A Prospective Controlled Trial on Effect of Percutaneous Transluminal Angioplasty on Functioning Arteriovenous Fistulae Survival

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Abstract. Balloon angioplasty (PTA) is an established treatment modality for stenosis in dysfunctional arteriovenous fistulae (AVF), although most studies showing efficacy have been retrospective, uncontrolled, and nonrandomized. In addition, it is unknown whether correction of stenosis not associated with significant hemodynamic, functional, and clinical abnormality may improve survival in AVF. This study was a prospective controlled open trial to evaluate whether prophylactic PTA of stenosis not associated with access dysfunction improves survival in native, virgin, radiocephalic forearm AVF. Sixty-two stenotic, functioning AVF, *i.e.*, able to provide adequate dialysis, were enrolled in the study: 30 were allocated to control and 32 to PTA. End points of the study were either AVF thrombosis or surgical revision due to reduction in delivered dialysis dose. Kaplan-Meier analysis showed that PTA improved AVF functional failure-free survival rates ($P = 0.012$) with a fourfold increase in median survival and a 2.87-fold decrease in risk of failure. Cox proportional hazard model identified PTA as the only variable associated with outcome ($P = 0.012$). PTA induced an increase in access blood flow rate (Qa) by 323 (236 to 445) ml/min ($P < 0.001$), suggesting that improved AVF survival is the result of increased Qa. PTA was also associated with a significant decrease in access-related morbidity by approximately halving the risk of hospitalization, central venous catheterization, and thrombectomy ($P < 0.05$). This study shows that prophylactic PTA of stenosis in functioning forearm AVF improves access survival and decreases access-related morbidity, supporting the usefulness of preventive correction of stenosis before the development of access dysfunction. It also strongly supports surveillance program for early detection of stenosis.

Transluminal percutaneous angioplasty (PTA) is an established treatment modality for vascular access stenosis (1), although most of the data showing its efficacy in extending access survival have been obtained from either retrospective or prospective nonrandomized trials with historical rather than concurrent controls. The few prospective controlled randomized studies available report conflicting results, with improved or unchanged patency rates after PTA in both grafts (2–5) and arteriovenous fistulae (AVF) (6,7), and further studies of this kind are clearly needed (8).

Due to the lack of prospective trials, it is also unknown whether prophylactic correction of anatomic stenosis unassociated with any significant functional, hemodynamic, or clinical abnormality can extend access survival, particularly in respect to AVF, which show excellent longevity and can remain patent even at access blood flow rate (Qa) lower than the prescribed blood pump flow rate (Qb) (1).

Yet prophylactic measures are currently judged to be unwarranted for stenosis unassociated with a delivered dialysis dose reduction (1), though a recent short-term preliminary prospective study suggested that PTA is more effective in improving patency rates in AVF with subclinical (9) than in those with clinically evident stenosis (10).

Our aim was to perform a prospective, controlled, open trial to evaluate whether prophylactic PTA of stenosis unassociated with impaired delivery of dialysis (*i.e.*, in a functioning access) can affect survival in mature, virgin (*i.e.*, with no prior surgical or percutaneous interventional procedure) (4), native forearm AVF.

Material and Methods

This study was a single-center pilot trial performed at the Hemodialysis Unit, Ospedale Policlinico in Verona, between January 1995 and December 2001.

Study Design

Subject Eligibility. Of the 141 subjects on dialysis at the unit during the study period, 96 had functioning, mature, virgin, native

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forearm AVF and were therefore eligible for the study. The other 45 subjects were excluded from the study either because they had a vascular access other than mature native forearm AVF or because they had mature forearm AVF unable to provide spKt/V $>$ 1.2 in a 4-h dialysis session, or that were not virgin.

Subject Allocation. All eligible subjects underwent angiography if they met the Qb, recirculation, and Qa criteria specified below. Fistulography identified 62 AVF in 60 subjects with significant stenosis (>50% reduction of luminal diameter compared with an adjacent nonstenosed segment). All stenotic AVF were considered as functioning because they were providing a spKt/V $>$ 1.2 in a 4-h dialysis session (11). In the majority of AVF, the anastomosis was located at the wrist (dAVF); whereas, in a minority, it was situated in the mid-portion of forearm (pAVF), either electively or due to a more peripheral AVF failing to mature.

All 62 stenotic AVF were enrolled in the study, and the first 12 subjects, enrolled in January 1995, were allocated either to the observational, no-intervention arm (Control) or to the PTA-treatment arm (PTA), depending on their dialysis shift, by tossing a coin: five subjects treated in the afternoon shift were assigned to Control, and seven subjects treated in the morning shift were assigned to PTA. Subjects were thereafter allocated to one or the other group using the minimization technique (12,13), a method aiming to reduce the imbalance between groups. Subjects were assigned to whichever arm would minimize the imbalance in term of the number of AVF and the subjects' clinical and demographic characteristics, including age, gender, prevalence of diabetes, and symptomatic cardiovascular disease (*i.e.*, coronary artery and/or cerebral and/or peripheral vascular disease), but irrespective of their dialysis shift.

At the end of December 2001, 30 AVF (from 30 subjects) were assigned to the Control and 32 AVF (from 30 subjects) to PTA. None of the subject were lost to follow-up, so all AVF were included in the final analysis. The study was not blinded, because the identification of thrombosis is based on objective criteria, and the adequacy of dialysis, as an indication for surgical revision of the access, was evaluated by the investigators. No sample power calculation was performed before the study. All subjects gave informed consent to the protocol of the study, which was approved by the local Ethical Committee.

Access Surveillance

Access surveillance program was based on Qb monitoring and urea-based access recirculation (Ru) during the period between January 1995 and January 1998 and on Qb monitoring, ultrasound dilution recirculation (Rhd), and Qa measurements by Transonic HD01 monitor (14) from February 1998 onwards.

Qb was monitored during each dialysis session: the prescribed Qb ranged from 300 to 350 ml/min, and Negative Arterial pre-pump Pressure (NAP) alarm was set at -250 mmHg; any decrease in Qb prompting continuation of dialysis due to high NAP on at least two consecutive hemodialysis runs (dQb, ml/min) was recorded.

Qa was measured quarterly by ultrasound dilution technique with Transonic HD01 monitor (Transonic System Inc., Ithaca, NY), as described elsewhere (14). AVF were cannulated with 15-gauge needles, and the "arterial" needle was placed in the main trunk of the feeding vein proximal to any collateral veins and facing the incoming blood flow (15). Qa measurements were taken in triplicates 30 to 90 min after starting dialysis, and the measurements were then averaged.

R was evaluated with the urea-based method (Ru) using the two-needle slow-flow technique (16) and with the ultrasound dilution technique using the Transonic HD (Rhd). Tests were performed 30 min after starting dialysis.

For Ru measurement, arterial (A) and venous (V) samples were draw at Qb 300 to 350 ml/min and the systemic (S) sample was drawn from the arterial line after reducing Qb at 50 ml/min for 20 to 30 s. BUN was measured in all samples and Ru was calculated as follows:

$$Ru\ (\%) = (S - A) \div (S - V) \times 100$$

Angiography was indicated where dQb $>$ 30 ml/min in at least two consecutive hemodialysis sessions in 25 AVF, 20 of which were evaluated before the ultrasound dilution monitoring technique became available; Ru $>$ 5% in 4; Rhd $>$ 0 in 1; ultrasound dilution Qa $<$ 850 ml/min in 32.

Fistulography

Fistulography was performed before dialysis using the "arterial" needle for contrast medium injection. The AVF was then visualized in its integrity inverting the flow in the venous limb with the aid of an inflated sphygmomanometer. On the five occasions when it was difficult to visualize the anastomosis, the fistulogram was obtained by puncturing the brachial artery in a dialysis-free day.

Intervention

PTA of stenotic segments was performed under light anesthesia, puncturing the AVF by the Seldinger technique. Before angioplasty, an intravenous dose of 5000 IU of heparin was administered. Balloons 6 to 9 mm in size were used, inflated to a pressure of 12 atmosphere for 40 to 60 s. Lesions resistant to dilatation were sequentially subjected to multiple dilatation up to 20 atmosphere of pressure. An angiogram was performed immediately after PTA, and the procedure was considered anatomically successful if less than 30% of residual stenosis was recorded. The initial interventional procedure was always performed within 3 wk from the diagnosis of stenosis, and no access failed between angiography and PTA. After the initial PTA, all AVF remained under surveillance, and fistulography was performed if they met the previously outlined criteria. All restenoses were treated again by PTA.

Outcome

Study end point was access functional failure, defined either as thrombosis or surgical revision due to a decrease in spKt/V to a value $<$ 1.0, as an indicator of inadequate dialysis delivery (17). AVF functional survival was evaluated as the time interval from angiography to thrombosis or surgical revision, disregarding any repeat PTA for restenosis. Subjects were censored in the event of death or transplantation or upon reaching the end of the study period with functional AVF (18).

Statistical Analyses

Data are reported as percentage, mean $\pm$ SD, or median (95% confidence interval), as appropriate. Normally distributed data were analyzed by Fisher exact test or nonpaired *t* test, skewed data by Mann-Whitney *U* test. The primary outcome of the analysis was the computation of the functional access failure-free survival rates according to the Kaplan-Meier method (19), and survival curves were compared using the log-rank test. In addition, Cox proportional hazard model was used to evaluate whether subjects and AVF-related prognostic features other than treatment could influence outcome (20). Significance was set at two-sided $P < 0.05$. Statistical analyses were performed using the SPSS version 10.0 (SPSS Inc., Chicago, IL).

Results

The characteristics of the subjects and AVF are reported in Tables 1 and 2, respectively. The Control and PTA arms were well matched for prognostic factors associated with AVF survival, including subjects age and gender, presence of diabetes and symptomatic cardiovascular disease, age of the access, hemodynamic status, and number, degree, length and distribution of stenoses. The median length of follow-up was also comparable, *i.e.* 13.0 mo (11.9 to 23.4 mo) in Control group and 17.5 mo (15.7 to 39.9 mo) in PTA group ($P = 0.075$).

During the study, four subjects in the Control group died and three were transplanted, whereas five died and five were transplanted in the PTA group. Kaplan-Meier analysis showed that PTA arm had significantly higher unadjusted functional failure-free AVF survival rates than Controls ($P = 0.012$), as shown in Figure 1. Median AVF survival was 84.0 mo (51.8 to 116.2 mo) in the PTA group and 21.0 mo (9.8 to 32.2 mo) in Controls ($P < 0.001$).

Cox multivariate proportional hazard analysis identified PTA as the only variable significantly associated with thrombosis or surgical revision (Exp(B) = 3.28; 95% CI = 1.30 to 8.27; $P = 0.012$), while all other variables included in the model (subjects' age and gender, diabetes, cardiovascular disease, AVF age, and location of anastomosis) were NS.

After the initial PTA, 28 restenoses were documented in 17 AVF (restenosis rate = 0.388 event/AVF − year at risk); the median time to restenosis was 8.0 mo (6.8 to 15.0 mo). The anatomical success rate of PTA was 93.3% and the degree of residual stenosis was 12 ± 13% ($P < 0.001$). There was only one major thrombotic complication of PTA, corresponding to a 1.7% complication rate.

PTA was associated with a significant improvement in AVF hemodynamic status. Immediately after PTA, *i.e.*, within a week of the procedure, Qb returned to the prescribed level in all AVF increasing by 29.0 ± 35.2 ml/min, R was abolished in the three AVF in which it had been documented, and Qa rose significantly by a median 323 (236 to 445) ml/min ($n = 26$, $P < 0.001$), as shown in Figure 2.

The effects of PTA on unadjusted vascular access–related morbidity are shown in Table 3, the data are presented as event per AVF per year at risk, and the relative risk is also calculated. Sixteen AVF in the Control arm and 9 in PTA arm failed; 14 AVF thrombosed in Control and 6 in PTA; and the proportion of thrombosed AVF differed significantly between the two arms ($P = 0.029$), while the proportion of AVF undergoing elective surgery was comparable.

Sixteen Control subjects and eight PTA subjects were hospitalized ($P = 0.036$), while temporary hemodialysis central venous catheters were needed in 11 Control and 6 PTA subjects ($P = 0.038$).

Discussion

PTA is regarded as an established treatment modality for stenosis in vascular access for hemodialysis, although the vast majority of trials reporting its efficacy are uncontrolled (8) and the few available prospective randomized controlled studies report inconsistent results. Short-term prospective randomized

Table 1. Subjects' demographic and clinical characteristics

	Control	PTA
Number of patients	30	30
Age (yr)	61.5 ± 13.4	57.3 ± 16.7
Gender (male/female)	20/10	18/12
Prevalence of elderly (>65 yr) (%)	36.7	33.3
Prevalence of diabetes (%)	26.7	23.3
Prevalence of cardiovascular disease (%)	33.3	40.0
sp Kt/V	1.33 ± 0.11	1.28 ± 0.06

Table 2. AVF Characteristics

	Control	PTA
Number of AVF	30	32
AVF age (mo)	15.5 (2.0 to 28.5)	10.0 (1.5 to 28.0)
AVF anastomosis location (%)		
wrist (dAVF)	83.3	84.4
mid-forearm (pAVF)	16.7	15.6
Degree of stenosis (%)	71 ± 9	76 ± 8
Prevalence of multiple stenoses (%)	33.3	34.4
Prevalence of stenoses >3 cm (%)	10.0	7.2
Location of stenoses (%)		
arterial	2.3	1.8
venous perianastomotic (initial 4 cm)	78.9	75.0
venous distal (after the initial 4 cm)	18.8	23.2
Prevalence of Ru > 5% or Rhd > 0 (%)	6.7	9.4
Decrease in Qb to continue dialysis (ml/min)	40 (14 to 49)	36 (15 to 41)
Access blood flow (ml/min)	473 ± 236 ($n = 14$)	451 ± 168 ($n = 18$)

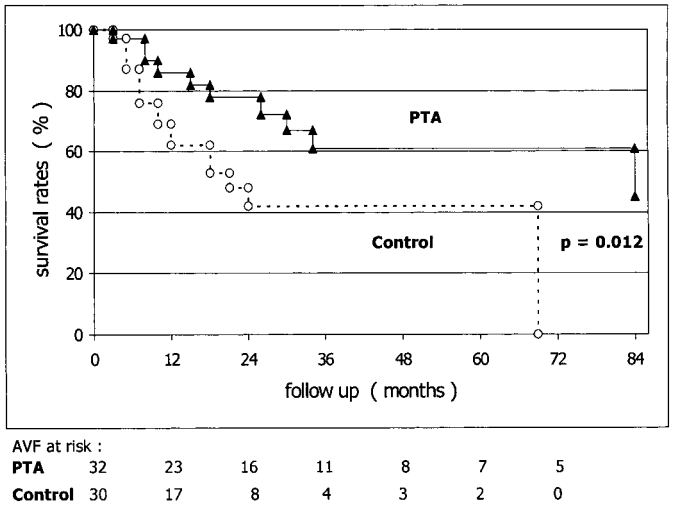

Figure 1. Unadjusted functional arteriovenous fistulae (AVF) failure-free survival rates according to Kaplan-Meier analysis in Control (open circles, dashed line) and balloon angioplasty (PTA) (closed triangles, solid line) groups.

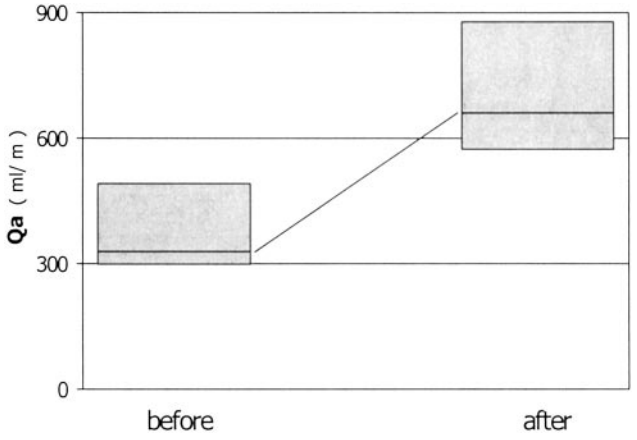

Figure 2. Effect of PTA on Qa levels. Data are expressed as median (95% CI). Pre- and post-PTA Qa values are significantly different ($n = 26$, $P < 0.001$).

studies on AVF have produced conflicting data; the same investigators found that PTA significantly decreased (7) or failed to influence (6) the thrombosis rate.

Moreover, the best time for PTA has yet to be clearly defined; while there is evidence to support elective intervention on a malfunctioning access, correction of stenosis in the absence of significant hemodynamic, functional, or clinical impairment of the access is not warranted because there are no prospective studies to demonstrate its effectiveness (1). This opinion may seem particularly applicable to AVF, for which preventive PTA may prove neither beneficial nor cost-effective, given its already low failure rate.

Our findings (that prophylactic PTA reduces functional failure rates in functioning AVF) support the usefulness of PTA for the preventive treatment of stenosis, before the onset of significant access dysfunction, *i.e.* in AVF that are still functioning well in spite of stenosis-induced hemodynamic changes. PTA was associated with a fourfold increase in median functional failure-free survival and a 2.87-fold reduction of AVF relative risk of failure, although repeated treatments were often needed due to the high restenosis rate in most accesses.

The exclusive role of treatment in determining functional fistula survival is confirmed by the Cox proportional hazard analysis, which identified PTA as the only variable associated with AVF failure, while all other potential prognostic factors did not influence outcome.

PTA was consistently associated with an improved AVF hemodynamic status, because it abolished R, restored Qb to the prescribed value, and, as reported by others (9,21–23), it produced a direct median 323 ml/min increase in Qa, which was constant over the whole range of baseline Qa levels. In addition, post-PTA Qa levels were always higher than 300 ml/min, a threshold below which the risk of incipient thrombosis is reported very high (24).

These findings suggest that the improved functional survival after a program of repeat PTA is due to the hemodynamic effect of PTA, in line with the notion that blood flow is a major, if not the main, determinant of patency in AVF (25).

Our data confirm that a program of repeat PTA of stenosis is associated with negligible complication rates, demonstrating that its implementation in functioning AVF halves vascular access-related morbidity, providing further support for the usefulness of elective stenosis correction by PTA even in this type of vascular access, which already has low failure and complication rates.

Finally, our findings provide ample justification to the implementation of surveillance program aiming for the early detection of stenosis in AVF.

We are aware that our study has some limitations, mainly the lack of true randomization and blinding. We also recognize

Table 3. Unadjusted vascular access-related morbidity

	Control (event per AVF-yr)	PTA (event per AVF-yr)	Relative Risk (Control/PTA)
Hospitalization (d)	1.994	0.603	1.81 (1.09 to 2.99)
AVF failure	0.363	0.111	2.87 (1.21 to 6.80)
Thrombectomy	0.317	0.074	1.84 (1.14 to 2.97)
Elective surgical revision	0.046	0.037	0.81 (0.27 to 2.46)
Central venous catheter placement	0.250	0.049	1.81 (1.14 to 2.88)

that it does not provide a final answer to the question of the role of preventive PTA in extending functioning AVF life span and further, larger studies with a better design are needed.

In conclusion, our prospective, controlled study indicates that a program of prophylactic repeat PTA for stenosis in functioning forearm AVF is safe, it improves functional survival rates by improving the hemodynamic status of the access, and it reduces access-related morbidity. Our findings also suggest the utility of stenosis correction by PTA before the onset of significant fistula dysfunction and strongly support the use of surveillance program for the early detection of stenosis.

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