Short-term outcomes of borderline stenoses in vascular accesses with PTFE grafts

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Abstract

Background. There are controversial data about vascular access stenoses surveillance by ultrasonography. The definition of stenosis significance varies among centres. We performed a retrospective study to describe short-term outcomes of borderline asymptomatic stenoses defined by precise criteria and to determine possible risk factors of stenosis progression.

Methods. We studied the outcome of borderline stenoses in accesses with PTFE grafts. Stenosis was considered significant if there was a combination of >50% lumen reduction and peak systolic ratio >2, together with at least one of the following additional criteria: (1) residual diameter <2.0 mm and (2) flow reduction of >25% or actual flow volume <600 ml/min. Stenosis was considered borderline in the absence of the additional criteria.

Results. Of the 102 borderline stenoses, after 11 ± 6 weeks, 55 remained non-progressive, in 38 the degree of the stenosis progressed, in 8 a percutaneous transluminal angioplasty (PTA) was performed due to clinical indication and only 1 thrombosed. A significant relative risk of developing significant stenosis especially after prior PTA. We believe that the definition of precise criteria of stenosis significance is necessary for the benefit of ultrasound surveillance.

Conclusions. Delaying PTA of borderline stenoses is safe using this watch-and-wait strategy and stenoses remain stable over at least short time, but with higher risk of progression especially after prior PTA. We believe that the definition of precise criteria of stenosis significance is necessary for the benefit of ultrasound surveillance.

Keywords: borderline stenosis; duplex Doppler ultrasound; haemodialysis vascular access

Introduction

Vascular accesses are ‘lifelines’ for patients on haemodialysis. Unfortunately, their patency is limited [1], and their management is associated with significant morbidity and costs [2,3]. The major cause of vascular access dysfunction is stenosis with a subsequent decrease of blood flow, inadequate dialysis dose or thrombosis leading to obliteration [4–6]. The risk of thrombosis is 0.2 events per patient/year for autogenous arteriovenous fistula (AVF) and 0.8–1 event per patient/year for access with polytetrafluoroethylene (PTFE) graft [2].

Percutaneous transluminal angioplasty (PTA) is the stenosis therapy of first choice [7,8]. Thrombolysis and subsequent angiography of acutely thrombosed grafts usually reveal the presence of at least one significant stenosis; e.g. in the study of Cohen et al. [9] this was observed in 85% of cases. The presence of a stenosis is associated with increased thrombosis rate: more than half of the patients with >50% stenosis in PTFE suffered from vascular access thrombosis within 6 months [10].

On the other hand, the long-term outcomes after PTA are poor. Six-month unassisted patency rates after PTA are 25% for grafts and 50% for AVF [11]. Furthermore, it is known that not all grafts with a blood flow decrease and/or a venous pressure increase are at risk of thrombosis [12,13]. According to McDougal, only ~50% of such grafts are at risk of thrombosis within 1 year [12]. Allon therefore suggested in a recent review that aggressive referral for preemptive PTA would necessarily result in many superfluous interventions [14]. It is also obvious that any unnecessary PTA results in patients’ discomfort and increased costs.

The question therefore is: which stenoses should be treated and when? In our centre, we performed a randomized trial, which proved that ultrasound graft surveillance significantly prolongs graft patency [4]. Already in this study, we introduced the so-called borderline stenosis category. Such stenoses were indicated to repeated duplex Doppler ultrasonography (DDU) examination within 6 weeks. During this time period, high attention was paid at the haemodialysis units, which were instructed to perform angiography immediately if any clinical suspicion of stenosis progression develops. PTA was directly indicated by the ultrasound only when the stenosis was clearly...
haemodynamically significant. Such ‘watch-and-wait’ strategy in asymptomatic borderline stenoses probably also reduces the number of PTAs. Due to the small number of borderline stenoses in this study, we were not able to statistically evaluate the safety of this approach. Therefore, we conducted the present study aiming to (1) test the hypothesis that it is safe to delay borderline stenosis treatment in patients without clinical evidence of graft dysfunction in stenoses both with and without prior PTA; (2) determine possible risk factors of stenosis progression; and (3) determine the long-term outcome of constant stenosis.

Subjects and methods

For the purpose of this retrospective study, we searched our database of participants of the stenosis surveillance programme of accesses with PTFE grafts in General University Hospital, Prague, Czech Republic. The patients came from 17 dialysis units in Czech Republic. Grafts were examined every 3 months using duplex Doppler ultrasound [broad-band linear-array 3–11 MHz probe of SONOS 5500 device (Phillips, USA)], as described earlier [4]. In brief, B-mode images and colour-coded images were obtained from the feeding artery, arterial anastomosis, the whole graft, the venous anastomosis and the outflow vein. Centreline systolic and end-diastolic velocities were obtained from the feeding artery and from the venous anastomosis in all grafts. Blood flow was measured in the venous part of the graft at least 2 cm distal to the venous anastomosis. When stenosis was suspected (aliasing in colour-Doppler mapping and/or narrowing in B-mode), systolic velocity in the stenotic and pre-stenotic regions was recorded to calculate peak systolic velocity ratios (PSR). PSR was defined as the ratio of the peak velocity inside the stenosis and the peak velocity in an adjacent unaffected pre-stenotic segment.

Stenoses were considered significant if there was a combination of >50% lumen reduction in B-mode and PSR > 2; together with at least one of the following additional criteria: (1) residual diameter < 2.0 mm and/or (2) low blood flow (< 600 ml/min) or the blood flow reduction of >25%. Stenosis was considered borderline in the absence of any of the additional criteria. Patients with significant stenosis were referred to PTA, while those with borderline stenosis were advised to come for a re-examination after 6–8 weeks. Within this period, the watch-and-wait strategy was maintained—i.e. direct referral to PTA in any suspicion of stenosis progression or other doubts in the haemodialysis unit (i.e. rise of venous pressure, changes in regular physical examination of the access . . .).

Patients with borderline stenoses were divided into two groups according to their prior PTA history: PTA-naive group (no prior PTA was performed on the stenosis before the inclusion) and PTA-experienced group (where at least one PTA was performed at the location of the stenosis).

To estimate the safety of PTA delay, we defined the following combined endpoint: the progression of the stenosis into significant as defined above or clinical indication to PTA due to clinical suspicion on stenosis progression and/or thrombosis of the graft. Subjects, who developed any of these endpoints, composed the ‘Progression group’ for the purpose of risk factor analysis. The others (non-progressive stenosis) formed a Constant group (stable DDU characteristics during both examinations).

To determine risk factors of stenosis progression, we recorded patients’ characteristics (gender, age, presence of diabetes mellitus, dyslipidaemia) and specific vascular access graft characteristics [stenosis location, number of stenoses found during the examination, access flow (Qa), graft age and the history of previous PTA]. We compared the Constant and the Progression groups first for all borderline stenoses and then separately for the PTA-naïve and PTA-experienced groups.

Mid-term outcomes (same endpoints) were studied in the Constant group. The time to endpoint was calculated since the inclusion, i.e. since the first ultrasonography, which detected borderline stenosis.

Data were expressed as mean ± SD for numerical variables and frequencies as percentage. For access age, we used median, minimal and maximal values. For comparison between groups, we used the unpaired t-test or the chi-squared test as appropriate. Risk ratios (RR) of combined endpoint and their 95% confidence intervals (CI) were calculated for all variables. All calculations were performed using statistical software (STATISTICA CZ 6, StatSoft, Inc., USA, 2003). Only for RR and CI calculations, we used the OpenEpi software (Dean AG, Sullivan KM, Soe Version 2.2.1 www.OpenEpi.com, updated 26 October 2008). The value of P < 0.05 was considered significant.

Results

We found 106 borderline stenoses in PTFE grafts in our database during the last 3 years; four were excluded from analysis because the outcome and the appropriate history could not be obtained (Figure 1). The median access age at inclusion was 290 days (interquartile range: 447 days). Patients’ characteristics are summarized in Table 1. The mean time interval between examination and subsequent DDU control increased due to logistic problems to 11 ± 6 weeks. The stenoses characteristics at inclusion are summarized in Table 2.

The results are summarized in Figure 2. Endpoints occurred in 47 (46.1%) of 102 stenoses: in 38 (37.3%), stenosis progression was evident on the next ultrasonography, in 8 (7.8%), a PTA was performed due to a clinical indication and 1 graft (1.0%) thrombosed. Fifty-five borderline stenoses (54.0%) remained stable. In the PTA-naïve group, 42 (65.6%) stenoses remained constant, 19 (29.7%) progressed to significant, in 2 (3.1%) a PTA was performed and 1 (1.6%) thrombosed. In the PTA-experienced group, 13 (34.2%) stenosis remained constant, 19 (50.0%) progressed to significant, and PTA was performed in 6 (15.8%) cases.

Stenoses with any endpoint differed significantly from stable stenoses by the history of previous PTA (53% versus 24%, P = 0.0011), female gender (79% versus 47%,
Baseline DDU record:
>50% stenosis and PSR>2
n = 260

Additional DDU criteria?
- residual diameter < 2mm
- and/or Qa < 600ml
- and/or ΔQa > 25%

Yes
Significant stenosis
n = 154

No
Borderline stenosis
n = 106

Percutaneous transluminal angioplasty

Outcome data not available
n = 4

Included into this study
n = 102

Fig. 1. Strategy of patient selection into this study. DDU, duplex Doppler ultrasonography; PSR, peak systolic velocity ratio; Qa, blood flow through the vascular access.

Borderline stenosis
n = 102

Repeated DDU
(14 ± 6 weeks)

Progressive
n = 47
- Progression n = 38
- PTA n = 8
- Thrombosis n = 1

Constant
n = 55

Observation
(29 ± 18 weeks)

Progressive
n = 19

Constant
n = 5

Lost to follow-up
n = 20

Percutaneous transluminal angioplasty
Further observation

Fig. 2. Flow chart of borderline stenoses outcome. PTA, percutaneous transluminal angioplasty; Qa, access flow; ΔQa, change of access flow since the last examination.

\[ P = 0.002 \] (Table 3) and by lower blood flow measured during the first ultrasonography (774 ml/min versus 865 ml/min, \( P = 0.05 \)). The two groups were similar in all other characteristics mentioned in the Subjects and methods section. When the same analysis was performed separately in the PTA-naive and the PTA-experienced groups, only gender remained significant in both (\( P = 0.01 \)). The relative risk of the combined endpoint was statistically significant in female gender [RR = 2.29, (95% CI: 1.291, 4.063), \( P = 0.001 \)] and previous PTA [RR = 1.91 (95% CI: 1.272, 2.88), \( P = 0.002 \)]. All other potential risk factors were non-significant.
The mid-term (30 ± 18 weeks) follow-up of the stenoses in the Constant group was as follows: 19 of 54 constant stenoses progressed to significant ones and then were indicated to PTA, 8 had PTA instead of the next DDU, 2 thrombosed, 5 remained constant during the observation period. In the remaining records (N = 20), the follow-up data are not available. The time to detection of stenosis progression was 230 ± 150 days (range 32, 609 days), the time to thrombosis in the two cases was 196 and 231 days and the time to evaluation of constant stenosis was 252 ± 92 days (range 158, 350 days).

**Discussion**

The main finding of this study is that more than a half of borderline stenoses (defined by the aforementioned DDU criteria) in PTFE grafts remain stable and that delaying PTA by 3 months is safe in centres where close clinical monitoring is performed. Our results indicate that this approach could be safe in both types of stenoses, with and without prior PTA. However, the occurrence of the endpoint was more likely in stenoses with prior PTA and in female gender. The majority of borderline stenoses progress later into significance.

The definition of stenosis severity is, according to our opinion, crucial for the evaluation of its significance. Several trials of ultrasound surveillance that failed to prove its profit used 50% diameter reduction in B-mode as the only criterion of significant stenosis [15,16]. This approach can easily lead to overestimation as well as underestimation of the stenosis severity due to technical limits caused by the presence of calcifications in the vessel wall, inappropriately high gain, cross section, etc. [17]. A possible presence of these confounding factors is known also in the case of ultrasound examination of arteries, and this is why a stenosis must be described also by the velocity change obtained by Doppler examination. The velocity increase (i.e. peak velocity ratio) [3,4,18] is mandatory for the detection of significant stenosis in some centres, [19,20] including ours.

Blood flow decline is another used criterion [7] that we also use because there is limited availability of intradialytic access flow measurement in our country. We use another additional criterion—the residual diameter of 2 mm in grafts [4]. It is a clear cut-off value, and in 5–6 mm PTFE grafts, a residual diameter of 2 mm corresponds to 66% stenosis (diameter reduction).

Blood flow decline is the strongest predictor of future graft failure [7]. According to Paulson, a haemodynamically significant stenosis should be associated with a decline in blood flow [21]. Mathematical haemodynamic simulations indicate that flow decreases by <20% until the stenosis process produces a 40–50% decrease in a luminal diameter. As the degree of stenosis increases to 80%, the flow decreases rapidly [22]. On the other hand, Krivitski presented a mathematical model, where he documented that not all >50% stenoses manifest by a >25% decrease of access flow, which is a value when intervention is recommended by K/DOQI [7]. It is especially the case of those stenoses, which cause lower resistance than the arterial anastomosis, namely in grafts with higher blood flow (1250–2500 ml/min).

Stenoses remain stable in some grafts, but progress rapidly in others [23]. In the study of Sivanesan et al., the progression rate of a stenosis in native fistulas depended on the stenosis location. Progressive stenosis developed more often in patients with previous access surgery [24].

The attempt to preemptive PTA differs among centres and trials. A recent meta-analysis by Tonelli [25] concluded that graft surveillance and pre-emptive PTAs do not prolong graft patency. Criticism of this meta-analysis was published [26,27], directed especially to the selection of the studies, which used different diagnostic criteria. In some studies, preemptive PTA failed to prolong graft patency when >50% stenosis was diagnosed and corrected in asymptomatic grafts [15,16,18]. On the other hand, the corrections of 50% stenosis in virgin grafts prolonged patency [4,28]. Stenoses after PTA develop faster than do de novo access stenoses [29]. Unnecessary PTA could stimulate progression of stable stenotic lesions [23]. Increased cell proliferation activity in post-PTA restenotic lesions of haemodialysis vascular access was documented [30]. We can therefore speculate that delaying the first PTA in a stable graft stenosis could theoretically prolong graft patency due to a slower progression of the stenosis. On the other hand, in rapidly progressing stenoses, such approach could be dangerous. Our study indicates that this watch-and-wait approach to borderline stenoses does not lead to access loss in >99% of grafts within 3 months. The randomized study, which tested the effect of ultrasound surveillance of grafts on their longevity performed in our centre, was one of the few with positive results [4,28]. We think that besides other differences, the approach to the borderline stenoses could, at least partly, explain positive results. There is no doubt that symptomatic stenoses, i.e. those jeopardizing the graft function, should be treated [7,8]. The situation is different when borderline stenosis is found in asymptomatic patients with well-functioning grafts.

Previous PTA, blood flow <800 ml/min and female gender were all associated with the increased relative risk of developing significant stenosis, but even in these patients delaying the correction of borderline stenosis was safe. Females had shorter patency of PTFE vascular accesses.

| Table 3. Proportion of constant versus progressive stenosis according to gender and previous PTA history (percent of the Constant and Progression groups, respectively) |
|---------------------------------|---------------------------------|
| **Constant group** | **Progression group** |
| **Number** | **% of the group** | **Number** | **% of the group** |
| Females, PTA experienced | 8 | 14.5% | 21 | 44.7% |
| Females, PTA naive | 18 | 32.7% | 16 | 34.0% |
| Males, PTA experienced | 5 | 9.0% | 4 | 8.5% |
| Males, PTA naive | 24 | 43.6% | 6 | 12.8% |

PTA, percutaneous transluminal angioplasty.
[31] and higher progression rates of stenosis also in other studies [32]. The higher relative risk of endpoints in females in this study is in accordance with these observations.

Even in the Constant group, stenoses progressed to significant when the follow-up was long enough. From the 34 stenoses, in which we could obtain the mid-term follow-up, only 5 remained constant. The majority of stenoses in our population progressed to significant. It would be interesting to perform a prospective study of borderline stenoses outcome.

The main limitation of our study is its retrospective design. For accurate evidence-based recommendations, a prospective randomized control trial should be performed to prove if this approach leads to lower costs, less discomfort for the patients and possibly lower graft patency.

From all above, we think that PTA should be performed in any dysfunctional stenosis and that in borderline stenoses it should be delayed. It is crucial to clearly define the sonographic criteria for stenosis significance and not to rely only on B-mode detection of >50% stenosis.

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References


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