Impaired acute collateral recruitment as a possible mechanism for increased cardiac adverse events in patients with diabetes mellitus

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Background The mortality of coronary artery disease is increased in diabetic patients. An impaired collateral function is considered a possible explanation. This study should assess the influence of diabetes on collaterals by direct invasive assessment of collateral function.

Methods In 90 consecutive patients with a chronic coronary occlusion (TCO) of >2 weeks duration a recanalization was done. Thirty patients with diabetes (33%) were compared with 60 (67%) without diabetes. Blood flow velocity and pressure were measured distal to the occlusion by intracoronary Doppler and pressure wires before PTCA, and again after PTCA during a final balloon reocclusion to assess acute recruitment of collaterals. Resistance indexes for collaterals (RColl) and peripheral microcirculation (RP) were calculated.

Results The RColl (diabetics: 8.1±6.8 vs nondiabetics: 8.7±6.7 mmHg cm⁻¹ s⁻¹; p=0.68) and RP (5.6±4.2 vs 6.6±3.8 mmHg cm⁻¹ s⁻¹; p=0.30) were similar in diabetic and nondiabetic patients before recanalization. During balloon reocclusion both RColl and RP increased. This increase was significantly more pronounced in diabetic than in nondiabetic patients in TCOs <3 months duration. In TCOs of longer duration (≥3 months) these differences were no longer detectable between both patient groups.

Conclusions Diabetic patients with TCOs have similarly developed collaterals as nondiabetic patients. However, in TCOs <3 months duration the acute recruitment of collaterals in case of reocclusion is impaired. This could explain some of the higher complication rate and mortality after coronary interventions in diabetic patients.

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KEYWORDS
Chronic coronary occlusion;
Collateral circulation;
Diabetes mellitus;
Percutaneous transluminal angioplasty;
Intracoronary Doppler

Introduction
The adverse influence of diabetes mellitus on the development and prognosis of coronary artery disease is well established.1–5 In diabetic patients specific mechanisms are discussed such as an impaired endothelial function6 and an impaired arteriogenesis.7 A recent clinical study using angiographic assessment of collateral vessels reported a difference in collateral development in patients with diabetes mellitus as compared to nondiabetic patients.8 However, such a difference was not reported by others.9–12 These conflicting reports were based on the angiographic assessment of collaterals,13 which does not correlate well with quantitative parameters of collateral function.14–17 Recent developments in microsensor technology
make it possible to study collateral perfusion pressure and flow, and calculate resistance indexes in order to quantify collateral vascular function.\textsuperscript{16,18,19}

We applied these techniques to analyse collateral function in chronic total coronary occlusions (TCOs) by advancing a probing catheter through the occlusion to assess the distal coronary flow before PTCA.\textsuperscript{20,21} The aim of this study was to test the hypothesis that diabetes mellitus impairs collateral function in man. We selected patients with TCOs who completely depend on collateral supply. The comparison of the baseline collateral function before recanalization with measurements after recanalization would also assess differences in acute collateral recruitment as a possible cause of the increased cardiac event rate in diabetic patients in the setting of acute myocardial infarction and coronary interventions.\textsuperscript{2,4}

Methods

Patients

From July 1999 through March 2002 125 consecutive patients underwent a recanalization of a TCO. Inclusion criteria were: (1) duration of the occlusion $\geq$2 weeks; (2) no antegrade opacification of the distal vessel (TIMI 0 coronary flow); (3) spontaneously visible collaterals. Indication for PTCA was ischaemia due to the occlusion, and prognostic considerations.\textsuperscript{22,23} The PTCA was successful in 93 patients. In three patients the occlusion could not be passed with the Doppler and pressure wire before the initial balloon dilatation according to the study protocol described below. They were excluded from the study group which consisted of 90 patients. The study protocol was approved by the institutional ethics committee.

Angioplasty procedure

Patients who were current smokers refrained from smoking at least 12 h prior to the angioplasty. After the occlusion was crossed by a 0.014” guide wire, an over-the-wire exchange catheter (Transit\textsuperscript{TM}, Cordis, Roden, The Netherlands) or low profile over-the-wire balloon catheter (Bandit\textsuperscript{TM}, Scimed, Galway, Ireland) was advanced distal to the occlusion. The Doppler and pressure recordings followed as described below, and then PTCA was completed with stent implantation.

Intracoronary Doppler and pressure recording

Nitroglycerine (0.1 mg) was injected through the exchange catheter before a 0.014” Doppler wire (Endosonics Corporation, Rancho Cordova, CA) was advanced distal to the occlusion. A potential problem of the basal collateral flow recording could be an unaccounted contribution of antegrade flow along the exchange catheter within the occlusive lesion. This could be ruled out by lack of contrast passage during proximal contrast injection into the occluded segment while the exchange catheter was in place. The Doppler signal of collateral flow did not change during this injection.

The Doppler wire was exchanged for a 0.014” pressure wire (RADI Medical Systems AB, Uppsala, Sweden) to record distal coronary pressure ($P_{\text{Occl}}$). Before pressure wire insertion the zero calibration was done at the level of the aortic root, at the same level as the pressure transducer for the aortic pressure ($P_{\text{Ao}}$). Care was taken to position the transducer at the identical location of the Doppler wire tip. $P_{\text{Ao}}$ was recorded via the fluid filled 7F guiding catheter (Fig. 1). The mean pressures were used for further computation.

After the stent implantation was completed, 0.1 mg nitroglycerine was injected intracoronary, and the Doppler wire was reintroduced to the previously documented position to record the antegrade coronary flow velocity. The stent balloon was reinflated within the stent, and the recruitable collateral flow was recorded. As the Doppler wire position is critically dependent on its location it was moved within a range of 10 mm to obtain the recording with the maximum flow velocity integral as the baseline recording. The pressure wire was then reintroduced and $P_{\text{Occl}}$ recorded during balloon occlusion.

Intracoronary flow and pressure analysis

Fig. 1 shows an example and schematic drawing of the recording of Doppler and pressure distal to the occlusion. All Doppler flow signals were digitized and analysed as previously described,\textsuperscript{20} and the average peak velocity (APV) was obtained. A Doppler derived collateral flow index (CFI) was calculated before and after PTCA as the ratio of APV distal to the occlusion ($APV_{\text{Occl}}$) and antegrade APV as recorded after stenting at the same location as $APV_{\text{Occl}}$.\textsuperscript{19} A pressure-derived collateral pressure index (CPI) was calculated as the ratio of ($P_{\text{Occl}}$ - CVP)/($P_{\text{Ao}}$ - CVP), where CVP is the central venous pressure, which was substituted for by 5 mmHg.
In order to assess the contribution of the collateral donor pathway and of the peripheral microvasculature to blood flow in the collateral receiving segment distal to the TCO two resistance indexes were calculated (Fig. 1). The collateral resistance index was calculated as $R_{\text{coll}} = (P_{\text{Ao}} - P_{\text{Occl}})/\text{APV}_{\text{Occl}}$, and the peripheral resistance index was calculated as $R_{p} = P_{\text{Occl}}/\text{APV}_{\text{Occl}}$, both before recanalization and at the time of balloon reocclusion. A simplified formula for vascular resistances was used assuming steady laminar flow and constant vessel diameters, and flow velocity was used instead of flow volume.18,24

**Angiographic analysis**

The regional myocardial function distal to the occluded coronary artery was graded as normokinetic or moderately hypokinetic, and as severely hypokinetic or akinetic based on a biplane left ventriculography performed at the diagnostic procedure preceding the PTCA. The left ventricular ejection fraction was measured with a standard software program (LVA 4.0, Pie Medical Imaging, Maastricht, The Netherlands). The collateral supply was graded according to the classification of Rentrop.13 Preinterventional angiograms showed either collateral flow grade 2 (partial epicardial filling of the occluded artery) or grade 3 (complete epicardial filling of the occluded artery). All gradings were done independently by two experienced investigators, and in case of discordance consensus was obtained.

**Subgroup analysis**

Subgroups were analysed according to the duration of the TCO. In patients with clinically documented Q wave myocardial infarction (MI), the definition for duration of the occlusion was based upon the
date of the MI. In patients without MI, the onset or sudden worsening of angina pectoris determined the time of occlusion. An additional subgroup analysis included only those patients with MI.

Statistics

Data are given as the mean value±standard deviation. Student t-test, or a χ²-test when appropriate, was used to analyse differences between groups. Repeated measures ANOVA was used to compare changes of parameters between groups before and after PTCA. A level of p<0.05 was considered significant. All calculations were done on a PC using the statistical software SPSS for Windows (Version 10, SPSS Inc.).

Results

Clinical and angiographic characteristics

Thirty patients with type 2 diabetes mellitus (13 of them insulin-dependent) were compared with 60 patients without diabetes. The ratio of diabetic patients was similar in those with failed recanalization. In patients with diabetes hemoglobin A1c was 7.49±1.19 g/100 ml (upper limit of lab normal values: 6.6). Hypertension was more frequent in diabetic patients (Table 1). There was no difference in the rate of prior MI, regional and global left ventricular ejection fraction and duration of occlusion (median 3.3 months) between both groups. Diabetic patients had less severe symptoms of angina pectoris, but slightly more severe symptoms of heart failure, and a higher LVEDP. There was a trend towards more multivessel disease in diabetic patients, whereas the angiographic vessel diameters of the target arteries were comparable. The presence of significant lesions in the donor artery segment proximal to the collateral takeoff was similar in both groups with 13% in nondiabetic and 10% in diabetic patients. The quantitative angiography showed similar results after PTCA in both groups (Table 1).

Baseline and recruitable collateral function

The collateral flow was observed during the complete cardiac cycle in 60% of nondiabetic, and in 53% of diabetic patients (p=0.65). The quantitative Doppler flow parameters of baseline collateral flow were similar in both groups with a trend for a higher P_Coll and CPI in diabetic patients (Table 2). The resistance indexes R_Coll and R_P, which combined Doppler and pressure parameters, showed a wide distribution of individual values but no significant difference of the mean values (Fig. 2). As there was a different distribution of right and left coronary occlusions between both groups, the aforementioned indexes were calculated for right coronary artery occlusions separately. This yielded similar results for both Doppler and pressure parameters.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and angiographic characteristics</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No diabetes (n=60)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.2±10.3</td>
</tr>
<tr>
<td>Gender (female) (%)</td>
<td>22</td>
</tr>
<tr>
<td>Number of diseased arteries (1/2/3) (%)</td>
<td>48/35/17</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>65</td>
</tr>
<tr>
<td>Angina pectoris (CCS 0–4) (%)</td>
<td>0/2/37/61/0</td>
</tr>
<tr>
<td>Heart failure (NYHA 0–4) (%)</td>
<td>2/45/41/12/0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>65</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>72</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>45</td>
</tr>
<tr>
<td>Duration of occlusion (/3 months) (%)</td>
<td>53</td>
</tr>
<tr>
<td>Time since occlusion (months)</td>
<td>23±52</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>58.5±17.7</td>
</tr>
<tr>
<td>Regional dysfunction (%)</td>
<td>63</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>15±8</td>
</tr>
<tr>
<td>Target vessel (right/LAD/LCX) (%)</td>
<td>50/45/5</td>
</tr>
<tr>
<td>Collateral grade (Rentrop 2/3) (%)</td>
<td>27/73</td>
</tr>
<tr>
<td>Epicardial collateral pathway (%)</td>
<td>27</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.61±0.51</td>
</tr>
<tr>
<td>Minimum stent diameter (mm)</td>
<td>2.13±0.54</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1.9±1.0</td>
</tr>
</tbody>
</table>

CCS-classification of chest pain according to the Canadian Cardiovascular Society.
NYHA-classification of heart failure according to the New York Heart Association. LAD=left anterior descending; LCX=left circumflex; LVEDP=left ventricular end-diastolic pressure.
Recruitable collateral function was assessed after completion of the PTCA during a final balloon occlusion of 3 min duration. The time delay between baseline measurement and reocclusion was identical in both patient groups (diabetics: 36±16 vs nondiabetics: 33±16 min; p=0.50).

### Duration of occlusion and collateral function

The starting point of collateral development was approximated by either the date of a previous MI in 65% of patients, or the onset of clinical symptoms. Patients with a recanalization within 2–4 weeks after a MI had both a higher baseline and recruitable $R_{\text{Coll}}$ than those with a longer duration of the occlusion (Fig. 3). To reduce the uncertainty of the occlusion date we analysed patients with MI separately and observed the same time-dependent relation for $R_{\text{Coll}}$.

### Discussion

The present study assessed the collateral function of TCOs by intracoronary Doppler and pressure sensors before and after a PTCA. No differences in parameters of collateral function between diabetic and non-diabetic patients were observed indicating a similar development of collaterals in TCOs. However, the acute recruitment of collateral function after recanalization as assessed during a balloon reocclusion was impaired in diabetic patients with an occlusion of <3 months duration.

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**Table 2** Parameters of collateral function

<table>
<thead>
<tr>
<th></th>
<th>No diabetes (n=60)</th>
<th>Diabetes (n=30)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$APV_{\text{Occl}}$ (cm/s)</td>
<td>10.7±5.8</td>
<td>10.2±5.8</td>
<td>0.64</td>
</tr>
<tr>
<td>$P_{\text{Occl}}$ (mmHg)</td>
<td>44±14</td>
<td>50±12</td>
<td>0.07</td>
</tr>
<tr>
<td>CPI</td>
<td>0.39±0.12</td>
<td>0.43±0.10</td>
<td>0.14</td>
</tr>
<tr>
<td>CFI</td>
<td>0.39±0.25</td>
<td>0.40±0.30</td>
<td>0.91</td>
</tr>
<tr>
<td>$R_{\text{Coll}}$ (mmHg/cm/s)</td>
<td>8.1±6.8</td>
<td>8.7±6.7</td>
<td>0.68</td>
</tr>
<tr>
<td>$R_p$ (mmHg/cm/s)</td>
<td>5.6±4.2</td>
<td>6.6±3.8</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*p-value is shown. Data are mean ± SD.

APV=average peak velocity; CFI=collateral flow index; CPI=collateral pressure index; $P_{\text{Occl}}$=distal mean coronary pressure; $R_{\text{Coll}}$=collateral resistance index; $R_p$=peripheral resistance index.
Assessment of collateral function

Blood supply to myocardial segments distal to an occluded artery depends on the conductance of the collaterals between the donor and recipient artery. As there are often more than one collateral connection present, which cannot be assessed individually, a simplified approach was developed to assess the functional capacity of all collateral connections together by a collateral resistance index.18,21,24

This index contains also the resistance of the donor...
artery segment proximal to the collateral takeoff (Fig. 1). Despite these simplifications the invasive approach to collateral function is superior to angiographic techniques.\textsuperscript{15,17} Well-developed collaterals are characterized by a low collateral resistance. In TCOs the collateral resistance was in the lower range of that observed in nonocclusive lesions with well-developed collaterals.\textsuperscript{21,24}

Collateral function in diabetes mellitus

There is an ongoing discussion whether arteriogenesis is impaired in diabetes mellitus despite an increased angiogenesis.\textsuperscript{7,25,26} Our data show no difference in collateral development between diabetic and nondiabetic patients with TCOs. Except for slightly more multivessel disease in diabetic patients, the rate of prior MI and left ventricular function were similar in both groups. A similar percentage of patients with normal left ventricular function in both patient groups indicated that a gradual development of the occlusion lead to a sufficient compensation of blood supply via collaterals to prevent regional dysfunction both in diabetic and nondiabetic patients.

Collateral development in diabetics

Angiographic studies had shown the first appearance of collaterals within 2 weeks after acute MI.\textsuperscript{27,28} Our data show a further maturation of collaterals during the first 12 weeks after occlusion.\textsuperscript{21} This is in analogy with animal studies where collateral development required about 8 weeks.\textsuperscript{29,30} It is difficult to determine the starting point of collateral development in man, but both in the total study group and in the subset of patients with documented MI there was no evidence for a difference in the development of collateral function between diabetic and nondiabetic patients. \(R_{\text{Coll}}\) was higher in both diabetic and nondiabetic patients in the first weeks after the occlusion, and it decreased to a similar level in TCOs of \(\geq 3\) months duration.

In a previous retrospective analysis by Abaci et al.\textsuperscript{8} an impaired collateral development in diabetics was reported, but there are considerable differences in method, design and patient selection as compared to our study. Their analysis contained a large number of nonoccluded lesions while we studied only TCOs. There may be a difference in collateral development for nonocclusive lesions, however, a number of other angiographic studies which also assessed mainly nonocclusive lesions did not observe such differences between diabetic and nondiabetic patients.\textsuperscript{9–12} We cannot solve the discrepancy between the above studies in nonocclusive lesions, but for totally collateral-dependent TCOs we can conclude that the functional capacity of collaterals measured before a recanalization procedure was not impaired by diabetes mellitus.

Collaterals regress after PTCA,\textsuperscript{31} but some collaterals remain recruitable,\textsuperscript{32,33} especially when a reocclusion occurred gradually.\textsuperscript{34} We had recently shown that after recanalization of a TCO the collateral function is considerably attenuated during acute reocclusion,\textsuperscript{20} which is a specific feature in TCOs as compared to collaterals in nonocclusive lesions.\textsuperscript{35} This observation provides an explanation for the incidence of acute MI after PTCA of previously well collateralized TCOs in case of an acute reocclusion.\textsuperscript{36,37}

Recruitable collateral function after recanalization was reduced more in TCOs of \(< 3\) months duration than in TCOs \(\geq 3\) months. This can be explained by the aforementioned difference between newly developing collaterals with a monolayer muscular wall and limited capacity to respond to modulators of vascular tone, and mature collaterals with a multilayer wall structure.\textsuperscript{29,30,38} The former collaterals might collapse once the pressure gradient is abolished by a recanalization and would not instantaneously reopen during a reocclusion, in contrast to mature collaterals. Our study demonstrated an impaired recruitment of collaterals in diabetic patients in TCOs \(< 3\) months duration, whereas recruitment improved in TCOs \(\geq 3\) months duration. This difference between diabetic and nondiabetic patients may be due to a delayed development of collaterals,\textsuperscript{25,26} and/or an impaired endothelial function of the collaterals in diabetic patients, which impeded the rapid recovery of collateral function.

Peripheral myocardial resistance and diabetes

The impaired collateral recruitment in diabetic patients was accompanied by a pronounced increase of the microvascular resistance. This correlates well with the observation of an impaired microvascular function in diabetic patients.\textsuperscript{39–41} Together with the collateral resistance, the microvascular resistance determines the blood flow distal to an occluded coronary segment. The difference observed between diabetic and nondiabetic patients adds to the impaired blood supply through collaterals during reocclusion in diabetic patients.
Limitations of the study

The calculation of $R_{\text{Col}}$ and $R_p$ is simplified by assuming steady flow instead of pulsatile flow, and is based on flow velocity rather than volume flow. The same approach was chosen by other investigators, well aware that the vessel diameter before and after an occlusion could vary. In order to minimize the influence of diameter changes, nitroglycerine was given during the procedure. The CVP, which influences the calculation of the pressure-derived CPI, was not directly measured. But as we assume no relevant change during the procedure this would not influence the interpretation of our data.

The number of patients in this study is small as compared to some of the previous studies using angiography to assess collaterals in diabetics. However, this is outweighed by the use of a quantitative assessment of collateral function, whereas the angiographic method is a semiquantitative grading of collateral contrast filling, highly sensitive to the variability of manual contrast injection, and with a poor relation to invasive parameters of collateral function.

The angiographic assessment of coronary artery disease may not represent the true extent of atherosclerosis, which is better assessed by intravascular ultrasound. There was a trend towards more multivessel disease in diabetic patients, and this may indicate more advanced atherosclerosis in that group. A certain selection bias cannot be completely ruled out. More advanced atherosclerosis in diabetics may limit collateral function by a reduced pressure gradient in the donor artery segment. That the degree of atherosclerosis did not influence the pressure gradient is also shown by the similar CPI in both groups.

Clinical implications

The rapid recruitment of preformed collaterals for the protection of the myocardium during an acute coronary reocclusion is impaired in patients with diabetes mellitus. In addition we observe an impaired microvascular function which may, together with the impaired collateral recruitment, provide a possible explanation for the higher cardiac adverse event rate of patients with diabetes after an acute MI or coronary interventions.

Acknowledgement

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References