\) which independently predict development of cardiovascular disease and cardiovascular death in T2DM\(^11\).

Myocardial perfusion can be accurately measured and quantified using cardiovascular magnetic resonance (CMR). CMR also allows detailed assessment of myocardial structure and function. In this study, we investigated the association between myocardial perfusion reserve (MPR) by CMR and diabetic complications as well as left ventricular structure and function in a large cohort of patients with T2DM and control subjects without T2DM.
Methods

Study population

The study complies with the declaration of Helsinki and was approved by the local ethics committee (SJ-490). All participants gave written, informed consent. Participants were recruited from the outpatient clinic at the Department of Endocrinology at NSR Hospital, Region Zealand, Denmark from January 2016 to March 2018. Patients aged 18-80 diagnosed with T2DM for at least 3 months were eligible to participate in the study. Exclusion criteria were: permanent atrial fibrillation, eGFR<30 ml/min/1.73m^2, contraindications to adenosine or MRI. Patients with previous coronary artery bypass surgery, typical anginal chest pains or angina equivalents were excluded. In addition, 25 age and sex matched control subjects without T2DM (HbA1c<40 mmol/mol) or known CAD (negative history of myocardial infarction, percutaneous coronary intervention (PCI) or CABG and the absence of typical symptoms or ischaemic lesions on late gadolinium enhancement (LGE) images) were included in the study. Control subjects were allowed to receive treatment for hypertension and hypercholesterolemia.

Study design

The study was designed as a cross-sectional survey. All participants underwent echocardiography, clinical examination, electrocardiography (ECG), and CMR. Blood and urinary sampling was performed prior to CMR. History of diabetic complications, hypertension, CAD and medication was retrieved from the electronic patient journal or from the patients themselves. Hypertension was defined as a resting blood pressure >140/90 mmHg, an active prescription of antihypertensive medication or a positive confirmation from the patient. CAD was defined as previous myocardial infarction, PCI, angiographically verified coronary stenosis or ischaemic lesions on LGE images. Autonomic nervous function was evaluated from beat-to-beat variation and orthostatic blood pressure measurements at ½, 1½, 3, 5 and 7 minutes after standing up. Patients with a drop in
systolic blood pressure >25 mmHg or more in any of the measurements\textsuperscript{12} or a beat-to-beat variation <4 beats/min\textsuperscript{13} were diagnosed with autonomic neuropathy. Albuminuria was defined as a urinary albumin/creatinine ratio (ACR) >30 mg/day and retinopathy was evaluated as present or absent from the patients’ latest fundus photography, routinely performed in the diabetes outpatient clinic. For subgroup analysis, albuminuria was divided into micro- (ACR 30-300 mg/day) and macroalbuminuria (ACR>300 mg/day) and retinopathy into simplex- and severe retinopathy (maculopathy, proliferative retinopathy and previous laser photocoagulation).

**CMR Protocol**

All participants refrained from caffeine consumption for 24 hours prior to the scan. CMR was performed on a 1.5T scanner (Siemens Avanto) with spine- and surface coil, ECG gating and patients in the supine position. Anatomical images were acquired during breath-hold. Following scout images left ventricular (LV) and left atrial (LA) function was evaluated from a cardiac short axis stack (steady-state in free precession cine imaging) covering the entire heart from the pulmonary arteries to the apex of the heart (TR/TE/flip angle 49.81/1.25/80°, slice thickness 8 mm, interslice gap 2 mm, matrix 168x208, spatial resolution 1.6x1.6 mm, 25 phases per heartbeat).

Myocardial perfusion images were obtained from 3 short-axis slices (basal, mid-ventricular and apical) using a saturation recovery pulse sequence with spoiled gradient echo readout (TR/TE/flip angle 162.25/1.1/12°, slice thickness 10 mm, spatial resolution 2.4x2.4 mm, matrix 144x160, FOV 342x380 mm). Myocardial perfusion was determined during adenosine stress (IV infusion; 140 \( \mu \)g/kg/min) administered for 3 minutes prior to and during the stress scan and repeated >10 minutes later during rest. 0.075 mmol/kg of gadobutrol (Gadovist\textsuperscript{®}, Bayer AG, Germany) was administered at a rate of 5 ml/s followed by 20 ml of saline for both stress and rest perfusion imaging.
T$_1$ maps were acquired during breath-hold in 3 short-axis slices matching the slice position of the perfusion sequences, using a Shortened Modified Look-Locker Inversion recovery (ShMOLLI) sequence (TR/TE/flip angle 279.8/1.13/35°, slice thickness 8 mm, spatial resolution 1.98x1.98 mm, matrix 144x256). Native T$_1$ mapping was performed prior to the stress perfusion sequence and post-contrast T$_1$ mapping was carried out a minimum of 10 minutes after the first contrast injection and just before the rest perfusion sequence.

Three minutes after the second contrast injection TI-scout images were performed to determine inversion time at which myocardial signal was nulled. LGE images were acquired in the full LV short axis stack and the 2-, 3- and 4-chamber views using a phase sensitive inversion recovery reconstruction sequence (TR/TE/flip angle 4.5/2.2/30°, slice thickness 8 mm, gap 2 mm, matrix 256x256, FOV 340x340 mm). LGE was considered positive if present in 2 or more views. If needed, inversion time was adjusted as the study progressed to maintain nulled myocardium and acquisitions with artefacts (breathing, moving, wrap) were repeated.

**CMR data analysis**

LV volumes, mass and ejection fraction were calculated with cmr42© (Circle Cardiovascular Imaging Inc., Calgary Canada, v. 5.5.1) by semiautomatic tracing of the endocardial and epicardial contours in end diastolic and end systolic phases. LA max volume was manually traced in the LV end systolic frame.

Quantification of myocardial blood flow (MBF) was performed for the mid-slice perfusion data using an in-house tool developed in MATLAB 2015b (MathWorks, Nattick, MA, USA). Mid-slice perfusion images were divided into 6 segments based on the American Heart Association 17-segment model and additional regions were drawn in the LV blood pool in both the perfusion images and T$_1$ map. The non-linear response of signal intensity to contrast agent concentration was corrected for based on the baseline signal intensity and T$_1$ data$^{14}$. Data were cropped to the end of
the first-pass and Fermi-constrained deconvolution\textsuperscript{15} was performed to yield segmental MBF estimates. MPR was calculating by dividing MBF during stress with MBF during rest.

Hyperenancement in LGE was deemed positive if present in two or more projections. Myocardial segments with LGE or visually significant perfusion defects (figure 2) were excluded from the quantitative blood flow analysis.

Echocardiography

Echocardiography was performed on a GE healthcare Vivid E9 cardiovascular ultrasound system, using a GE Vivid S5 probe. LV diastolic function was evaluated in the apical 4-chamber view. Peak E was defined as the highest early mitral inflow velocity and measured by placing a pulse wave Doppler across the mitral valve. Septal and lateral mitral annular motion (e*) was measured using tissue Doppler imaging and by placing a pulse wave Doppler in the lateral and septal mitral annulus. Average E/e* was calculated as the mean of the lateral and septal E/e*.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as absolute values and percentages. Unpaired student’s t-test was used to compare continuous variables and categorical variables were compared using the $\chi^2$-test or Fishers exact test as appropriate. Univariable correlations were performed to identify predictors of reduced MPR and E/e*. Variables significant at a 10\% level were included in a backwards stepwise multivariable analysis based on a linear regression model. A two-tailed p-value <0.05 was considered statistically significant. All calculations were made in SAS Enterprise Guide v. 7.15 (SAS Institute inc., Cary, NC, USA)

Results

A total of 423 T2DM patients were approached of whom 95 declined participation. Eighty-one patients had one or more exclusion criteria leaving 247 patients eligible to participate. Forty-five
patients had incomplete CMR studies for a variety of reasons (fig. 1). Nine patients had scans of insufficient quality for quantitative perfusion analysis. In total, 193 patients with T2DM and 25 controls were included in the final analysis. Of the 193 patients with T2DM, 70 had albuminuria, 54 had retinopathy and 49 had autonomic neuropathy. Seventy-one patients had no complications.

Characteristics of the study groups are shown in table 1. Patients with T2DM had a higher BMI (31.1±4.6 vs 25.1±3.3 kg/m², P<0.05) and resting heart rate (72±12 vs. 59±10 BPM, P<0.05) than control subjects. CAD (13 vs. 0%, P<0.05) and hypertension (69 vs. 16%, P<0.05) were more prevalent in the group of patients with T2DM and patients also had higher HbA1c (63±15 vs. 35±3 mmol/mol, P<0.05) and lower LDL cholesterol (2.0±0.9 vs. 2.9±1.0 mmol/L, P<0.05) and total cholesterol (4.3±1.1 vs. 5.1±1.2 mmol/L, P<0.05) compared to controls. There were no significant differences between patients with T2DM and controls for age, sex, smoking history and serum creatinine.

Patients with albuminuria, retinopathy or autonomic neuropathy had a higher prevalence of hypertension (83, 78 and 82 vs. 55%, P<0.05) and angiotensin converting enzyme inhibitor/angiotensin-II receptor blocker (ACE-i/ARB) usage (89, 87 and 88 vs. 59%, P<0.05) compared to patients without these complications. The proportion of males was higher in patients with albuminuria and retinopathy (83 and 81 vs. 59%, P<0.05) compared to patients without complications. Furthermore, patients with albuminuria had a higher serum creatinine (85±31 vs. 73±21 µmol/L, P<0.05) and more often had a history of tobacco usage (83 vs 59%, P<0.05).

Patients with retinopathy and autonomic neuropathy had a longer history of diabetes (17±8 and 15±8 vs. 11±7 years, P<0.05) and a higher prevalence of exogenous insulin usage (78 and 67 vs. 48%, P<0.05) compared to patients without complications. No significant differences in age, BMI, systolic blood pressure, resting HR, prevalence of CAD, HbA1c or lipid status were observed between patients with and without diabetic complications.
LV structure and function

There were no significant differences in end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV), ejection fraction (EF) or LA max volume between any of the groups. LV mass (138±38 vs. 121±25 g, P<0.05) and average E/e* (7.8±2.8 vs. 6.6±1.5, P<0.05) were higher in patients with T2DM compared to controls. Patients with albuminuria, retinopathy and autonomic neuropathy had higher LV mass (149±39, 147±40 and 144±40 vs. 126±33 g, P<0.05) and average E/e* (8.3±2.8, 8.1±2.2 and 8.6±2.8 vs. 7.0±2.5, P<0.05) compared to patients without complications. We observed no significant differences in LV mass or E/e* between control subjects and patients without complications (table 2).

Myocardial perfusion reserve

Patients with T2DM had higher rest MBF (0.81±0.19 vs. 0.63±0.12 ml/min/g, P<0.05) and lower stress MBF (2.41±0.9 vs. 3.11±0.81 ml/min/g, P<0.05) resulting in an overall decrease in MPR in patients with diabetes compared to controls (3.0±1.2 vs. 5.1±1.5, P<0.05). Patients with albuminuria, retinopathy and autonomic neuropathy had lower MPR compared to patients without complications (2.4±0.9, 2.6±0.7 and 2.6±0.9 vs. 3.8±1.0, P<0.05), who in turn had lower MPR than controls (3.8±1.0 vs. 5.1±1.5, P<0.05)(table 2).

When MPR was differentiated on the degree of albuminuria and retinopathy (fig. 3), MPR was significantly lower in patients with micro- or macroalbuminuria compared with normoalbuminuric patients (2.5±1.0 and 2.1±0.7 vs. 3.4±1.1, P<0.05), but there was no significant difference in MPR between patients with micro- and macroalbuminuria. Patients with severe retinopathy had significantly lower MPR compared to patients without retinopathy (2.4±0.7 vs. 3.2±1.2, P<0.05), however, simplex retinopathy was not significantly associated with decreased MPR.
Increased urinary albumin/creatinine ratio was significantly correlated with decreased MPR (P=0.001).

**Multiple regression analysis**

In the univariate regression analysis, age, diabetes duration, HbA1c, albuminuria, retinopathy, autonomic neuropathy, CAD, hypertension, LV mass and smoking were correlated with reduced MPR. In the multivariate analysis, age (P=0.004), albuminuria (P<0.001), retinopathy (P=0.002) and hypertension (P=0.01) were significantly associated with reduced MPR. Age, diabetes duration, MPR, albuminuria, autonomic neuropathy and hypertension and LV mass were correlated with increased E/e* in the univariate analysis. In the multivariate analysis, age (P=0.001), hypertension (P=0.04) and MPR (P=0.01) were significantly associated with increased E/e* (table 3).

**Discussion**

We demonstrated that uncomplicated T2DM is associated with reduced MPR and that reduced MPR significantly correlates with increased E/e* as an echocardiographic measure of diastolic function. The relation between MPR and E/e* remained significant even after multiple adjustment of variables known to affect diastolic function. Furthermore, we found that T2DM complicated with albuminuria or retinopathy – both related to renal and retinal microvascular disease – is associated with an even greater reduction in MPR compared to uncomplicated diabetes.

Previously, reduced MPR has been shown to be caused by changes in either rest- or stress MBF exclusively, however, in our cohort of T2DM patients MPR was decreased due to a combination of increased basal MBF and a decrease in maximal MBF during stress. The most obvious explanation for this could be differences in prevalence of micro- and macrovascular complications in our study population compared to previously reported data. Furthermore, with our control groups rest- and stress MBF being in the lower and higher end respectively of what has
previously been observed, may explain why the MPR in our study is slightly higher than reported in past literature.

Our findings are consistent with a recent observational study using Positron Emission Tomography by Potier et al. who demonstrated that micro- and macroalbuminuria in T2DM were associated with a three- and eight-fold increased risk of impaired MPR respectively, even after adjustment for known cardiovascular confounders. Interestingly, this previous study showed no difference in MPR between control subjects and normoalbuminuric patients with T2DM which contrasts the findings in our study. We observed a reduction in MPR in both patients with micro- and macroalbuminuria compared to controls. We also observed a trend towards reduced MPR in patients with macroalbuminuria compared to patients with microalbuminuria but the difference was not significant. We did find a significant inverse correlation between ACR as a continuous variable and MPR, but, due to our exclusion criteria (eGFR<30 ml/min/1.73m²) we only had 12 patients with macroalbuminuria. With this in mind, we cannot exclude that the insignificance is caused by a type 2 error.

Reduced flow in the left coronary descending artery has previously been reported in patients with retinopathy. We found a general decrease in MPR in our group of patients with retinopathy mainly driven by decreased MPR in patients with severe retinopathy and to a lesser extent simplex retinopathy. Our results are coherent with previous findings, showing that even early retinal changes in T2DM is associated with an increased risk of CAD and cardiovascular death and that the risk of incident cardiovascular disease increases even further as retinal changes became more severe.

Another diabetic complication previously associated with reduced coronary flow reserve is autonomic neuropathy. We did find reduced MPR in our group of patients with autonomic neuropathy, but, in the multiple regression model autonomic neuropathy was not associated with
reduced MPR which may be explained by some patients having multiple complications and albuminuria and retinopathy being stronger predictors.

Elevated HbA1c is a known cardiovascular risk factor and previous research has shown that a 1% reduction in HbA1c reduces the risk of both macro- and microvascular disease by 21% and 37% respectively\(^3\), however, the reduction in microvascular disease was mainly driven by reductions in retinal photocoagulation and to a lesser extent microalbuminuria. Accordingly, the importance of optimizing glycaemic control to prevent coronary microvascular disease is still debated. We found no association between HbA1c and MPR, however, a previous small study of 24 patients with T2DM showed that the prevalence of coronary microvascular disease was doubled in patients with HbA1c above 54 mmol/mol\(^27\). An explanation for this discrepancy could be that HbA1c may not be a good indicator of long term glycaemic control in an observational study such as ours, as the HbA1c at the time of the CMR scan only reflects glycaemic control for the past 3-4 months. Another possible explanation for the divergent results is statistical errors in the relatively modest sample size of 24 patients in the previous study. Increased diabetes duration, which has previously been shown to be a strong predictor of microvascular events\(^28\), was not significantly associated with reduced MPR in our study. However, the time between disease onset and diagnosis of T2DM can vary significantly which may contribute to the uncertainty of the variable.

Ageing\(^30\), hypertension\(^17\) and diabetes\(^31\) are all associated with increased risk of LV diastolic dysfunction and in the present study we demonstrated that these variables were also associated with reduced MPR. In addition, increasing age, hypertension and reduced MPR were found to be associated with increasing E/e* as a sign of diastolic dysfunction. A similar study was conducted by Korosglou et al.\(^32\) which reported no association between myocardial perfusion and diastolic function. However, no information about the diabetic complication status of their study population was presented in this previous report and the number of patients with uncomplicated diabetes, in
which we also found diastolic function comparable to that of our control group, may have been higher in their sample. We found the lowest MPR, increased E/e* and LV mass in our patients with diabetic complications which corroborates the findings of a previous albeit smaller study comparing LV structure and diastolic function with the presence of microalbuminuria.

Although the observational design of our study precludes us from commenting on the timing of events, our findings suggest that albuminuria and retinopathy are not only indicators of single organ disease, but also more widespread vascular dysfunction with a strong association between diabetic complications in the heart and other organs. This, together with previous research, where coronary microvascular disease has been associated with heart failure with preserved ejection fraction, indicates that microvascular abnormalities should be considered as an early change in diabetic cardiomyopathy and an important contributor to developing heart failure in T2DM. Therefore, to further understand the role of coronary microvascular disease in diabetic cardiomyopathy, future prospective studies need to evaluate how reductions in MPR affect cardiac function and if interventions aimed at increasing MPR can prevent the development of heart failure in patients with T2DM.

**Conclusions**

MPR is reduced in patients with uncomplicated T2DM compared to control subjects without T2DM and patients with T2DM complicated with albuminuria or retinopathy have increased LV mass, impaired diastolic function and reduced MPR compared to patients with uncomplicated T2DM. Reduced MPR is significantly associated with increased average E/e* and the association remains significant when adjusted for age and hypertension, suggesting a link between coronary microvascular disease and cardiac diastolic function.
Limitations

The cross-sectional design of our study itself is a limitation as we are unable to conclude on causality. Presence of epicardial coronary stenosis in our study cohort was excluded by the absence of typical symptoms, no LGE on CMR scan or no previous history of CAD and coronary angiography was not routinely undertaken. That being said, CMR has shown to have both excellent sensitivity and specificity in detecting functionally significant CAD\textsuperscript{35} and any significant coronary stenosis would most likely have been exposed during the stress perfusion scan. However, any non-significant stenosis with a minimal flow limitation or a coronary artery system with balanced ischaemia would not be detected and as such we cannot exclude this as a confounding factor. We found a significant correlation between CAD and MPR in a univariable analysis, but, the correlation dissipated after further adjustment in the multivariable analysis, which may be due to our relatively modest amount of patients with established CAD. The three patient groups with diabetic complications had a higher consumption of ACE-i/ARB compared to the group with uncomplicated diabetes, which may be explained by the higher prevalence of hypertension or perhaps due to previously recognized microalbuminuria now in remission due to ACE-i/ARB treatment. Our results may have been influenced by this, but according to the findings of Hesse et al.\textsuperscript{21} MPR would have been expected to improve in patients treated with ACE-i/ARB.

Supplementary data

Subgroup analysis of patients with and without LGE (table S1) and patients with CAD with and without LGE (table S2). Observer variability analysis and baseline characteristics of patients who completed the full CMR scan compared to patients whose CMR scan was of insufficient quality or terminated prematurely (table S3).
Acknowledgements

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Conflicts of interest: none declared
References


magnetic resonance myocardial perfusion imaging with fractional flow reserve for the
# Text tables

## Table 1: Clinical characteristics of study population

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<th>Patients with T2DM</th>
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Data presented as mean±SD or as nominal values. Percentage of nominal values in parentheses.

*P<0.05 compared to controls

†P<0.05 compared to no complications
Table 2: Measurements of LV structure, function and perfusion

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<td>LV mass (g)</td>
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<tr>
<td>LA max volume (mL)</td>
<td>99±24</td>
<td>96±25</td>
</tr>
<tr>
<td>Ischaemic LGE</td>
<td>0</td>
<td>17(9)*</td>
</tr>
<tr>
<td>Rest MBF (ml/min/g)</td>
<td>0.63±0.12</td>
<td>0.81±0.19*</td>
</tr>
<tr>
<td>Stress MBF (ml/min/g)</td>
<td>3.11±0.81</td>
<td>2.41±0.9*</td>
</tr>
<tr>
<td>MPR</td>
<td>5.1±1.5</td>
<td>3.0±1.2*</td>
</tr>
<tr>
<td>Average E/e*</td>
<td>6.6±1.5</td>
<td>7.8±2.8*</td>
</tr>
</tbody>
</table>

Data presented as mean±SD or as nominal values

Percentages of nominal values in parentheses

*P<0.05 compared to controls

†P<0.05 compared to no complications
Table 3: Univariable and multivariable regression analysis of patients with T2DM

<table>
<thead>
<tr>
<th></th>
<th>MPR</th>
<th>E/e*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>Beta</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>-0.35</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.17</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI</td>
<td>0.77</td>
<td>-0.02</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>&lt;0.001</td>
<td>-0.25</td>
</tr>
<tr>
<td>MPR</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.18</td>
<td>-0.18</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.02</td>
<td>-0.17</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>&lt;0.001</td>
<td>-0.41</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>&lt;0.001</td>
<td>-0.27</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>0.005</td>
<td>-0.20</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.005</td>
<td>-0.20</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.002</td>
<td>-0.31</td>
</tr>
<tr>
<td>LV mass</td>
<td>0.01</td>
<td>-0.18</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.02</td>
<td>-0.23</td>
</tr>
</tbody>
</table>

Beta and P-values for selected variables. Beta values for the multivariable analysis is only presented for the final model.
**Figure legends**

**Figure 1:**
Consort flow chart of patients included in the study

**Figure 2:**
Sub-endocardial scar visualized by late gadolinium enhancement (A) and coherent sub-endocardial perfusion defect visualized on perfusion sequence (B). Affected myocardial segments were excluded from the quantitative perfusion analysis.

**Figure 3:**
Mean MPR with 95% confidence intervals according to the degree of albuminuria (top) and retinopathy (bottom)
Figures

Figure 1:

Met inclusion criteria (n=423)
- T2DM > 3 months
- Age 18-80
- Informed consent

Respectfully declined participation (n=95)

Excluded (n=81)
- Contraindications to MRI (n=32)
- Atrial fibrillation (n=22)
- eGFR < 30 ml/min/m² (n=20)
- Previous CABG (n=7)

Eligible (n=247)

Scan discontinued due to patient feeling unwell (n=45)
- Claustrophobia
- Back pain
- Side effects to adenosine

Insufficient image quality (n=9)

Patients included (n=193)
Controls included (n=25)
Figure 2:
Figure 3:

![Bar chart showing data for different conditions with statistical significance notes and MPR values.](image)