Global myocardial perfusion and diastolic function are impaired to a similar extent in patients with type 2 diabetes mellitus and in patients with coronary artery disease—evaluation by contrast echocardiography and pulsed tissue Doppler

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Abstract

Aims/hypothesis Using modern echocardiography, we quantified the extent of global myocardial function and perfusion abnormalities in patients with type 2 diabetes and compared this with the hypothetically similar extent of impairments in patients with coronary artery disease (CAD).

Subjects and methods This case–control study (66 patients) compared four age-matched groups: control, type 2 diabetic, CAD, and diabetic subjects with CAD (DCAD) and left ventricular ejection fraction >50%. CAD patients had 1–2 vessel disease. Diastolic and systolic myocardial velocities were assessed with pulsed tissue Doppler. Global myocardial perfusion was assessed with contrast echocardiography as indices of capillary blood volume and myocardial blood flow at maximal vasodilatation. In CAD and DCAD patients, functional and perfusion parameters were additionally assessed in the territory with a normal coronary angiogram

reading, providing a model for comparison with the global data from control and diabetic patients.

Results Comparing diabetic with control subjects, myocardial velocity at early diastole was impaired (8.8 ± 1.8 vs 10.1 ± 1.7 cm/s; $p=0.02$) and correlated inversely with age, HbA_{1c} and pulse pressure ($R^2=0.761$). Capillary blood volume (16.6 ± 5.0 vs $24.4 \pm 4.9\%$) and blood flow (56 ± 35 vs 114 ± 40) were decreased ($p=0.001$). In CAD patients, myocardial velocity at early diastole was similarly decreased ($p=0.02$). CAD and DCAD patients were receiving more cardiovascular preventive therapy for the same extent of impaired global perfusion as in the less extensively treated diabetes group without CAD ($p<0.002$), but had superior perfusion of the ‘normal’ coronary territory than that group ($p<0.05$).

Conclusions/interpretation In patients with diabetes, global diastolic function and myocardial capillary blood volume and blood flow are impaired to the same extent as in patients with CAD. These impairments could form the basis of new therapeutic concepts.

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Tissue Doppler · Type 2 diabetes mellitus

Abbreviations

CAD	coronary artery disease
CBVI	capillary blood volume index
DCAD	type 2 diabetes mellitus combined with coronary artery disease
LV	left ventricular
MBFI	myocardial blood flow index
SI	signal intensity

Va	late diastolic myocardial velocity
Ve	early diastolic myocardial velocity
Vs	systolic myocardial velocity

Introduction

A re-definition of the relationship between type 2 diabetes mellitus and coronary artery disease (CAD) [1] and heart failure is taking place, based on the combined incidence of cardiovascular disease and disturbed glucose metabolism [2, 3]. Indeed, hyperglycaemia is increasingly being recognised as an equivalent to CAD [4]. This raises the question of whether type 2 diabetes in its present definition [5] and CAD stem from common pathophysiological mechanisms. If this is the case, one might expect both diseases to also be associated with similar myocardial disturbances in the essential performances of function and perfusion.

CAD is associated with impaired filling properties of the myocardium and with reduced myocardial perfusion [6, 7]. Both abnormalities have also been observed in patients with type 1 and type 2 diabetes using techniques like traditional echocardiography [8, 9], angiography and positron emission tomography [10–12]. However, there is a lack of evidence-based treatment strategies for these abnormalities in the diabetic heart, probably because the techniques mentioned above are not well suited for sequential studies after pharmacological intervention. However, the recent introduction of tissue Doppler allows serial quantification of systolic and diastolic myocardial function in patients with and without overt heart disease [7, 13, 14], and myocardial contrast echocardiography combined with contrast-specific imaging modalities [15, 16] allows repetitive quantification of myocardial perfusion [17, 18] and capillary blood volume [18–20].

Despite the growth of scientific knowledge of the close relation between CAD and disturbed glucose metabolism, the majority of general practitioners, as well as specialists in internal medicine and diabetes, still consider a patient with type 2 diabetes as a normal cardiac entity, unless there are clinically obvious signs and symptoms. The aim of this study, therefore, was to quantify myocardial function and perfusion abnormalities in the myocardium of patients with type 2 diabetes, who had near-normal glucose metabolism and no symptoms of heart failure, in comparison with patients with established CAD (1–2 vessel disease), with a view to testing the hypothesis that the extent of impairments is similar in both diseases.

Subjects and methods

Subjects

The extent of impairment of global myocardial diastolic function and of global microvascular perfusion was compared in four age-matched groups: control subjects ($n=14$), type 2 diabetic ($n=17$), 1–2 vessel non-diabetic CAD ($n=17$) and type 2 diabetic patients with 1–2 vessel CAD (DCAD) ($n=18$). Accordingly, a total of 66 patients was recruited from outpatients attending the Karolinska hospital: 35 patients with type 2 diabetes and 31 non-diabetic control subjects. Inclusion criteria were: (1) a left ventricular (LV) ejection fraction of $>50\%$ (modified Simpson's method); and (2) sinus rhythm. Exclusion criteria were: microvascular complications, other than mild ones, of type 2 diabetes; CAD with 3 vessel disease; a history of previous myocardial infarction; history of LV failure; valvular heart disease other than mild; malignant hypertension; LV wall thickness >13 mm; obstructive airways disease; hepatic disease, other than mild (alanine aminotransferase >59 U/l); renal disease, other than mild (serum creatinine >130 $\mu\text{mol/l}$); or advanced malignancy. Coronary artery disease, defined as a $>50\%$ reduction of the lumen in the proximal or mid-arterial tree, was assessed by coronary angiography in the 35 patients with CAD and DCAD. It was excluded by coronary angiography in 11 individuals and by traditional stress echocardiography [21] in the 20 remaining subjects who lacked clinical signs and symptoms and a history of coronary disease. We decided to define diabetes in this comparative study as use of antidiabetic medication or a fasting plasma glucose concentration >7.0 mmol/l [5], because this is still a generally employed technique for the screening of diabetes.

Table 1 presents the demographic data, metabolic data, cardiovascular risk factors and cardiac medication in these four groups.

Ethics approval

The Ethics Committee of the Karolinska Hospital, Stockholm, approved the study protocol and all participants gave written informed consent to the study, which was designed in accordance with the Declaration of Helsinki.

Study protocol

Patients were studied after an overnight fast and without their morning medication by blood tests and ultrasound during the morning period. Resting blood pressure was measured to the nearest 2 mmHg with a mercury sphygmomanometer with the patient in the supine position

Table 1 Pertinent patient characteristics in all patients

Characteristic	Control	Diabetes	<i>p</i> value	CAD	<i>p</i> value	DCAD	<i>p</i> value
<i>n</i>	14	17		17		18	
Age (years)	58±7	59±7		60±8		59±8	
Male (%)	71	71		82		88	
BMI (kg/m ²)	27±4	28±4		28±4		29±4	
Hyperlipidaemic (%)	14	43		76 ^a	0.002	67	0.009
Hypertension (%)	21	41		41		58	0.024
Smoker (%)	36	47		29		25	
Beta blocker (%)	15	25		94 ^c	0.001	72 ^c	0.001
ACE inhibitors (%)	8	25		35		28	
Aspirin (%)	23	25		94 ^c	0.001	67 ^b	0.005
Statins (%)	0	38	0.02	76 ^b	0.001	50	0.002
Triglycerides (mmol/l)	1.5±0.6	2.7±2.6		1.8±1.0		1.9±1.3	
Cholesterol (mmol/l)	4.4±0.7	5.2±1.2	0.05	4.7±0.8		4.8±1.0	
HDL (mmol/l)	1.4±0.4	1.0±0.3	0.04	1.3±0.4		1.2±0.4	
LDL (mmol/l)	2.6±0.5	3.1±1.0		2.5±0.7 ^a		2.7±0.7	
Fasting glucose (mmol/l)	5.9±0.6	9.8±2.8	n.a.	6.1±0.5 ^{n.a.}		8.8±2.5	n.a.
HbA _{1c} (%)	5.8±0.4	6.7±1.1	0.007	5.9±0.4 ^b		6.4±1.2	0.04

With the exception of *n*, all values are means±SD. *p* values are from post hoc test and denote significance vs control subjects.

CAD Coronary artery disease, DCAD diabetes with CAD, n.a. not applicable

^a *p*<0.05

^b *p*<0.01

^c *p*<0.001 for significance vs diabetes

after a 5-min rest. Heart rate, blood pressure, ECG and ultrasound were recorded at rest and during hyperaemic stress (dipyridamole 0.84 mg/kg). Two ultrasound systems were placed at either side of the patient and preset for tissue Doppler (System FiVe VingMed; General Electrics, Milwaukee, WI, USA) or myocardial contrast echocardiography (HDI 5000; ATL, Bothell, WA, USA). Myocardial velocity measurement was selected as a parameter of myocardial dysfunction because strain and strain rate were less efficient in assessing diastolic dysfunction in subclinical disease [14, 22]. By nature, myocardial blood flow index (MBFI) and capillary blood volume index (CBVI), as measured by contrast echocardiography, are relative data and do not measure perfusion in ml per gram tissue. They do, however, allow comparative and non-ionising evaluation of myocardial perfusion [16–20].

This study on myocardial function and perfusion compares the effects of type 2 diabetes, as distinct from those of CAD, which is a regional macrovascular disease. Adequate comparison, therefore, must focus on global LV perfusion and function parameters in analogy to the well-accepted assessment of LV ejection fraction. Additionally, the study design acknowledged the regional character of CAD. Thus, according to the inclusion criterion for 1–2 vessel disease, all CAD and DCAD patients had one angiographically normal coronary artery. Accordingly, perfusion data from the three to five segments composing this ‘normal’ territory were averaged to serve as a model for comparison with the

situation in the control and type 2 diabetes groups without macrovascular disease.

Tissue Doppler

Pulsed Doppler myocardial velocity tracings were recorded as previously described [13, 23]. In short, the Doppler sampling gate was consecutively placed at the very basal and the mid position of each wall whilst imaging the apical four-, two- and three-chamber views. Thus, 12 myocardial velocity traces of longitudinal LV function were recorded in the septal, antero-septal, anterior, lateral, posterior and inferior wall. According to individual coronary arterial distribution, these segments were combined to reflect the territories of the coronary arteries. With typical distribution of coronary arteries, the apical septum, anterior septal and anterior segments were ascribed to the left anterior descending artery, basal septum and inferior segments to the right coronary artery, and lateral and posterior segments to the circumflex artery [24]. The following peak velocities were determined from three consecutive cardiac cycles: systolic myocardial velocity (*V_s*), early diastolic myocardial velocity (*V_e*) and late diastolic myocardial velocity (*V_a*). Patient-based global myocardial function was derived as an average value from the 12 regions. Additionally in CAD and DCAD patients, the myocardial velocities of the ‘normal’ coronary territory, as defined by angiography, were averaged from the respective three–five segments as *V_{s, norm}*, *V_{e, norm}* and *V_{a, norm}*.

Myocardial contrast echocardiography

Myocardial contrast echocardiography was performed as recently described [16, 20] using a broadband transducer at 1.77 MHz, pulse inversion grey scale imaging at a mechanical index of 1.2 and an intravenous infusion of the galactose-based contrast agent Levovist (Schering, Berlin, Germany) at 600 mg/min for 7 min. Five end-systolic, triggered, two-dimensional images were recorded at incremental microbubble replenishment times of one, two, three, four, six and eight cardiac cycles in the apical four- and two-chamber view.

Using a dedicated image analysis program (HDI Lab version 1.83; ATL, Bothell, WA, USA), quantitative analysis of the digital images was performed by experienced observers (V. Dounis, H. von Bibra) who were unaware of the patients' clinical data. Background subtracted signal intensity (SI) was measured by densitometry (arbitrary units) in large myocardial regions of interest and in the LV cavity (Fig. 1). The relation between SI and the increasing trigger intervals [17, 20] allowed the calculation of the initial slope, which correlates to flow velocity, and of SI_{plateau} , which correlates to myocardial capillary blood volume. The

Fig. 1 An original example of myocardial perfusion imaging in the four-chamber view demonstrating six large regions of interest encompassing the myocardium for the assessment of global myocardial perfusion parameters as averaged value from all myocardial regions of interest. The signal intensity of these regions of interest is normalised for the instantaneous signal intensity in the left ventricular blood pool

CBVI was calculated as the mean value of SI at six and eight cardiac cycles replenishment time and normalised for the instantaneous signal intensity in the LV blood pool (%). The MBFI was calculated as CBVI multiplied by the initial slope and coronary flow reserve index as the quotient of the respective values during stress and rest. The global perfusion parameters CBVI, flow velocity index and MBFI were averaged from the 12 regions of interest in each patient. Additionally, in the CAD and DCAD individuals, the perfusion parameters $CBVI_{\text{norm}}$, initial slope_{norm} and $MBFI_{\text{norm}}$ were averaged from the segments composing the 'normal' coronary territory.

Statistical methods

Sample size calculation: based on previous results [20, 23], a clinically relevant effect size of 1.5 between two groups was assumed. A sample size of 14 in each group will have 80% power to detect an effect size of 1.5 using a two-group *t*-test with a 0.008 two-sided significance level. The level of significance was reduced according to Bonferroni's correction for multiple testing. Statistical analysis was performed using SPSS version 11.5. Data are expressed as mean $\pm$ standard deviation in text, tables and plots. The four study groups (control, type 2 diabetes, CAD and DCAD) were compared with respect to parameters of myocardial perfusion and function using one-way ANOVA followed by post hoc least squared differences to correct for multiple testing problems. The significance level was set for two-tailed tests at $p=0.05$. Linear regression analysis was performed by least squares fitting. Univariate and multivariate analysis were used in the pooled data to examine correlations between *Ve*, *Vs* or CBVI and potential metabolic predictors of impaired myocardial function or perfusion.

Results

Diabetes characteristics

Demographic data were comparable between type 2 diabetic and DCAD patients (Table 1). The duration of diabetes was 7 ± 8 and 7 ± 6 years in the type 2 diabetic and the DCAD groups. Antidiabetic treatment was insulin in 53 and 42% of patients, respectively, with a mean dose of 38 ± 19 and 41 ± 26 U per day. A subanalysis was performed for type 2 diabetic patients with insulin therapy vs those without insulin therapy and repeated for the pooled type 2 diabetic and DCAD patients, both of which demonstrated similar myocardial function and perfusion parameters for these two subgroups. Metformin was being taken by 29 and 46%, and sulfonylurea by 65 and 63% of the diabetic patients, respectively. Microvascular complications were

mild retinopathy in 29% of patients, mild nephropathy in 12% and mild polyneuropathy in 15%, with no significant difference between the two groups.

Comparison of type 2 diabetes with control

In type 2 diabetes, V_e was reduced ($p=0.02$) at rest and during hyperaemic stress (Table 2, Fig. 2).

At rest, global perfusion parameters were comparable between both groups. At maximal vasodilatation, the global CBVI was significantly lower (Table 2, Fig. 3) in type 2 diabetic patients due to a diminished increase during hyperaemic stress ($p=0.001$). This was associated with a reduction of the indices of myocardial blood flow velocity, myocardial blood flow and coronary flow reserve. With respect to haemodynamic data, pulse pressure was increased ($p=0.05$, Fig. 2), as was the rate-pressure product at stress ($p=0.05$, Table 3).

Comparison of CAD with control

In patients with CAD, V_e was reduced to a similar extent as in type 2 diabetic patients, both in global myocardial function and in the ‘normal’ territory (Fig. 2), at rest and at stress ($p=0.001$). V_s was reduced ($p=0.008$).

At maximal vasodilatation, all indices of global myocardial perfusion were reduced in comparison with control subjects, the reduction being to the same extent as in type 2 diabetic patients (Table 2). In the ‘normal’ territory, however, the indices of regional perfusion were comparable with control subjects (Fig. 3) and superior to global perfusion data in type 2 diabetes ($p=0.03$). Of haemodynamic criteria, heart rate was lower ($p=0.04$) than in control and type 2 diabetic patients. CAD patients had hyperlipidaemia more often ($p=0.009$) and, as could be expected, were using more cardiovascular drugs, e.g. beta blockers ($p=0.001$), aspirin ($p=0.001$), and statins ($p=0.002$; Table 1),

Table 2 Global and regional function and perfusion in the four groups of patients

Parameter		Control	Diabetes	<i>p</i> value	CAD	<i>p</i> value	DCAD	<i>p</i> value
<i>n</i>			14	17		17		18
V_s resting (cm/s)	Global	7.1±1.1	6.5±1.4		6.0±1.1	0.008	6.1±0.8	0.02
	‘Normal’				6.5±1.2		6.6±1.0	
V_s s (cm/s)	Global	7.7±1.4	7.4±1.6		6.9±1.4		6.5±0.9	0.03
	‘Normal’				7.4±1.2		7.3±1.2	
V_e resting (cm/s)	Global	10.1±1.7	8.8±1.8	0.02	7.7±1.2 ^a	0.001	7.6±1.4 ^b	0.001
	‘Normal’				8.1±1.3	0.001	8.1±1.9	0.001
V_e s (cm/s)	Global	11.0±2.2	9.5±1.7	0.03	8.4±1.3 ^a	0.001	8.4±1.3 ^a	0.001
	‘Normal’				8.7±1.5	0.001	9.4±1.7	0.02
V_a resting (cm/s)	Global	9.0±1.5	10.0±2.0		7.9±1.6 ^{b,d}		9.1±1.8	
	‘Normal’				8.5±1.8 ^{a,d}		10.1±2.2	
V_a s (cm/s)	Global	9.1±1.9	10.2±2.0		8.7±1.6 ^b		9.7±1.8	
	‘Normal’				9.1±1.7 ^{a,d}		10.6±2.3	0.05
<i>e–a</i> resting (cm/s)		1.1±2.1	–1.2±2.7	0.02	–0.2±2.0		–1.5±2.6	0.004
<i>e–a</i> s (cm/s)		1.8±3.3	–1.3±2.8	0.003	–0.3±1.6	0.03	–1.3±2.2	0.001
CBVI s (%)	Global	24.4±4.9	16.6±5.0	0.001	19.4±4.1 ^d	0.005	16.1±4.0	0.001
	‘Normal’				25.9±6.0 ^{c,d}		21.4±4.2 ^b	
Slope s	Global	4.6±1.0	3.1±1.3	0.001	3.3±0.8	0.003	3.0±1.2	0.001
	‘Normal’				4.0±0.7 ^a		3.3±1.4	0.003
MBFI s	Global	114±40	56±35	0.001	65±25	0.001	53±30	0.001
	‘Normal’				100±31 ^c		71±36	0.002
ΔCBVI	Global	8.2±2.4	2.2±2.9	0.001	4.0±4.4	0.001	2.7±3.3	0.001
	‘Normal’				8.5±7.2 ^b		7.8±5.4 ^b	
CFRI	Global	2.9±0.9	1.7±0.9	0.04	2.6±2.1		2.0±1.4	
	‘Normal’				3.6±3.1		4.5±4.0 ^b	

With the exception of *n*, all values are means±SD. *p* values are from post hoc test and denote significance vs control subjects.

DCAD Diabetes and CAD, *s* dipyridamole stress, V_s systolic velocity, V_e early diastolic velocity, V_a late diastolic velocity, *e–a* early minus late diastolic velocities, CBVI capillary blood volume index, Slope index of myocardial blood flow velocity, MBFI myocardial blood flow index, ΔCBVI stress-induced increase of capillary blood volume index, CFRI coronary flow reserve index

^a $p<0.05$

^b $p<0.01$

^c $p<0.001$ for significance vs diabetes

^d $p<0.05$ for significance vs DCAD

Fig. 2 Function-related parameters in the four groups: **a** early diastolic velocity; **b** early diastolic minus late diastolic velocity; and **c** pulse pressure. Control, white bars; CAD, dotted bars; diabetes without CAD, hatched bars; diabetes with CAD, black bars. The reduction of early diastolic velocity was similar in the CAD and

diabetic groups. Only in the diabetes groups was it associated with an increase of late diastolic velocity so that the normal diastolic pattern, early diastolic > late diastolic velocity, was inverted compared to the control. Pulse pressure was increased in both diabetic groups, but not in the CAD group

than control and type 2 diabetic patients. However, lipid values and HbA_{1c} were comparable to control.

Comparison of DCAD with control

In patients with CAD and diabetes, V_e was reduced at rest and dipyridamole stress both in global function (Fig. 2) and

in the 'normal' territory (Table 2). V_s was reduced ($p=0.02$).

All global myocardial perfusion indices at rest were comparable to the other three groups. At stress, they were reduced to a similar extent as in type 2 diabetic and CAD patients (Fig. 3). However, the indices of the 'normal' perfusion territory were comparable with control (Fig. 3) and significantly superior to type 2 diabetic

Fig. 3 The following perfusion indices during maximal vasodilatation in the four groups are shown: global capillary blood volume (a); global stress-induced increase of capillary blood volume index (b); and global myocardial blood flow index (c). Control, white bars; CAD, dotted bars; diabetes without CAD, hatched bars; diabetes with CAD, black bars. Partially concealed bars, values of the 'normal'

territory for superimposed darker bars. Global CBVI and Δ CBVI and MBFI were reduced in all patients' groups, see p values. The flow indices CBVI_{norm} and MBFI_{norm} from the normal coronary territory in the CAD and, in particular, in the DCAD group were not different from control subjects. CBVI_{norm} was higher in DCAD ($p < 0.006$) and in CAD ($p < 0.02$) than CBVI in type 2 diabetes

Table 3 Haemodynamic data of all patients

Parameter	Control	Diabetes	<i>p</i> value	CAD	<i>p</i> value	DCAD	<i>p</i> value
<i>n</i>	14	17		17		18	
HR, resting (bpm)	65±10	68±10		57±10 ^b	0.04	64±10	
HR, <i>s</i> (bpm)	81±12	82±9		77±11		78±12	
BP systolic, resting (mmHg)	125±14	136±14		127±14		137±23	0.06
BP systolic <i>s</i> (mmHg)	115±11	134±13	0.001	127±15	0.04	135±19	0.001
BP diastolic resting (mmHg)	77±6	81±9		77±8		73±11	
BP diastolic <i>s</i> (mmHg)	69±11	77±9		73±7 ^b		68±10 ^a	
RPP resting (mmHg/min)	8,192±1,888	9,583±1,887	0.05	7,318±1,563 ^{b,c}		8,780±1,868	
RPP <i>s</i> (mmHg/min)	9,310 ±1,797	10,850±1,704	0.05	10,036±2,250		10,514±2,111	
PP resting (mmHg)	48±14	58±15	0.05	51±10 ^c		63±18	0.007
PP <i>s</i> (mmHg)	46±8	60±11	0.003	53±12 ^d		67±16	0.001

With the exception of *n*, all values are means±SD. *p* values are from post hoc test and denote significant differences vs control subjects.

CAD Coronary artery disease, DCAD diabetes and CAD, *s* dipyridamole stress, HR heart rate, BP blood pressure, RPP rate pressure product, PP pulse pressure

^a *p*<0.05

^b *p*<0.01 for significance vs diabetes

^c *p*<0.05

^d *p*<0.01 for significance vs DCAD

patients (*p*=0.006). Expectedly, cardiovascular drugs were used more intensively, e.g. beta blockers (*p*=0.001), aspirin (*p*=0.005) and statins (*p*=0.002, Table 1), in comparison with the control and type 2 diabetes groups (*p*=0.001, 0.005 and 0.012, respectively). Within regard to haemodynamics, pulse pressure was increased (*p*=0.007, Table 3). Additionally, hypertension and hyperlipidaemia were more frequent (*p*=0.03 and *p*=0.009, respectively).

Control and type 2 diabetes subgroups without hypertension

In order to avoid the impact of hypertensive heart disease in control and type 2 diabetic patients, subgroups were established for patients in these groups with resting blood pressure ≤140/90 mmHg and no antihypertensive treatment (*n*=10 in control and in type 2 diabetes groups). Similar decreases of *Ve* (*p*=0.05), impairment of all parameters of perfusion (*p*=0.02) and increase of pulse pressure (*p*=0.05) were observed in the diabetic subgroup, this being associated with a similar distribution of clinical data and cardiac medication as demonstrated in Table 1 for type 2 diabetes and control (Table 4).

Correlations for parameters of function and perfusion

The pooled data of the four groups demonstrated significant inverse correlations of myocardial function or perfusion values with metabolic parameters as detailed in Table 5. Diabetes duration, triglycerides and total cholesterol did not correlate with parameters of function or perfusion. When all

the associated factors for *Ve* were entered into a forward stepwise regression model, the results showed only HbA_{1c}, *Vs* and pulse pressure to be independent predictors (*R*²=0.761).

There were similar correlations for the combined control and type 2 diabetes groups as detailed in Table 5, but even closer inverse correlations between *Ve* and age or HbA_{1c}, HDL and the daily dose of insulin. Similarly, CBVI had closer inverse correlations with BMI or with the daily dose of insulin, systolic blood pressure and HbA_{1c}.

Discussion

Using modern ultrasound technology, abnormalities of global myocardial perfusion and diastolic function were quantified and compared between patients with type 2 diabetes and age-matched individuals without and with 1–2 vessel CAD. We found that *Ve* was reduced in the type 2 diabetes group by the same extent as in the CAD group, and that the reduction correlated with pulse pressure, which was increased. Global perfusion parameters were markedly reduced at maximal vasodilatation to the same extent as in the CAD and DCAD groups. Both of the latter were using more beta blockers, aspirin and statins than type 2 diabetes or control patients, and this was associated with improved perfusion data of the ‘normal’ coronary territory in DCAD patients compared to the type 2 diabetic group.

Myocardial dysfunction in type 2 diabetes

The well-known diastolic dysfunction of patients with diabetes mellitus [8, 9, 20, 25] was confirmed by our data

Table 4 Control and type 2 diabetes subgroups of individuals without hypertension

Characteristic	Control	Diabetes	<i>p</i> value
<i>n</i>	10	10	
Age (years)	59±8	60±7	
HbA _{1c} (%)	5.6±0.4	7.0±1.2	
BMI (kg/m ²)	26±3	27±5	
Statins (%)	0	40	0.06
Triglycerides (mmol/l)	1.4±0.6	2.2±1.0	
Cholesterol (mmol/l)	4.2±0.7	5.1±0.9	
HDL (mmol/l)	1.4±0.4	1.1±0.4	
LDL (mmol/l)	2.6±0.6	3.4±0.9	
HR (bpm)	64±10	68±12	
BP systolic (mmHg)	120±10	138±16	
BP diastolic (mmHg)	77±6	82±11	
RPP (mmHg/min)	7,711±1,606	9,674±2,082	0.05
PP (mmHg)	43±11	61±17	0.05
Vs (mmol/l)	1.4±0.4	1.0±0.3	
Ve (mmol/l)	2.6±0.5	3.1±1.0	0.03
Slope s	4.6±1.2	3.0±1.5	0.005
CBVI s (%)	23.7±5.3	17.9±5.0	0.007
MBFI s	110±45	58±41	0.003

With the exception of *n*, all values are means±SD.

BP blood pressure, *CBVI* capillary blood volume index, *HR* Heart rate, *MBFI* myocardial blood flow index, *PP* pulse pressure, *RPP* rate pressure product, *s* dipyridamole stress, *Slope* index of myocardial blood flow velocity

from tissue Doppler-derived velocity measurements of LV long axis function during early diastole, a finding that is consistent with other reports [14, 20, 26]. Diastolic dysfunction has been mainly attributed to structural changes of the diabetic myocardium [27, 28] but there is also increasing evidence that metabolic [29] and other dynamic changes are involved, e.g. mismatch of oxygen demand and supply [13] and modification of afterload, tissue perfusion, possibly endothelial function [8, 30], and finally antidiabetic therapy [20, 30]. As early diastolic function is energy-consuming, it can be speculated that limited availability of metabolic substrates for energy production on the basis of impaired tissue perfusion contributes to the underlying pathophysiology. Abnormal early diastolic function relates to impaired vital prognosis [31, 32], but evidence-based medicine still lacks studies for effective therapy.

Despite the basic and close correlation between systolic and diastolic function, systolic longitudinal LV function was not significantly impaired in our patients. In the early stage of diabetic heart disease, this may be related to compensation by increased short-axis LV function [14, 26], and also to an increase of late diastolic filling velocities, which counterbalances the reduction in early diastolic relaxation properties of the diabetic myocardium, thereby maintaining global filling and, thus, systolic function. Our observation in the present type 2 diabetes group was in line with this latter mechanism (Fig. 2). The observed mechanisms of diastolic dysfunction in patients with CAD were different and were associated with impaired systolic function.

Diastolic dysfunction correlated to pulse pressure

The magnitude of early *Ve* in type 2 diabetic and control groups correlated inversely with age, confirming earlier reports [23, 33]. In this context, it can be speculated that stiffening of the arterial wall contributes to diastolic dysfunction, as it is the leading vascular abnormality of old age and diabetes mellitus [34]. Indeed, pulse pressure, a surrogate of arterial stiffening, was significantly elevated only in the groups with diabetic individuals (Fig. 2), and was confirmed as an independent predictor for disturbed *Ve*. Increasing pulse pressure is known to impair the functional interaction between central arterial wall and left ventricle [35], partially due to reduced myocardial perfusion pressure and elevated endsystolic afterload [36, 37]. The benefits of therapeutic afterload reduction are known in diabetic patients [38]. Arterial stiffening, therefore, could conceivably become a target of therapeutic strategies in the treatment of diastolic dysfunction. In patients with type 2 diabetes, this is in line with optimising glucose metabolism as suggested by the inverse correlation between *Ve* and HbA_{1c}.

Diastolic dysfunction in CAD patients

Expectedly, global early diastolic function was reduced in CAD patients (Fig. 2). This observation has been attributed to ischaemia-induced regional asynchrony of myocardial contraction and relaxation [6, 7]. Although the magnitude

Table 5 Pearson correlation coefficients of significant correlations

Parameter	Pooled data from	Myocardial function		Indices of myocardial perfusion		
		Vs	Ve	Flow velocity	Capillary blood volume	Blood flow
Age	4 groups	n.s.	−0.441	n.s.	n.s.	n.s.
	C+D	n.s.	−0.515	n.s.	n.s.	n.s.
Systolic blood pressure	4 groups	n.s.	−0.239	n.s.	n.s.	n.s.
	C+D	n.s.	n.s.	−0.381	−0.433	−0.459
Pulse pressure	4 groups	n.s.	−0.260	n.s.	n.s.	n.s.
	C+D	n.s.	n.s.	n.s.	n.s.	n.s.
Rate pressure product	4 groups	n.s.	n.s.	n.s.	n.s.	n.s.
	C+D	n.s.	n.s.	n.s.	n.s.	−0.359
BMI	4 groups	n.s.	n.s.	n.s.	−0.295	−0.268
	C+D	n.s.	n.s.	n.s.	−0.485	−0.374
HbA _{1c}	4 groups	n.s.	−0.365	n.s.	n.s.	n.s.
	C+D	n.s.	−0.449	n.s.	−0.401	−0.427
Insulin (units/day)	4 groups	n.s.	n.s.	n.s.	−0.393	n.s.
	C+D	n.s.	−0.538	n.s.	−0.486	−0.428
HDL	4 groups	n.s.	n.s.	n.s.	n.s.	n.s.
	C+D	n.s.	−0.422	n.s.	n.s.	n.s.
LDL	4 groups	n.s.	n.s.	−0.286	n.s.	n.s.
	C+D	n.s.	n.s.	−0.438	n.s.	n.s.
Vs	4 groups		0.632	n.s.	n.s.	n.s.
	C+D		0.672	n.s.	n.s.	n.s.
Ve	4 groups	0.632		n.s.	n.s.	n.s.
	C+D	0.672		n.s.	n.s.	n.s.
Slope hyperaemic stress	4 groups	n.s.	n.s.		0.749	0.932
	C+D	n.s.	n.s.		0.796	0.946
CBVI, hyperaemic stress	4 groups	n.s.	n.s.	0.749		0.909
	C+D	n.s.	n.s.	0.796		0.922
MBFI, hyperaemic stress	4 groups	n.s.	n.s.	0.932	0.909	
	C+D	n.s.	n.s.	0.946	0.922	

C Control, CBVI capillary blood volume index, D type 2 diabetes, MBFI myocardial blood flow index = flow velocity index × capillary blood volume index, n.s. no correlation at significant level ($p < 0.05$), Slope index of myocardial blood flow velocity

of the decrease in Ve was similar to that observed in type 2 diabetes patients, it was not associated with a compensatory increase of Va, but with significantly reduced systolic function, reflecting different pathophysiological mechanisms than in the type 2 diabetes group.

Myocardial perfusion in type 2 diabetic patients

The adaptive modifications of tissue perfusion to metabolic demands are based on dynamic capillary blood volume changes transmitted by recruitment or derecruitment of capillaries [16–20, 39, 40]. It has not been shown before that patients with diabetes had markedly reduced capillary blood volume during maximal vasodilatation (Fig. 3) irrespective of the presence or absence of hypertension. Notably, it was the stress-induced percentage increase of capillary volume that was predominantly reduced (17 vs 50% in control subjects). These data suggest that the diabetic myocardium at hyperaemic stress cannot recruit sufficient additional capillaries to facilitate metabolic

exchange. This limitation is particularly disadvantageous, as the diabetic heart works on a higher level of oxygen demand than the heart of CAD patients, at least as reflected by the rate–pressure product. Our observation that myocardial blood flow during stress and coronary flow reserve are also reduced is in line with the above findings, confirming observations by PET and angiography [10–12].

A noteworthy observation, and one not shown before, was that global perfusion in patients with macrovascular CAD was impaired to the same extent as in diabetic patients with microvascular disease (Fig. 3). These microvascular abnormalities are probably linked to endothelial dysfunction, which is known to deteriorate with hyperglycaemia and other cardiovascular risk factors [40–42] as confirmed in the present data by the inverse correlations between myocardial perfusion and metabolic and haemodynamic parameters (Table 5). However, the interaction between endothelial dysfunction and microvascular perfusion abnormalities also contains dynamic and reversible components. Indeed, first reports have been published on

improvement of myocardial perfusion by short-term pharmacological action [20, 30, 43].

In this context, the present data demonstrate some therapeutic potential in diabetic patients. Thus the global perfusion parameters and surrogate parameters for myocardial oxygen demand were similar between the type 2 diabetes and DCAD groups. However, the perfusion values of the 'normal' vascular territory were significantly superior in DCAD than in type 2 diabetic patients and no longer different from control subjects and CAD patients (Fig. 3). This was associated with significantly increased use of beta blockers, aspirin and statins in the DCAD group, so that interpretation of the origin of flow enhancement is limited. Further prospective studies are needed to evaluate the effects of preventive therapy on the reversible components of impaired perfusion in the diabetic heart. The potential of antidiabetic therapy was also confirmed in the present data by the inverse correlation between MBFI and HbA_{1c}, which was significant ($p=0.007$, Table 5) in the combined type 2 diabetes and control groups.

Prediabetes and metabolic syndrome

The striking likeness of global perfusion impairment between patients with macrovascular CAD versus patients with type 2 diabetes and microvascular abnormalities was based on the definition of diabetes according to the established diagnostic marker of fasting serum glucose ≥ 7 mmol/l [5]. There is a large body of evidence with convincingly similar results worldwide, which suggests a fairly high prevalence (around 51–63%) of impaired glucose regulation in patients with CAD and non-diabetic fasting glucose values [3, 44–46]. Moreover, the increased but similar BMI between our CAD and type 2 diabetes patients suggests a high and similar prevalence of metabolic syndrome or insulin resistance in both age-matched groups. It can be assumed, therefore, that the similar impairment of myocardial perfusion in both groups is related, in the majority of patients, to the disturbed glucose metabolism and/or insulin resistance that are typical of the metabolic syndrome, all of which have been shown to be associated with endothelial dysfunction [41, 47]. This is in line with the significant and inverse correlations of perfusion data with BMI in the pooled data of all groups. The present data thus support the 'common soil' theory for diabetes mellitus and coronary artery disease and point to important options for preventive therapy.

Study limitations

The numbers of patients in the four groups were small but sufficient to yield statistically meaningful results. According to recent surveys [44, 48, 49], the definition of diabetes

on the basis of an additional OGTT could have led to 0.7 persons (5%) in the control group and 2.4 patients (14%) in the CAD group being diagnosed with diabetes mellitus. This, however, is unlikely to weaken our very significant differences between control subjects and the three patient groups, since exclusion of false negative patients in CAD would instead increase the power of the test.

All diabetes-specific observations were confirmed in each of the diabetic groups, irrespective of CAD or hypertensive effects. The effects from abnormal serum viscosity and red blood cell rheology or microangiopathy cannot be differentiated from the more dynamic impairment of capillary recruitment during stress observed by us. The normal range of perfusion parameters in the resting state, however, points to the predominant influence of the latter mechanism.

In the CAD groups, cardiac medication created an additional influence to the effects of the disease. Obviously, the present study of function and perfusion could not be designed without the effects of chronic cardiac or anti-diabetic medication, as it would have been unethical to stop these. The evaluation of the specific effects of the respective medications used by these patients should be undertaken in future prospective studies. Most diabetic patients without CAD were not on cardiac medication. In the DCAD group, however, it cannot be ruled out that some beneficial effects of cardiac therapy masked the expected increasingly detrimental effects of combined diabetes and CAD (Figs. 2 and 3).

Finally, a more uniform application of angiography for the exclusion of coronary disease would have been warranted, but was not clinically applicable for ethical reasons in asymptomatic diabetic and non-diabetic patients. However, the exclusion of CAD by traditional 2-dimensional stress echocardiography was supported by a simultaneous lack of stress-induced myocardial velocity reduction in the combined traditional echocardiographic and tissue Doppler stress test [13].

Clinical implications

The present study in patients with type 2 diabetes demonstrates new findings with potentially important therapeutic implications:

- (1) Impaired diastolic myocardial velocity is inversely related to age, HbA_{1c} and pulse pressure.
- (2) Myocardial capillary volume at maximal vasodilatation is reduced leading to an impairment of global myocardial blood flow.
- (3) The observed limitations of microvascular perfusion in patients with diabetes mellitus are similar in extent to the macro/microvascular abnormalities in coronary

artery disease, but may apparently be compensated by the use of preventive cardiovascular therapy, an optimisation of glucose metabolism or other ways of ameliorating endothelial function, all of which appear promising as therapeutic targets. Similarly, diastolic dysfunction appears to be related to arterial stiffening, also a potentially important therapeutic target.

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