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Primary Failure of Arteriovenous Fistulae in Auto-Immune Disease

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Key Words
Chronic haemodialysis, primary arteriovenous fistula failure · Vascular access · Primary venous access failure · Thrombophilic risk

Abstract
Background/Aim: Chronic haemodialysis depends on an arteriovenous fistula. Primary failure of vascular access is a common problem which is mainly related to thrombosis. As ambulatory surgery is common, it is mandatory to identify patients with a high thrombophilic risk to allow better prevention (anticoagulation) and direct re-intervention after thrombosis. The purpose of this study was to determine thrombophilic risk factors for primary access failure in order to identify patients at risk before the operation. ***Methods:*** We performed a retrospective study on 62 chronic haemodialysis patients who received permanent vascular access. We evaluated established risk factors for chronic access failure as well as the number of earlier shunt operations in these patients. ***Results:*** The patients predominantly suffered from auto-immune diseases. The frequency of a successful first vascular access was above average (92.5%). We identified four major risk factors for primary access failure: number of previous vascular access thromboses ($p < 0.01$; $R = 0.96$), pre-existing thrombophilic risk factors ($p < 0.01$), pre-operative fibrinogen ($p < 0.02$), and vasculitis ($p < 0.01$). ***Conclusions:*** We identified four risk factors which allowed an individual risk evaluation. Among the factors investigated, the activity of the auto-immune disease was the most striking. Our data suggest not to perform a vascular access during an active period of vasculitis.

Introduction

Chronic haemodialysis depends on a vascular access such as the Brescia-Cimino arteriovenous fistula [1, 2]. However, in many cases vascular access fails due to thrombosis in the arteriovenous fistula [3]. Although a common problem, little is known about the primary reasons for thrombosis [4]. If thrombosis occurs within the first 30 days after surgery, it is generally considered to be a surgical problem [5].

Apart from faulty surgical techniques, other reasons such as inappropriate veins, poor arterial flow, age >65 years, and female gender have been discussed [6–8]. However, in most reports vessel grafts have been described, a technique which is popular in the USA, but not so in Europe, where primary fistulae are preferred.

Only few investigations correlated thrombophilic risk factors with primary arteriovenous fistula failure [9], and these primarily focussed on one specific factor [10]. How-

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ever, investigations including all relevant thrombophilic risk factors are needed to assess a personal thrombophilic risk. Unfortunately, this is hardly feasible due to the enormous costs of evaluation. Therefore, we opted to assess factors which are related either to the renal disease or arise from chronic haemodialysis.

The purpose of this study was to determine risk factors for primary access failure most likely not related to the surgical technique in order to identify patients at risk before the operation.

Patients and Methods

We evaluated 62 consecutive patients (32 males, 30 females; mean age 52 ± 16 years, age range 11–79 years) with end-stage renal disease who received a permanent vascular access at the University Hospital of Essen. All patients were of Caucasian background. The goal was to define risk factors other than surgical ones in order to predict a primary failure of the vascular access. Localization of permanent vascular access was chosen according to surgical feasibility. In general, the most distal localization was chosen, if artery and vein were clinically suitable (examination, Allen test). We routinely performed the Allen test and an ultrasound colour flow scan in combination with a pulse-generated run-off system prior to surgery. We defined veins and arteries suitable for access if their diameter exceeded 2 mm. Additionally, we excluded patients with peripheral and/or central venous stenosis and/or haemodynamic instability from the study. All operations were performed by the same experienced vascular surgeon over a period of 12 months.

Antiplatelet aggregation therapy was stopped 1 week before surgery. The forearm vein in radial position was anastomosed end to side to the radial artery at the wrist level or the area between wrist and elbow. The vena cephalica or the vena basalis was anastomosed to the brachial artery end to side. The first shunt puncture was performed more than 2 weeks after surgery. No standardized vascular access training was performed. Standardized heparinization was performed after surgery for at least 72 h, controlled by prolonged partial thromboplastin time.

Information on previous accesses, as well as on sex, race, age, and aetiology of renal failure was recorded. The number of previous vascular access thromboses as well as that of thromboses of other vessels was recorded. Diabetes mellitus was considered if the patient was treated with insulin, oral antidiabetics, diabetic diet, or if the patient's fasting or random plasma glucose concentration was >7.8 or >11.1 mmol/l, respectively.

Before the operation, haematocrit and fibrinogen were determined. In case of an underlying auto-immune disease, auto-antibodies (anticardiolipin antibody, antinuclear antibody, cytoplasmic antineutrophil cytoplasmic antibody, perinuclear antineutrophil cytoplasmic antibody, and single-stranded and double-stranded DNAs) were titrated. Furthermore, thrombophilic risk factors (protein C or S deficiency, activated protein C resistance, factor II or V mutation) were assessed. Peripheral arterial occlusive disease (Fontaine stage >2b) and history of myocardial infarction were defined as signs for manifest atherosclerosis.

Primary vascular access failure was defined as thrombosis during the first 30 days after operation. Vascular access thrombosis was assumed in case of lack of blood flow by palpation and auscultation. The presence of a thrombus was confirmed by ultrasound or surgery.

Data are given as mean values ± SD. To assess the statistical significance, a Student t test was performed. Correlation was assessed by using Spearman's correlation coefficient. $p < 0.05$ was considered statistically significant.

Results

In our study, auto-immune disease (29.5%), glomerulonephritis (16%), urological disease (14%), and diabetes mellitus (13%) were the most frequent underlying diseases (fig. 1). Comorbidities consisted of hypertension in 57 cases (92%), hypotension in 5 cases (8%), coronary heart disease in 22 cases (35.5%), and peripheral occlusive disease >2b in 5 cases (8%).

Sixteen vascular accesses were initiated at the wrist, 19 along the forearm, and 27 at the elbow. The selection criteria for wrist, along the forearm, and elbow arteriovenous fistulae were based on the availability of a sufficient artery and vein (>2 mm). With respect to the underlying renal disease, exclusion criteria were micro-angiopathy in diabetes mellitus and macro-angiopathy in auto-immune disease. We furthermore excluded the wrist after unsuccessful surgery or vascular access thrombosis at this location. In these cases, we preferably attempted a vascular access along the forearm. The elbow was chosen only if no artery or vein with a diameter >2 mm was available at wrist or forearm. The incidence of primary failure was 39% (24 of 62 patients). There were no incidence of primary access failure at the wrist, nine occlusions along the forearm, and 15 occlusions at the elbow. The fistula was created as a primary procedure in 27 cases (43.5%), while 35 patients (56.5%) had undergone an access procedure before. The primary access procedure was successful in 92.5% (25/27), while the secondary one had a success rate of only 37% (22/35).

Of our patients, 56% (35/62) had a history of vascular access thrombosis; 40% (14/35) of these patients had had one vascular access thrombosis, while 60% (21/35) had had more than one. The correlation between the number of previous vascular access thrombosis and primary access failure was significant ($r = 0.96$; fig. 2).

Six patients had a history of either a previous thrombosis not related to the vascular access or known thrombophilic risk factors. All of these developed a primary failure due to thrombosis ($p = 0.01$). Age or sex of the patients had no significant impact on primary access failure ($p = 0.3$). Manifest atherosclerotic alterations were evident in

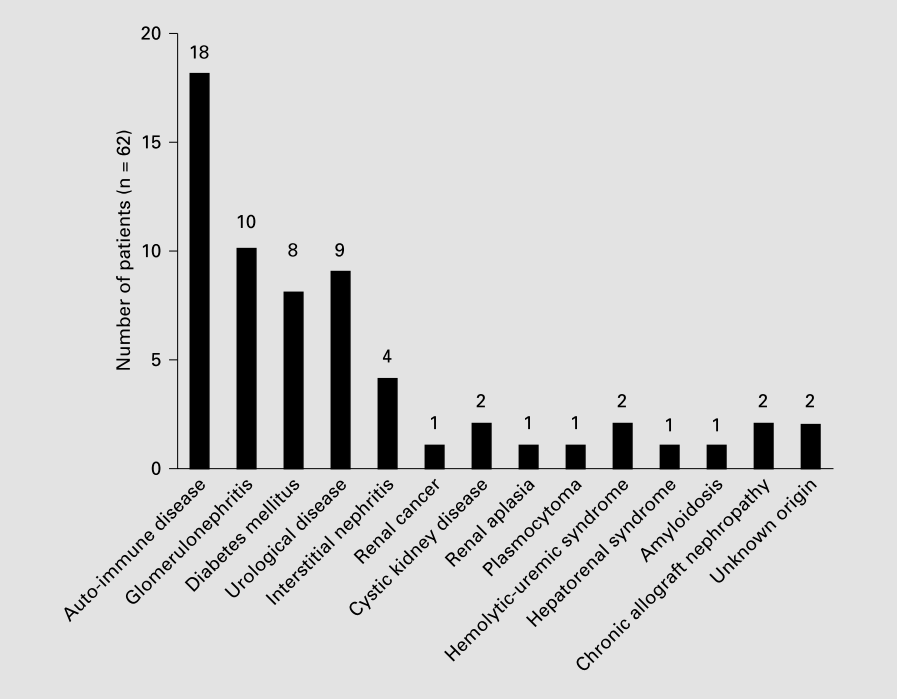

Fig. 1. Original diseases of the patients (n = 62); in contrast to previous studies, the number of patients with auto-immune diseases was high.

Table 1. Assessment of thrombophilic risk factors

	No primary access failure (n = 38)	Primary access failure (n = 24)
Age, years	50 ± 14	53 ± 16
Sex		
Male (n = 36)	21	15
Female (n = 26)	17	9
Diabetes mellitus (n = 11)	7	4
Manifest atherosclerosis (n = 27)	13	14
Previous vascular access thrombosis		
None (n = 27)	26	1
One (n = 14)	9	5
More than one (n = 21)	3	18
Total (n = 35)	38	24
Pre-existing thrombophilic risk factors	0	6
Pre-operative fibrinogen		
<450 mg/dl (n = 39)	36	3
>450 mg/dl (n = 23)	2	21
Vasculitis		
SLE (n = 8)	1	7
Wegener's disease (n = 4)	0	4
pANCA positive (n = 3)	0	3
Overlap (n = 1)	1	0
Unknown origin (n = 2)	1	1
Total (n = 18)	3	15

SLE = Systemic lupus erythematosus; pANCA = perinuclear antineutrophil cytoplasmic antibody.

27 patients; diabetes mellitus was evident in 11 patients. Interestingly, these diagnoses had no influence on the rate of primary access failure. The assessment of thrombophilic risk factors is given in table 1.

In all patients, we investigated the pre-operative fibrinogen level. The normal range of fibrinogen was defined as 200–450 mg/dl. One patient had a fibrinogen level <200 mg/dl due to liver cirrhosis; 38 patients demonstrated a normal fibrinogen level (380 ± 79 mg/dl), and 23 patients had elevated levels (490 ± 140 mg/dl). Vascular access was successful in 93% of the patient with a normal fibrinogen level <450 mg/dl, but only in 9% of those with elevated levels (>450 mg/dl, $p < 0.02$; fig. 3).

In our study, the largest fraction of patients suffered from auto-immune diseases (29.5%; 8 systemic lupus erythematosus, 4 Wegener's disease, 3 perinuclear antineutrophil cytoplasmic antibody positive vasculitis, 1 overlap syndrome, 2 auto-antibody constellation of unknown origin). Of these 18 patients, 15 had primary access failure due to thrombosis, and in only 3 patients the access was successful ($p < 0.01$). Additionally, we observed in several patients a correlation between degree of activity and vascular access function (fig. 4). If the vasculitis was active as judged by auto-immune antibody titres, the vascular access failed. However, due to the low number of patients we were not able to further elucidate this interaction.

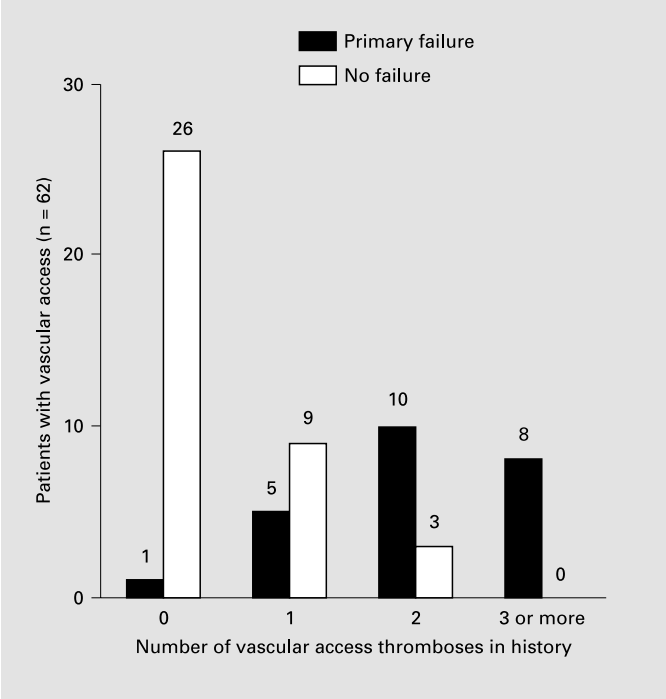

Fig. 2. Correlation of the number of previous vascular access thromboses with actual outcome (r = 0.96; p = 0.001).

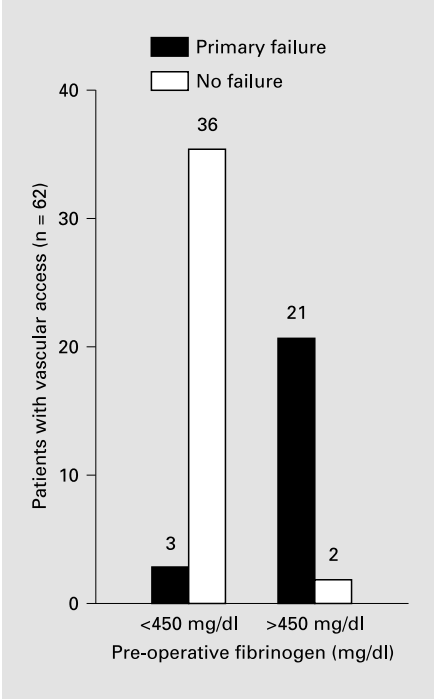

Fig. 3. Correlation of the outcome of vascular access with pre-operative fibrinogen. Fibrinogen >450 mg/dl increased the risk for access failure ($p < 0.02$).

While of the other factors investigated, no single factor had a major impact on vascular access thrombosis, failure of the vascular access was more frequent in those patients with more than one risk factor for thrombosis. While patients with up to one risk factor developed primary failure in 2 of 35 (6%) cases, in patients with more risk factors the primary vascular access failed in 22 of 27 cases (86%).

Discussion

In our study, we identified four major risk factors for primary access failure: number of previous vascular access thromboses, pre-existing thrombophilic risk factors, pre-operative fibrinogen, and vasculitis. These factors can be used to predict the cumulative risk for primary access failure.

The overall success rate was low (55%) as compared with results reported in the literature [12]. This can be explained by a higher percentage of first vascular access operations in other studies, while our study population was dominated by patients with repetitive previous access trials. Furthermore, a high number of our patients suffered from auto-immune diseases. The selection of our patients could also explain the surprisingly high rate of failures in elbow fistulae. These were patients who had no possible access on the wrist, thus, a more advanced stage of the underlying disease.

The rate of success was comparable to that of other studies in those patients who were operated for a vascular access for the first time (92.5%). Thus, the high number of risk factors and comorbidity in our population may have contributed to the lower overall success rate. Under these circumstances, the impact of primary access failure as a pure surgical problem has to be evaluated anew [5].

A comparison of the outcome of procedures may also result from different clinical centre policy. While American centres prefer polytetrafluoroethylene grafts [5], in Europe the major goal is to avoid such grafts. Furthermore, as the population is getting older and has a rising number of comorbidities, a discussion started to abandon any use of prosthetics in the forearm in favour of direct accesses in the arms [13].

When evaluating the individual risk of failure of the vascular access, an access thrombosis is a striking factor. However, it cannot be used in recipients with a primary

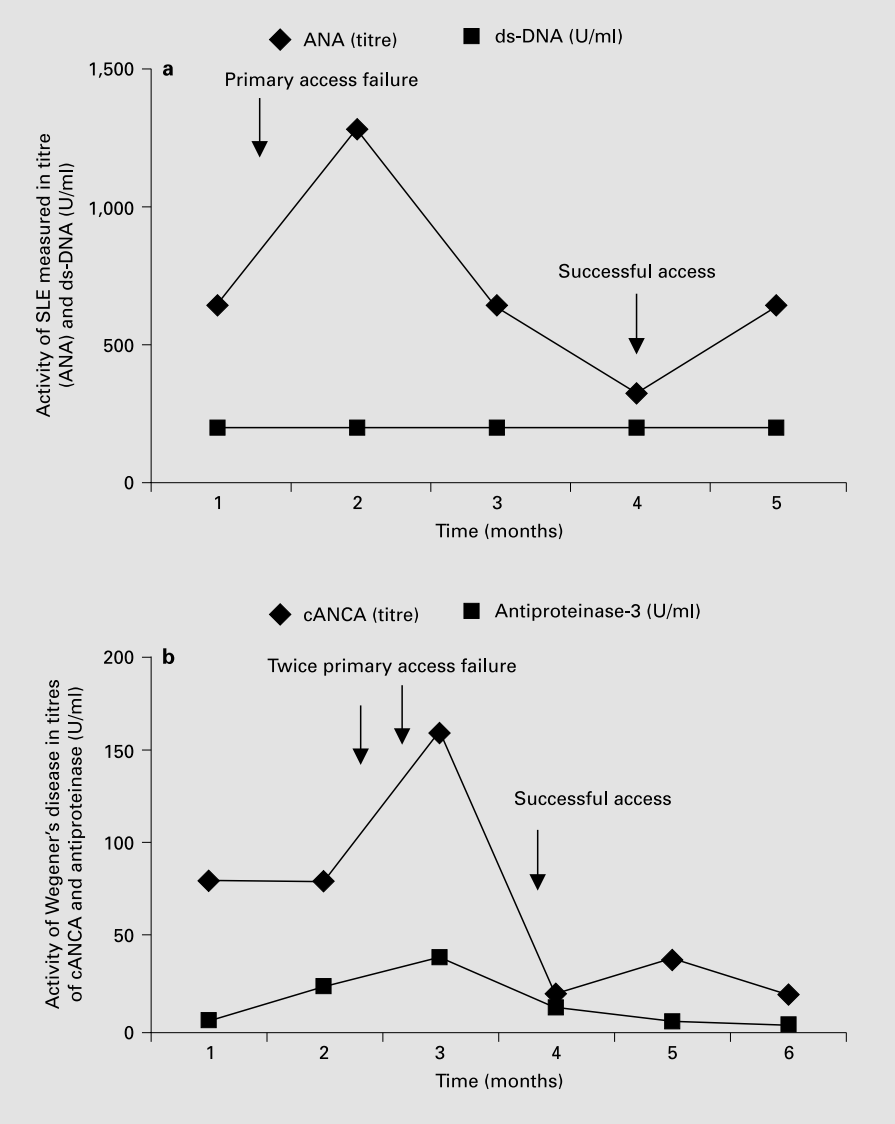

Fig. 4. a Patient with systemic lupus erythematosus (SLE) activity based on antinuclear antibody (ANA) and double-stranded DNA (ds-DNA) titres. Access failed during active SLE, while a vascular access was successfully performed during a period of lower activity. **b** Patient with Wegener's disease based on clinical findings and auto-antibodies. cANCA = Cytoplasmic antineutrophil cytoplasmic antibody. Access failed during activity, while a vascular access was successfully performed during a period of quiescence.

fistula. Thrombosis other than vascular access thrombosis or known thrombophilic risk factors are predictors of primary failure as well [10]. However, only a small percentage of our patients could be assigned to this group (7.5%).

Furthermore, there is a wide range of thrombophilic risk factors, and their impact on vascular access thrombosis is contradictorily discussed. While factor V [10] mutations are considered to be predictive of access thrombosis, activated protein C resistance is probably not [9]. Thus, the detection of a single risk factor for thrombosis may be useful, but no data are available so far to compare a combination of such factors, and it remains unclear which individual risk factor is the most important. Furthermore, these measurements are expensive.

However, one specific risk factor for thrombosis in general is not expensive to determine: fibrinogen. Fibrinogen correlates with activity and severity of atherothrombotic diseases [14]. Additionally, based on the Framingham Offspring Population, Stec et al. [15] correlated fibrinogen with the incidence of cardiovascular disease and suggested it as a screening tool to identify individuals at risk. Furthermore, ancrod (viper poison) induced defibrinogenation is favourable in patients with acute ischaemic stroke [16].

In our study, we investigated the pre-operative fibrinogen levels to evaluate the risk of access failure. Our data suggest that fibrinogen >450 mg/dl is a major risk factor for access failure, while levels <450 mg/dl mark a low risk.

As fibrinogen is also a marker of disease activity [17, 18], we evaluated the influence of systemic diseases in our study population. For systemic lupus erythematosus, cardiolipin antibodies correlate with arterial [19] and venous thromboses [20]. However, other forms of vasculitis such as Wegener's disease or perinuclear antineutrophil cytoplasmic antibody positive vasculitis have not been established as risk factors so far. In our study, any vasculitis was a risk factor for primary malfunction. This implies that vasculitis in general can be understood as systemic inflammation which activates endothelial cells along the vessel walls and, therefore, as a risk factor for access failure. Additionally, Wegener's granulomatosis is frequently associated with an antiphospholipid syndrome [21] which may also contribute to thrombosis due to increased vascular permeability. Ginsberg et al. [22] observed an increased thrombin generation in patients with active systemic lupus erythematosus. Our data suggest not to perform a vascular access during an active period of vasculitis.

Interestingly, atherosclerotic changes or diabetes mellitus did not pose a significant risk in our study. However, our numbers are very small. Although Konner [23] preferred large-diameter vessels because of micro-angiopathic changes, with the exception of those of Obialo et al. [24], no data exist to support a higher risk in this population.

Today, most vascular accesses are performed in ambulatory surgery, and it is mandatory to identify those patients who have to be put on the ward after surgery to allow better prevention (anticoagulation) and direct reintervention after thrombosis without further delay. Independent of the surgical technique, fibrinogen >450 mg/dl, active systemic disease, specific defects of the coagulation cascade or thrombocyte function, as well as previous access thromboses are risk factors for access failure which should be considered when the decision about an access is made.

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