CARDIOVASCULAR MEDICINE

Influence of diabetes mellitus on coronary collateral flow: an answer to an old controversy

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Objectives: To determine the influence of diabetes mellitus on coronary collateral flow by accurate means of collateral flow measurement in a large population with variable degrees of coronary artery disease.
Methods: 200 patients (mean (SD) age 64 (9) years; 100 diabetic and 100 non-diabetic) were enrolled in the study. Coronary collateral flow was assessed in 174 stenotic and in 26 angiographically normal vessels with a pressure guidewire (n = 131), Doppler guidewire (n = 36), or both (n = 33) to calculate pressure or flow velocity derived collateral flow index (CFI). Diabetic patients were perfectly matched with a non-diabetic control group for clinical, haemodynamic, and angiographic parameters.
Results: CFI did not differ between the diabetic and the non-diabetic patients (0.21 (0.12) v 0.19 (0.13), not significant). Likewise, CFI did not differ when only angiographically normal vessels (0.20 (0.09) v 0.15 (0.08), not significant) or chronic total coronary occlusions (0.30 (0.14) v 0.30 (0.17), not significant) were compared. Fewer patients in the diabetic group tended to have angina pectoris during the one minute vessel occlusion (60 diabetic v 69 non-diabetic patients, p = 0.15).
Conclusion: Quantitatively measured coronary CFI did not differ between diabetic and non-diabetic patients with stable coronary artery disease.

T he coronary collateral circulation is an alternative source of blood supply to myocardium supplied by a stenotic or occluded coronary artery. A well developed coronary collateral circulation has a favourable impact on the prognosis of patients with coronary artery disease (CAD).[1 2] So far, only a few pathogenetic factors have been consistently described as influencing the development of coronary collateral vessels, namely the severity of coronary artery stenosis[3] and the duration of myocardial ischaemic symptoms.[4]

Endothelial dysfunction, structural changes of the microcirculation, and the negative influence on the development and prognosis of CAD are well established features of patients with diabetes mellitus (DM)[5–7] On the other hand, the influence of DM on coronary collateral growth has been controversial. One clinical study by Abaci et al[8] reported reduced coronary collateral development in patients with DM compared with non-diabetic patients; Melidonis et al[9] reported exactly the contrary. These conflicting reports were based on angiographic assessment of coronary collaterals, which correlates only poorly with quantitative parameters of collateral function.[10] Recent developments in microsensor technology have made it possible to study collateral perfusion pressure and flow velocity and to calculate pressure and Doppler derived collateral flow indices, which correlate well with other means of perfusion measurement such as single photon emission computed tomography.[11] A recent study by Werner et al,[12] who used the mentioned invasive method, found no overall difference in coronary collateral flow between diabetic and non-diabetic patients. The major limitations of their study were the relatively small number of patients examined and the restriction to patients with chronic total coronary occlusion.

The purpose of our study was to determine the influence of DM on coronary collateral flow index (CFI) by means of accurate collateral flow measurement in a large population with variable degrees of CAD. Possible confounding factors were eliminated by matching patients with DM to a non-diabetic control group for age, sex, percentage diameter

coronary stenosis, serum lipids, and cardiovascular risk factors.

METHODS

Patients

Two hundred patients (age 64 (9) years; 156 men and 44 women) referred for diagnostic coronary angiography were enrolled in the study. Twenty six patients had angiographically totally normal coronary arteries and 174 patients had one to three vessel CAD. Coronary CFI was assessed in 174 stenotic and in 26 angiographically normal vessels (that is, with no wall irregularities and no stenotic lesions). One hundred patients had DM and 100 patients served as non-diabetic control group. Each diabetic patient was matched with a non-diabetic control patient for sex, age, serum lipids, percentage diameter stenosis of the vessel undergoing CFI measurement, and cardiovascular risk factors.

Patients with acute coronary syndrome, severe valvar heart disease, previous coronary artery bypass surgery, previous myocardial infarction in the area undergoing CFI measurement, or severe hepatic or renal insufficiency were excluded. The patients in this study have been described in part elsewhere.[3] These studies were approved by the local ethics committee and the patients gave written informed consent to participate. For ethical concerns about inflating a balloon in an angiographically normal vessel we refer to Wustmann et al.[13]

Coronary angiography

All patients underwent left heart catheterisation, including biplane left ventricular angiography and coronary angiography for diagnostic purposes. Coronary artery stenoses were assessed quantitatively as the percentage diameter lumen reduction by using the guiding catheter for calibration.

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Abbreviations: CAD, coronary artery disease; CFI, collateral flow index; CFI_p, pressure derived collateral flow index; CFI_v, velocity derived collateral flow index; CVP, central venous pressure; DM, diabetes mellitus; P_{ao}, mean aortic pressure; P_{occl}, distal coronary pressure at the end of a one minute balloon occlusion
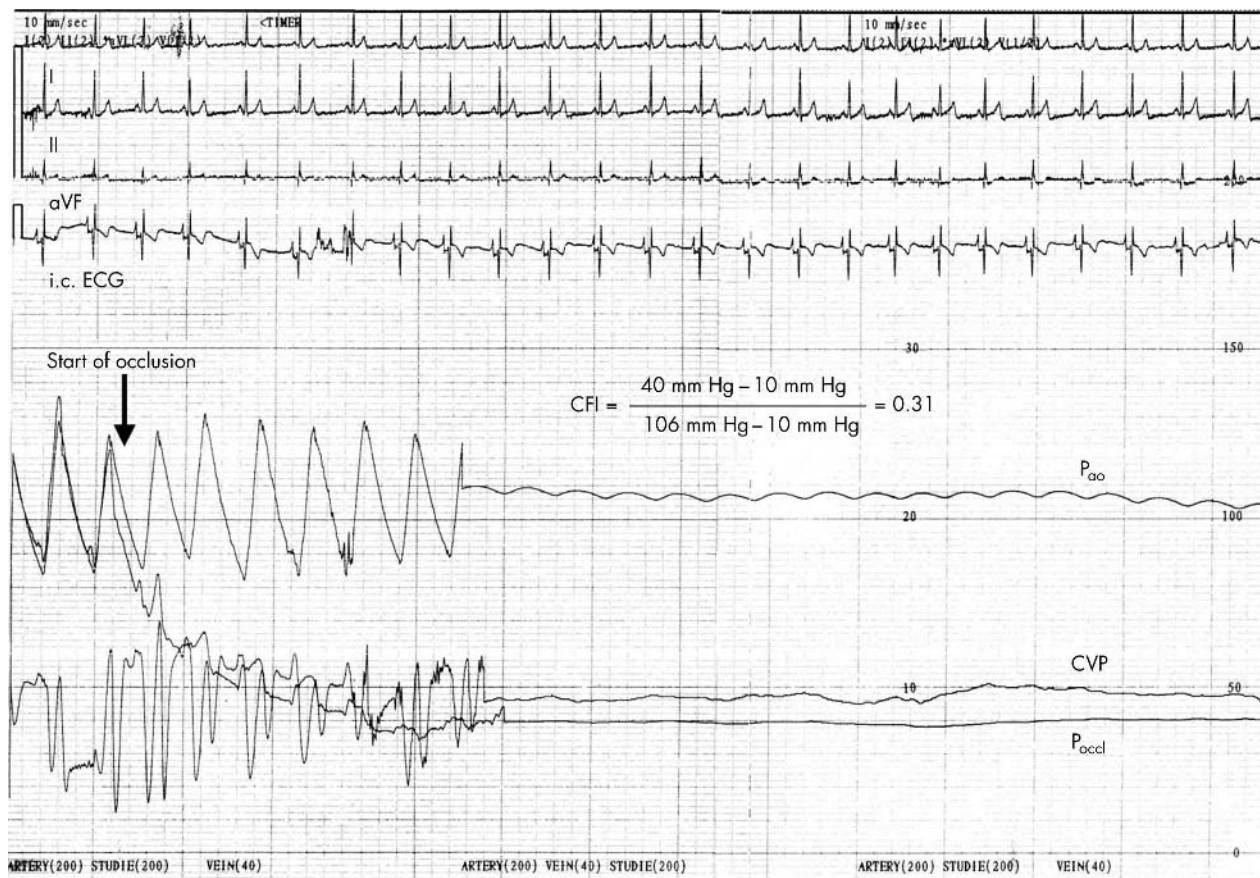
Figure 1 Coronary collateral flow assessment with an intracoronary pressure guidewire in a patient with insulin dependent diabetes mellitus with angiographically normal coronary arteries. Collateral flow index (CFI), expressing collateral flow to the balloon occluded coronary artery relative to normal antegrade flow during vessel patency, is determined from mean aortic pressure (P_{ao}), mean coronary pressure during balloon occlusion (P_{occl}), and central venous pressure (CVP) (phasic recordings of these pressures obtained during coronary patency are shown at left). After balloon occlusion, phasic and mean P_{occl} starts to decrease and plateaus at 40 mm Hg. Note the different scales for P_{ao}, P_{occl}, and CVP. CFI is calculated as (P_{occl} − CVP)/(P_{ao} − CVP). On the surface lead (I, II, aVF) and on the intracoronary ECG lead recorded through the sensor guidewire, no signs of myocardial ischaemia (ST segment changes) were observed during vessel occlusion when compared with the period before coronary occlusion. Additionally, the patient did not feel any chest pain during the one minute balloon occlusion.

Collateral vessel assessment

Either a 0.014 inch pressure sensor tipped guidewire, a Doppler guidewire, or both were used during balloon occlusion and percutaneous coronary intervention. The fibreoptic pressure guidewire (WaveWire, Endosonics, Rancho Cordova, California, USA; or PressureWire, Radi Medical Systems, Uppsala, Sweden) was set at zero, calibrated, advanced through the guiding catheter, normalised for aortic pressure at the ostium of the coronary artery, and positioned distal to the stenosis to be dilated or distal to the balloon occlusion in the angiographically normal vessels. Pressure derived CFI (CFI_p; no unit) was determined by simultaneous measurement of mean aortic pressure (P_{ao}; mm Hg) and of distal coronary pressure at the end of a one minute balloon occlusion (P_{occl}; mm Hg). If not measured simultaneously (n = 77), central venous pressure (CVP; mm Hg) was assumed to be 7 mm Hg (n = 87). CFI_p was calculated as (P_{occl} − CVP)/(P_{ao} − CVP)[10] (fig 1). CFI_p calculated from an estimated CVP did not differ from those based on a measured CVP (0.19 (0.11) v 0.22 (0.13), not significant).

Velocity derived CFI (CFI_v; no unit) was measured (n = 69) with a 0.014 inch Doppler guidewire with a 12 MHz piezoelectric crystal at its tip (FlowWire, Endosonics). CFI_v was determined as the flow velocity time integral distal to the balloon occluded artery divided by the baseline flow velocity time integral obtained at the same site before balloon occlusion. Bidirectional flow velocity signals were added to obtain the total collateral flow velocity.[10] In 33 patients pressure and Doppler derived CFI were measured simultaneously and CFI_p and CFI_v were averaged to determine CFI. There is a very good correlation between CFI_v and CFI_p[10] and the two methods are interchangeable.

Myocardial ischaemia during balloon occlusion was assessed by the occurrence of angina pectoris and by a simultaneously obtained intracoronary ECG. ST segment changes in the intracoronary ECG were defined as indicative of ischaemia if they were > 0.1 mV during the one minute balloon occlusion.

Statistical analysis

Data are expressed as mean (SD) for continuous variables and as number (percentage) for categorical variables. For comparison of continuous variables between the two groups, an unpaired Student's t test was used. Categorical variables between the two populations were compared by the χ^2 test. Significance was defined as p < 0.05.

RESULTS

With regard to clinical characteristics, the two groups differed significantly only in body mass index only (table 1).

Table 1 Clinical characteristics

	Diabetic patients (n = 100)	Non-diabetic patients (n = 100)	p Value
Men	78 (78%)	78 (78%)	NS
Age (years)	64 (9)	64 (9)	NS
Body mass index (kg/m^2)	28.4 (3.8)	26.2 (3.8)	0.0002
Mean aortic pressure (mm Hg)	91 (11)	91 (14)	NS
Heart rate (beats/min)	72 (13)	70 (13)	NS
LVEF (%)	64 (11)	63 (12)	NS
LVEDP (mm Hg)	12.9 (6.5)	12.3 (5.0)	NS
Duration of angina pectoris (months)	21 (42)	20 (41)	NS
Cardiovascular risk factors			NS
Systemic hypertension	73 (73%)	69 (69%)	NS
Smoking	36 (36%)	38 (38%)	NS
Hypercholesterolaemia	52 (52%)	54 (54%)	NS
Family history of CAD	31 (31%)	41 (41%)	NS
Cardiovascular medication			NS
Aspirin	86 (86%)	84 (84%)	NS
β Blockers	64 (64%)	69 (69%)	NS
Nitrates	39 (39%)	37 (37%)	NS
Statins	39 (39%)	42 (42%)	NS
ACE inhibitors	35 (35%)	25 (25%)	NS
AT II receptor antagonists	8 (8%)	4 (4%)	NS
Calcium antagonists	23 (23%)	15 (15%)	NS
Diuretics	29 (29%)	20 (20%)	NS
Blood chemistry			NS
Total cholesterol (mmol/l)	5.3 (1.2)	5.3 (1.0)	NS
HDL cholesterol (mmol/l)	1.1 (0.4)	1.2 (0.3)	NS
LDL cholesterol (mmol/l)	3.2 (1.0)	3.4 (0.9)	NS
Total cholesterol:HDL cholesterol	4.8 (1.7)	4.7 (1.6)	NS
Triglycerides (mmol/l)	2.2 (1.7)	2.1 (1.7)	NS
Fasting blood glucose (mmol/l)	8.9 (3.3)	6.0 (0.9)	<0.0001
Haemoglobin A1c (%)	7.2 (2.4) (n = 15)	5.9 (0.4) (n = 12)	0.05

Data are mean (SD) or number (%) of CFI measurements.
ACE, angiotensin converting enzyme; AT II, angiotensin II; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; NS, not significant.

Furthermore, fasting glucose and haemoglobin 1c differed significantly. Coronary angiographic data were similar in the two groups (table 2).

Figure 1 gives an example of CFI measurement in an insulin dependent diabetic patient with angiographically normal coronary arteries.

CFI did not differ between the diabetic and the non-diabetic groups (fig 2, table 2). Similarly, CFI did not differ when only angiographically normal vessels (fig 3, table 2) or chronic total coronary occlusions were compared (fig 4, table 2).

No difference between the two groups concerning ST segment change in the intracoronary ECG was found (table 2).

Fewer patients in the diabetic group tended to have angina pectoris during the one minute vessel occlusion (p = 0.15).

DISCUSSION

Quantitative means of measuring coronary CFI and careful accounting of cofactors influencing it detect no difference between diabetic and non-diabetic patients. Previous clinical studies of DM and coronary collateral flow have been controversial, possibly because of the use of inaccurate means of assessing coronary collateral flow or because differences in cofactors that influence collateral flow variably in diabetic and non-diabetic patients (serum lipids, severity

Table 2 Coronary angiographic data and collateral flow assessment

	Diabetic patients (n = 100)	Non-diabetic patients (n = 100)	p Value
Vessel undergoing CFI measurement			
Left anterior descending coronary artery	39 (39%)	51 (51%)	NS
Left circumflex coronary artery	29 (29%)	21 (21%)	NS
Right coronary artery	32 (32%)	28 (28%)	NS
Coronary angiographic data			NS
Percentage diameter stenosis	68 (320)	68 (30)	NS
Number of vessels diseased	1.8 (0.8)	1.8 (0.8)	NS
Number of stenoses	3.0 (2.0)	2.7 (1.9)	NS
Presence of chronic total coronary occlusion*	27 (27%)	21 (21%)	NS
Collateral flow assessment			NS
CFI†	0.21 (0.12)	0.19 (0.13)	NS
CFI in angiographically normal vessels	0.20 (0.09) (n = 13)	0.15 (0.08) (n = 13)	NS
CFI in chronic total coronary occlusions	0.30 (0.14) (n = 18)	0.30 (0.17) (n = 18)	NS
Angina pectoris during balloon occlusion	60 (60%)	69 (69%)	0.15
ST segment elevation in intracoronary ECG >0.1 mV	74 (74%)	79 (79%)	NS

Data are mean (SD) or number (%) of CFI measurements.
*36 chronic total coronary occlusions were targeted for CFI measurement.
†Average of velocity and pressure derived CFI when measured simultaneously (n = 36).
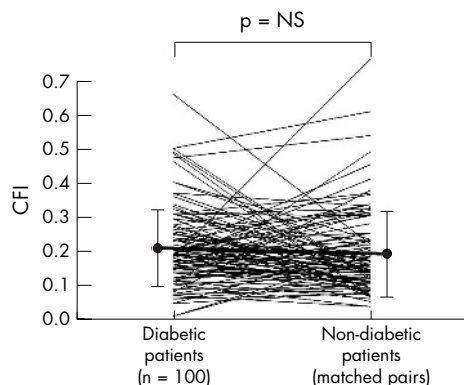
Figure 2 One hundred measurements in 100 diabetic patients are shown on the left and linked to matched control measurements in the non-diabetic group. Additionally, mean (SD) CFI values (vertical axis) are given (filled circles and vertical error lines).

of CAD[14]) were not accounted for. Additionally, differentiation between angiogenesis and arteriogenesis is important to understand the influence of DM on blood vessel development.

Angiogenesis versus arteriogenesis

Results from experimental investigations are very consistent concerning the pro-angiogenic effect of DM. This is well reflected by the fact that one of the major complications of DM is blindness caused by stimulated ocular angiogenesis (with the production of leaky capillaries lacking pericytes[15]). However, it is important to know that there are different forms of vessel growth: firstly, vasculogenesis (primarily occurring during embryonic development by differentiation of haematopoietic stem cells); secondly, angiogenesis (sprouting of new capillary-like vessels out of existing ones, occurring during embryonic development and under certain conditions in the adult); and thirdly, arteriogenesis (pre-existing collateral arterioles are remodelled into arteries by dilatation and by proliferation of smooth muscle cells and endothelial cells with consecutive acquisition of the typical arterial structure).[16] Collateral artery development is exclusively caused by arteriogenesis, unlike angiogenesis, which is responsible for the known ocular complication of DM.[17]
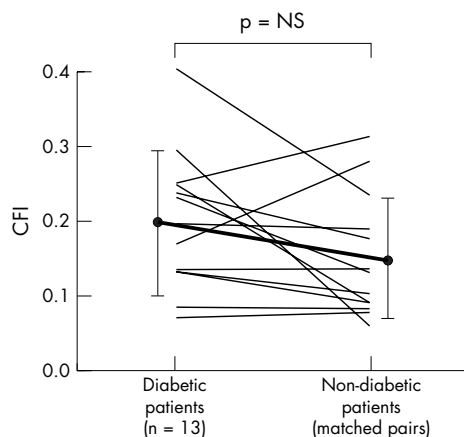

Figure 3 Individual CFI measurements in patients with angiographically normal coronary arteries. Measurements in diabetic patients (mean (SD)) are shown on the left linked to control measurements in the non-diabetic group.
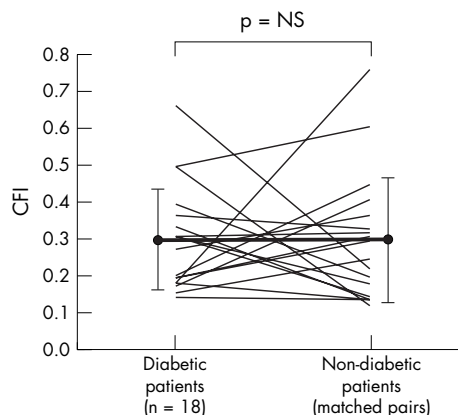

Figure 4 Individual CFI measurements in patients with chronic total coronary occlusion. Measurements in diabetic patients (mean (SD)) are shown on the left and control measurements in matched non-diabetic control patients are shown on the right.

Concerning the effect of DM and increased blood glucose concentrations on arteriogenesis, data from experimental studies are less consistent than investigations on angiogenesis. For example, basic fibroblast growth factor expression (a known proarteriogenic cytokine[18]) is increased in the eye, heart, lung, and brain of diabetic rats,[19] and plasma basic fibroblast growth factor concentrations are increased in male diabetic patients with proteinuria[20] suggesting a proarteriogenic influence. On the other hand, vascular endothelial growth factor induced chemotaxis of monocytes, which has a key role in arteriogenesis,[21] is attenuated in patients with DM.[22] Tamarat et al[23] observed reduced collateral flow in a hind limb ischaemia model in diabetic mice after 28 days of ischaemia.

Basic research experiments are certainly accurate models for studying one particular aspect relevant in collateral growth but they do not take into account many cofactors influencing the complex mechanism of arteriogenesis in humans. On the other hand, clinical studies would be the ideal tool to account for all these cofactors but the few studies done on this topic lack a careful selection of the non-diabetic control group and accurate means of collateral flow assessment. Summarised, clinical but also experimental studies have not been ideally designed to study the influence of DM on arteriogenesis (that is, collateral vessel development). The new aspect of the present study that removed the controversy is that we assessed coronary collateral flow with a very sensitive method (especially for low collateral flow values) in a large population with a variable degree of CAD; CFI did not differ between diabetic and non-diabetic patients.

There was a trend (p = 0.15) towards less angina during the one minute balloon occlusion in the diabetic compared with the control group. This is somewhat surprising given the general belief that diabetic patients have less angina pectoris than non-diabetic patients. However, angina pectoris in diabetic patients has not been investigated so far under the condition that diabetic and non-diabetic patients had identical CFI values. The non-significant difference may be caused by the relatively small number of patients having angina pectoris during balloon occlusion (n = 129). On the other hand, the diabetic group tended to have slightly higher CFI (although not significant) than the control group. If angina pectoris did differ greatly (according to common belief) between diabetic and non-diabetic patients, there should have been a significant difference with 200 patients examined.

Study limitations

Collateral arteries take several weeks to develop,[24] and we measured CFI only once in all the study patients. We know from multiple CFI measurements in patients with stable CAD that under stable conditions (for example, no percutaneous coronary intervention or no change in cardiovascular risk factors) CFI remains constant over several weeks. This suggests that under stable conditions a balance between proarteriogenic and antiarteriogenic forces or factors is reached, justifying a single measurement.

Coronary steal is defined as a fall in blood flow towards a certain vascular region in favour of another area during arteriolar vasodilatation. It is an infrequent phenomenon occurring in about 10% of patients with CAD (especially in patients with well developed collateral vessels). In our study only a few patients had CFI values to allow coronary steal and they were equally distributed between the two groups.

Conclusion

Our data show that (at a given time point) coronary collateral flow does not differ between diabetic and non-diabetic patients with stable CAD.

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