Diabetes and distal access location are associated with higher wall shear rate in feeding artery of PTFE grafts

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Abstract

Background. Surgical creation of permanent vascular access for haemodialysis leads to considerable haemodynamic changes. They could be implicated in the pathogenesis of access complications, which limit access survival, especially in diabetics. Physiologically, the relation between arterial diameter and blood velocity is maintained by wall shear stress (WSS), which is directly related to both blood viscosity and wall shear rate (WSR = blood velocity/internal diameter). Because of methodological difficulties, WSR is used as a measure of WSS. Extremely high values of WSS might induce hypercoagulable states, which might contribute to access thrombosis. We performed a study, which was aimed to (i) describe WSR values in feeding arteries of various polytetrafluoroethylene access types and (ii) prove that diabetic patients have higher WSR than non-diabetes.

Methods. A linear-array 11 MHz probe of SONOS 5500 (Phillips, USA) was used to obtain blood velocity and internal diameter in the feeding arteries of radial or brachial polytetrafluoroethylene grafts. WSR was calculated as $4 \times \text{blood velocity/internal diameter}$. We compared observed values of WSR according to feeding artery (radial vs brachial artery) and according to diabetic status using unpaired t-test.

Results. We included 106 patients (58 non-diabetic and 48 diabetic) in the study. WSR was significantly higher in radial arteries compared with brachial arteries independent of diabetes status. Diabetic subjects had significantly higher WSR in both radial and brachial arteries.

Conclusions. Diabetes mellitus and distal vascular access creation are associated with higher WSR in the feeding artery. This could be of relevance in the pathogenesis of access complications, e.g. thrombosis, and thus lower patency rates in diabetic patients.

Keywords: diabetes mellitus; haemodialysis; ultrasonography; vascular access; wall shear rate; wall shear stress

Introduction

Chronic haemodialysis treatment requires repeated entries into the blood stream. The so-called permanent vascular access is used for this purpose. Creation of the permanent vascular access leads to significant haemodynamic changes in both the limb and whole body. Moreover, despite called 'permanent', the lifespan of the accesses is very limited.

Native arterio-venous fistula (AVF) is usually the access of first choice because of longer patency and lower complication rates [1]. However, when superficial veins are not suitable for AVF creation, a polytetrafluoroethylene (PTFE) graft (AVG) is used.

Both types of vascular access, especially the latter, have limited patencies. Besides others, haemodynamic factors are involved in the pathogenesis of access complications. Blood flow increases in the feeding artery just after access creation because of a sudden decrease of peripheral vascular resistance. Increased blood flow (and velocity) leads to arteriodilation. Endothelial cells possess special receptors, which detect physical forces. The leading force is the wall shear stress (WSS), having the vector tangential (not perpendicular as in the case of blood pressure) to the arterial lumen. WSS is directly related to whole-blood viscosity and to wall shear rate (WSR) [2]. WSR is defined as the difference between adjacent velocities in the vascular lumen. The ratio between the maximum velocity at the centre of the artery and the vessel radius is a common approximation of WSR [3]. WSR can be used as an approximation of WSS [3,4]. High values of WSR and WSS play a role in endothelial wall injury, von Willebrand factor (vWF) activation and platelet aggregation, which are implicated in thrombus formation [4,5].
According to Poiseuille’s law, WSR is linearly related to blood flow and inversely to the third power of vessel diameter [5]. Vascular accesses originating from brachial artery have higher flow, suggesting higher WSR in proximal accesses. On the contrary, larger diameter and less pronounced medial calcification rate [6] in brachial artery insinuate lower WSR in brachial artery.

Altered haemodynamics also play an important role in the induction and progression of diabetic vascular complications [7]. There is an increasing proportion of diabetics in the haemodialysis population. They suffer from considerably more frequent access complications, such as shorter patency, lower access flow and hand ischaemia on the access side [8]. Diabetic peripheral arteriopathy, in contrast to common atherosclerosis, also affects upper extremities, which are used for access creation. These structural changes in the arterial wall limit the regulation of vessel diameter, but consequently, because of higher peripheral vascular resistance, also the access flow, the two determinants of WSR. We hypothesized that the vascular accesses of diabetic patients have higher values of WSR than that of non-diabetics.

We performed a study, which was aimed to (i) describe WSR values in feeding arteries of various access types and (ii) prove that diabetic patients have higher WSR than non-diabetics.

### Subjects and methods

During a 4-year period (2001–05) we consecutively included patients with a newly created, well-functioning upper extremity PTFE graft in the General University Hospital, Prague. Basic demographic data and diabetic status were recorded.

It is known that AVG maturates approximately within 14 days [1], so we examined vascular accesses 14–180 days after their creation. Linear-array 3–11 MHz probe of SONOS 5500 device (Phillips, USA) was used. After careful examination of the whole access by duplex Doppler ultrasonography, as described earlier [9], the attention turned to imaging and recording the artery. Ultrasound measurements were performed at the feeding artery 1–2 cm proximal to arterial anastomosis. The centreline peak, mean and minimal velocities and internal artery diameter were measured.

Patients with large arterial wall calcifications that made the exact assessment impossible were excluded from the study. Similarly, subjects with access complications (stenosis, thrombosis, inflammation and clinically apparent peripheral ischaemia) were also excluded.

WSR was calculated using the Poiseuille parabolic model of velocity distribution across the arterial lumen based on the assumption of laminar blood flow, according to the following formula [10–12]:

\[
WSR = 4 \times \frac{V}{ID}
\]

where WSR is the wall shear rate (s\(^{-1}\)), V is the blood velocity (m/s), and ID is the artery diameter (m). WSR was calculated separately for peak (systolic), mean and minimal (end-diastolic) blood velocity.

Recorded values were compared according to access types (radial vs brachial artery) and according to diabetic status using unpaired t-test. Data are expressed as mean ± SD.

### Results

A total of 106 patients was included in this study; 58 of them were non-diabetics and 48 diabetics. Basic demographic characteristics are listed in Table 1.

#### Brachial vs radial AVG comparison

Mean and minimal velocities were higher in the radial artery, but this difference was significant only in diabetic patients. Distal (radial) accesses were characterized by significantly lower feeding artery diameters in both diabetic and non-diabetic patients. Peak, mean and minimal WSR were significantly higher in distal accesses arteries.

#### Diabetics vs non-diabetics

Diabetic subjects had significantly higher peak and mean arterial blood velocities in radial, but not brachial AVGs. Arterial diameter was significantly lower in diabetic patients in both access types. Arterial WSR was significantly higher in diabetic patients in both radial and brachial AVGs.

The results are summarized in Table 2.

### Discussion

This study has shown that feeding arteries of vascular accesses are exposed to unusually high WSR. WSR is even higher in arteries of distal accesses and in diabetic subjects.

Physiologically, WSS controls the relation between arterial diameter and blood flow. An increase in the blood flow leads to higher WSS, which, in turn, is followed by arteriodilation and decrease of WSS. Similarly, a decrease in blood flow leads to vasoconstriction [5]. The adaptation of the vessel diameter represents an important feedback mechanism to keep WSS within a narrow, so-called physiological range [3,13]. The adaptation has two steps: (i) rapid dilation within minutes as seen in flow-mediated vasodilation [14] and (ii) long-term structural adaptation of vessel wall [2,15]. Rapid adaptation to the blood flow changes is mediated by changes in vascular smooth muscle tone, which is endothelium-dependent (e.g. flow mediated vasodilation) [16]. Arterial remodelling is a long-term, partly endothelium-dependent structural adaptation of the vessel wall [15].

Little differences in blood velocities do not explain substantial differences in arterial WSR in radial and brachial AVGs; this is rather the result of different internal diameter of these arteries and their capability to dilate. Brachial artery has a greater diameter than
Wall shear rate in feeding artery of vascular access

Table 1. Group characteristics

<table>
<thead>
<tr>
<th></th>
<th>Radial artery</th>
<th>Brachial artery</th>
<th>Non-DM Radial artery</th>
<th>Brachial artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>27 (47%)</td>
<td>21 (43%)</td>
<td>30 (53%)</td>
<td>28 (57%)</td>
</tr>
<tr>
<td>Age (mean ± SD) (years)</td>
<td>68 ± 10</td>
<td>66 ± 10</td>
<td>62 ± 17</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Men/women</td>
<td>6/21</td>
<td>7/14</td>
<td>10/20</td>
<td>7/21</td>
</tr>
<tr>
<td>Number of previous accesses (median)</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus. There were no significant differences in age and sex distribution between groups.

Table 2. Haemodynamic parameters in feeding arteries

<table>
<thead>
<tr>
<th></th>
<th>DM Radial artery</th>
<th>Brachial artery</th>
<th>Non-DM Radial artery</th>
<th>Brachial artery</th>
<th>P-value DM vs Non-DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>27</td>
<td>21</td>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>$V_{peak}$ (cm s$^{-1}$)</td>
<td>235 ± 73</td>
<td>206 ± 57</td>
<td>181 ± 70</td>
<td>178 ± 48</td>
<td>0.006</td>
</tr>
<tr>
<td>$V_{mean}$ (cm s$^{-1}$)</td>
<td>179 ± 55</td>
<td>149 ± 46*</td>
<td>145 ± 55</td>
<td>133 ± 33</td>
<td>0.021</td>
</tr>
<tr>
<td>$V_{min}$ (cm s$^{-1}$)</td>
<td>139 ± 46</td>
<td>108 ± 40*</td>
<td>118 ± 46</td>
<td>103 ± 23</td>
<td>0.100</td>
</tr>
<tr>
<td>ID (mm)</td>
<td>2.7 ± 0.8</td>
<td>4.1 ± 0.8***</td>
<td>3.3 ± 0.8</td>
<td>5.0 ± 0.8***</td>
<td>0.012</td>
</tr>
<tr>
<td>WSR$_{peak}$ (s$^{-1}$)</td>
<td>4040 ± 2889</td>
<td>2070 ± 670***</td>
<td>2512 ± 1623</td>
<td>1477 ± 582***</td>
<td>0.002</td>
</tr>
<tr>
<td>WSR$_{mean}$ (s$^{-1}$)</td>
<td>3043 ± 2041</td>
<td>1490 ± 528****</td>
<td>1985 ± 1169</td>
<td>1103 ± 401****</td>
<td>0.003</td>
</tr>
<tr>
<td>WSR$_{min}$ (s$^{-1}$)</td>
<td>2313 ± 1384</td>
<td>1075 ± 422***</td>
<td>1606 ± 913</td>
<td>848 ± 278***</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Values are means ± SD.
DM, diabetes mellitus; $V$, blood velocity (peak, mean, minimal); ID, internal diameter of the artery; WSR, wall shear rate (peak, mean, minimal).
Statistical significance of the difference between radial and brachial arteries is expressed by the asterisks in the particular column: *$P < 0.05$, **$P < 0.001$, ***$P < 10^{-3}$.
$P$-values comparing subjects with and without diabetes are listed at the right-hand side of the table separately for radial and brachial artery.

the radial artery even before access creation [6]. Furthermore, the vessel wall response to increased blood flow could be limited by structural changes of the vessel wall, such as calcification. Arterial medial calcification is more pronounced in diabetic patients, but uraemia per se also contributes to their development [17]. After access creation, blood-flow volume (and thus also WSR) increases in the feeding artery. High WSR induces the production of vasodilating nitric oxide in the endothelium. However, despite vasodilation, WSR is not normalized, probably due to the too high increase of blood flow. The difference between proximal and distal accesses arterial WSR could probably be explained by (i) higher baseline diameter of brachial artery and (ii) mediocalcinosis, which is more frequent in antebrachial arteries [6].

Konner [6] reported that the arterial calcification was less pronounced in the elbow than in the wrist region. In diabetic patients, atherosclerotic and calcified radial arteries do not undergo adaptive flow-mediated vasodilatation to deliver sufficient fistula blood flow [6]. In these patients, decreased vasodilation ability is probably a result of both endothelium dysfunction linked to hyperglycaemia [18] and structural vessel wall changes [17]. Distal arterial diabetic involvement (vessel wall calcifications and impaired-flow-mediated vasodilatation) probably explains higher WSR in the feeding arteries of diabetic subjects.

Early thrombosis and low access flow are major causes of graft failure in haemodialysed patients and especially in diabetics [6]. Subjects with diabetes mellitus have increased levels of the vWf and decreased levels of tissue plasminogen activator [18]. vWf plays a critical role in thrombus formation on PTFE surfaces. This is particularly efficient under conditions of high shear rate [19]. At such conditions, vWf is directly activated, binds to an exposed sub-endothelium and activates platelet accumulation. Pathologically high shear rates (around 8000 s$^{-1}$), such as those at atherosclerotic stenosis, may directly activate platelet aggregation [4]. Fibrin deposition increases also with an increasing shear rate [19]. All these pathological events lead to a local hypercoagulable state.

Huber et al. [20] have reported lower patency rates in distal PTFE AVGs compared with proximal ones. This could suggest that high WSR may play a role in lower patency rates in distal PTFE accesses, but further investigations are needed to ascertain this hypothesis. High WSR in accesses of haemodialysed patients, and diabetics in particular, may play a role in access thrombosis and possibly also in hand ischaemia.
A possible limitation of our study is the use of WSR measurement as an estimation of WSS, because endothelial cells sense directly WSS and not WSR. WSS depends linearly on WSR and on blood viscosity. Most papers [2,10] focus on WSS as a more accurate index of blood-flow influence on endothelial cells. Nevertheless, to obtain the exact value of WSS one needs to know blood viscosity. Some authors [2] use an arbitrary value for blood viscosity to estimate shear stress or use viscometry to measure it [10–12,14]. It was shown that even actual measurements of viscosity must not lead to real values of shear stress [4]. The use of an arbitrary value of blood viscosity would not change the statistical significance of the results. For these reasons, we used WSR measurement.

We can conclude that feeding arteries of dialysis vascular accesses are exposed to supraphysiological values of WSR shortly after access creation. High WSR may play a role in the development of access complications. Further research should reveal if long time exposition to high WSS is able to normalize or at least lower WSR.

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Conflict of interest statement. None declared.

References


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