Original paper

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Ultrasonographic diagnosis of stenosis of native arteriovenous fistulas in haemodialysis patients

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Abstract

Aims: Ultrasound (US) examination is an important tool in the diagnosis of arteriovenous (AVF) stenoses; different US measures are available for assessing the severity of stenoses. The aim of our study was to analyse risk factors and consequences of AVF stenosis and its severity and to compare the usefulness of different US measures of stenoses' severity. **Material and methods:** Ninety-seven prevalent patients from a single dialysis centre with patent AVF were included. We recorded history of disease, clinical and laboratory data. US was used to diagnosis the stenosis and to measure blood flow in the brachial artery, resistivity index (RI), and the diameter of the vessels (arteries, anastomosis, venous outflow). **Results:** Stenosis was present in 54.64% of the patients (59.6% juxtaanastomotic). Stenosis patients had higher age, lower diameter of the brachial artery, lower anastomosis diameter, and lower diastolic blood pressure (DBP). Atherosclerosis, delayed maturation of AVF, and statin treatment were more prominent in the stenosis group. Logistic regression disclosed delayed maturation, cholesterol, atherosclerosis, and DBP as significant predictors of stenosis. When severe stenosis was measured by the diameter reduction, stenosis patients had higher age, lower HDL cholesterol, and poorer dialysis efficacy. Flow in the brachial artery and RI were less useful for identifying risk factors or differences in outcome. **Conclusions:** Prevalence of stenosis was high in our cohort, more than half of the patients having some degree of stenosis. Risk factors for stenosis were related to atherosclerosis, low DBP, and delayed maturation of AVF. Diameter of stenosis is the most useful marker of severity.

Keywords: arteriovenous fistula, haemodialysis, Doppler ultrasonography, risk factors, atherosclerosis.

Introduction

Patients with chronic kidney disease treated with maintenance dialysis rely on a patent vascular access for efficient haemodialysis. Vascular access dysfunction is a major factor of morbidity and mortality in these patients. The costs of hospitalisation and treatment related to vascular access dysfunction are important in the United States and worldwide [1]. Arteriovenous fistula (AVF) failure might be an underestimated problem, reflected by the increasing prevalence of patients with long-life central venous catheters. Ultrasonography (US) is a major tool in the diagnosis of stenosis and thrombosis of the AVF in completion of the clinical examination [2,3]. US diagnosis of a stenosis is made by the determination of the pre/intrastenotic peak systolic velocity (PSV) ratio or by direct measurement of diameter of the vessel (artery, arteriovenous anastomosis, or venous outflow). A correct diagnosis represents a premise for the correct management of AVF dysfunction, including new therapeutic options (i.e. US or fluoroscopy guided intravascular procedures or surgical procedures) [4-6]. Whether optimal timing of such an intervention should merely rely on the positive diagnosis of stenosis, or a further evaluation of severity is needed, is a subject for an ongoing study, as

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the assessment of its stenosis' severity has been proven to have prognostic value for AVF failure. Various approaches have been proposed for determining the hemodynamic significance (severity) of a stenosis. The diameter of a stenosis is an important reflection of its severity; however, some studies claim that brachial blood flow and/or brachial resistivity index (RI) have prognostic value with regard to future AVF failure [7,8]. The relative importance of these US parameters of determining the severity of a stenosis is still a matter of debate.

The aim of our study was to present epidemiologic data and risk factors of AVF stenosis in a single dialysis centre, to determine whether the presence of stenosis engenders differences in dialysis efficacy as an outcome measure, and to compare clinical significance of three different methods of determining the severity of AVF stenosis: minimum stenosis` diameter (as a morphological parameter), fistula blood flow, and RI (as functional parameters).

Material and methods

We conducted an observational cross sectional clinical study in the dialysis centre of Deva, Romania, between August 2014 – July 2015. All the patients signed an informed consent and the study was approved by the local Ethics Committee. Inclusion criteria were: prevalent patients treated with chronic haemodialysis or haemodiafiltration thrice weekly; presence of a functional AVF. Exclusion criteria were evidence of significant inflammatory syndrome (acute infection, cancer) with possible impact on AVF thrombosis; patients with central venous catheters (temporary or permanent).

Laboratory parameters were collected with the occasion of the monthly evaluation of patients (pre and post-session blood samples collected on the first session of the second week of the month); clinical and US evaluation of patients was performed in one of the dialysis days of the same week, prior to start of the dialysis session. The history of vascular access (history of failure to mature, history of delayed maturation), presence of atherosclerosis related cardiovascular disease (defined as ischemic heart disease, history of stroke, peripheral arterial disease identified in patient's records), presence of diabetes mellitus, treatment (phosphate-binders, vitamin D, erythropoiesis stimulating agents, iron, hypolipemiant medication) were recorded. Clinical examination and measurement of blood pressure after 15 minutes' rest, measurement of weight and height were performed. Body mass index was calculated by dividing weight (in kilograms) by height squared (in meters). General and specific laboratory data were measured as follows: serum biochemical parameters: pre and post-dialysis urea and pre-dialysis creatinine, glucose, phosphorus, total calcium, albumin, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides (photometry), intact parathormone (iPTH), ferritin (electrochemiluminescence immunoassay), C-reactive protein (turbidimetry), and parameters of dialysis efficacy (Kt/V urea measured by the Online Clearance Measurement from Fresenius dialysis machines 4008 and 5008). Laboratory assessment was performed right away, by a single authorized laboratory. The US examination was performed by D.T. using General Electric Logiq e BT12 machines (linear transducer 10 MHz frequency). The diameters of the brachial artery at the elbow, of the feeding artery two centimetres before the anastomosis, of the anastomosis, and of the venous outflow (in pathological conditions: stenosis, aneurisms, delayed maturation) were measured. Blood flow (Q) in the brachial artery at the elbow was measured as follows: $Q = r^2$ x 3.14 x Vm x 60, where r is the radius of the vessel, Vm is the mean velocity of the blood flow measured at an angle of maximum 60° and a blood sample of 50-70% of the diameter of the vessel. RI was measured in the brachial artery according to the following formula: $RI = (Vmax\text{-}Vmin) / Vmax$, where V max represents the peak systolic velocity and V min represents the end diastolic velocity. Intima-media thickness (IMT) was measured on the posterior wall of the brachial artery at the elbow, in a longitudinal section, and was expressed as a mean of three consecutive measures. The presence of stenosis, aneurisms in the puncture areas (increase in vessel section resulting in a diameter >10 mm), blood flow and RI abnormalities were noted. The stenosis was defined as the reduction of the diameter of the vessel of more than 50% and an increase in peak systolic velocities (PSV) ratio (PSV in the stenotic area/ PSV upstream the stenotic area) >2:1 in the draining vein or >3:1 in the anastomotic area. A severe stenosis was defined by a) minimum diameter of the stenotic area < 3 mm, b) brachial artery blood flow<500 ml/min, or c) RI in the brachial artery > 0.6 [2,7-12]. Illustration for US diagnosis of stenosis and its severity is provided in figure 1. Delayed maturation was defined as the situation when an AVF cannot be used earlier of 3 months after its creation [13,14].

Statistical analysis was performed using SPSS 19.0, and Microsoft EXCEL software. Kolmogorov-Smirnov test or Shapiro-Wilk test were used to assess the normal distribution of data. Values are presented as mean±standard deviation for normally distributed variables, and as median (inter-quartile range) for non-normally distributed variables. For comparison of two means of independent samples, t-test or Man-Whitney test were used. For comparison of qualitative variables, Chi-square test or Fisher exact test was employed. To estimate a dichotomial dependent variable, multivariate

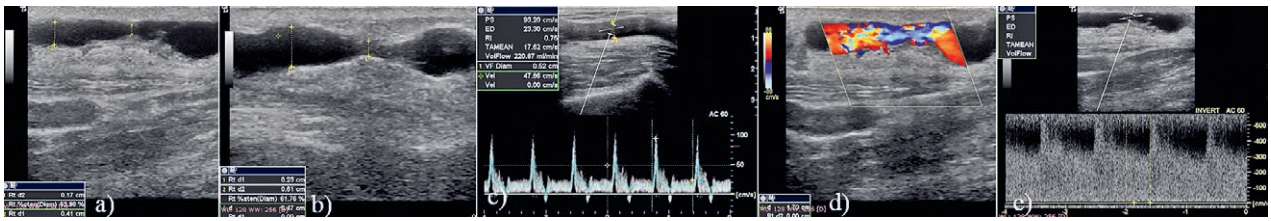


Fig 1. a) and b) Stenosis of an arterio-venous fistula (AVF), with a residual diameter under 3 mm and a reduction of the vascular lumen of more than 50%; c) Measurement of blood flow and Resistivity Index on the brachial artery of a patient with a severe stenosis of a brachio-cephalic AVF; d) and e) Stenosis of an AVF with aliasing in the stenotic area.

Table I. General characteristics of the patients and comparison of patients with/without stenosis

	All patients (n=97)	Stenosis + (n=53)	Stenosis – (n=44)	p
Risk factors for occurrence of stenosis				
Age (years)	61.28±12.90	64.36±12.30	57.57±12.76	0.01
Male (n%)	56 (57.7)	35 (66.0)	21 (47.7)	0.07
Body mass index	25.58 (21.25-29.40)	25.39 (21.29-29.20)	25.80 (21.22-28.65)	0.55
History of failure to mature (n%)	16 (16.5)	12 (22.6)	3 (6.8)	0.11
Delayed maturation (n%)	16 (16.5)	13 (24.5)	1 (2.3)	0.02
Brachial artery diameter (mm)	5.81 (5.04-6.94)	5.20 (4.70-5.80)	6.55 (5.18-7.53)	<0.001
Feeding artery diameter (mm)	4.60±1.59	4.27±1.16	4.98±1.93	0.27
Anastomosis diameter (mm)	4.85 (4.42-6.48)	4.00 (3.00-5.10)	5.45 (3.78-6.93)	0.01
Aneurisms >10 mm (n%)	49 (50.5)	22 (41.5)	28 (63.6)	0.03
Intima-media thickness (mm)	0.45±0.11	0.46±0.11	0.44±0.12	0.52
Systolic blood pressure (mmHg)	143 (135-152)	140 (130-158)	143 (130-161)	0.40
Diastolic blood pressure (mmHg)	73±13	70±12	78±15	0.04
Diabetes mellitus (n%)	23 (23.7)	15 (28.3)	8 (18.2)	0.25
Glycaemia (mg/dl)	123.14±54.71	132.86±63.30	111.29±39.54	0.05
Atherosclerosis (n%)	62 (63.9)	43 (80.1)	19 (43.2)	0.0001
High-density lipoprotein (mg/dl)	36.69±11.75	37.40±13.09	35.83±9.98	0.53
Total cholesterol (mg/dl)	183.29±41.20	174.40±39.35	194.12±41.28	0.02
Triglycerides (mg/dl)	172.70±103.16	158.45±99	190.08±106.65	0.15
Statin therapy (n%)	18 (18.6)	16 (30.2)	2 (4.5)	0.003
Haemoglobin (g/dl)	11.35 (10.41-12.03)	11.35 (10.43-12.35)	11.35 (10.40-11.90)	0.84
Ferritin (ng/ml)	710.61±365.98	706.45±399.34	715.62±325.78	0.90
Iron therapy (n%)	32 (32.9)	21 (39.6)	11 (25.0)	0.13
Erythropoietin therapy (n%)	73 (75.3)	44 (83.0)	29 (65.9)	0.07
Albumin (g/dl)	4.47 (4.30-4.71)	4.42 (4.31-4.64)	4.5 (4.30-4.73)	0.23
C-reactive protein (mg/dl)	1.13±1.96	1.10±1.93	1.17±2.03	0.87
Intact parathormone (pg/ml)	457.26±481.15	387.75±441.07	540.98±518.13	0.12
Total calcium (mg/dl)	8.66 (8.15-9.18)	8.71 (8.38-9.06)	8.61 (8.11-9.37)	0.57
Vitamin D therapy (n%)	55 (56.7)	27 (50.9)	28 (63.6)	0.23
Phosphate-binders with calcium (n%)	77 (79.4)	44 (83.0)	33 (75.0)	0.43
Phosphate-binders without calcium (n%)	12 (12.4)	5 (9.4)	6 (13.6)	0.53
Consequences of stenosis				
Kt/V	1.63±0.32	1.60±0.32	1.67±0.32	0.56
Pre-dialysis urea (mg/dl)	145.63 (118.45-174.18)	144.47 (113.89-174.02)	146.85(125.06-176.92)	0.44
Phosphorus (mg/dl)	5.10 (4.45-5.86)	5.29 (4.32-5.79)	4.69 (3.93-5.98)	0.79
Creatinine (mg/dl)	10.14 (8.46-11.80)	10.00 (8.26-12.17)	10.33 (9.10-12.05)	0.53
Puncture incidents (n%)	31 (32.0)	23 (43.4)	8 (18.2)	0.01

Stenosis+ – patients with stenosis, Stenosis– – patients without stenosis, puncture incidents- bleeding, difficult puncture, puncture site haematomas.

logistic regression was used (Enter method). Assumption (inclusive multicollinearity) was verified (Variation Inflation Factor<10). Odds ratio (OR), standard error, equation coefficients with confidence intervals (CI) and statistical significance for each parameter were presented. Statistical significance threshold was considered $\alpha = 0.05$.

Results

From 137 patients treated in our centre, 109 patients had functional AVF (the rest having central venous catheters for vascular dialysis access) and 97 patients met all the criteria for inclusion. General characteristics and the comparison between patients with or without stenosis are presented in table I.

Anatomic position of the AVF was 52% radio-cephalic, 32% brachio-cephalic, and 16% brachio-basilic. Stenosis was present in 54.64% of patients and was identified in the feeding artery (5.8%), juxta-anastomotic region (59.6%), puncture area (21.2%), proximal (in-between puncture area and central veins- 11.5%), and central veins (subclavicular, brachio-cephalic trunk, superior vena cava- 1.9%). Multiple stenoses were observed in 15.4% of patients. In patients with stenosis, the median value of the minimum diameter of the stenotic area was 2.4 mm (1.7-2.7 mm). For juxtaanastomotic localisation of stenosis, mean prestenotic velocities were 97.00±16.96 cm/s and mean intrastenotic velocities were 362.00±69.76 cm/s, with a PSV ratio of 3.90±1.12. For all the other localisations of stenosis, mean prestenotic velocities were 113±18.14 cm/s and mean intrastenotic velocities were 358.00±70.62 cm/s, with a PSV ratio of 2.84±1.23.

Logistic regression disclosed cholesterol, atherosclerosis, delayed maturation, and diastolic blood pressure as significant predictors of stenosis (table II).

In what concerns consequences of stenosis, only clinical events such as bleeding, puncture site hematomas, and difficult puncture were observed to be more frequent in the stenosis group, the other measures of dialysis efficacy being similar in patients with/without stenosis.

Severity of stenosis was assessed using the vessel diameter, blood flow and RI in the brachial artery. We compared differences in dialysis efficacy as an outcome measure (consequence) of severe versus non-severe stenosis defined according to each of these criteria. When severe stenosis was defined according to the diameter of the stenosis (above/below 3 mm), significant differences in parameters defining lower dialysis efficacy (decrease in Kt/V, increase in predialysis creatinine and borderline increase in predialysis urea) were identified.

When severity of stenosis was defined as the brachial artery flow <500 ml/min, no differences in outcome of

Table II. Logistic regression for risk factors of stenosis

	B	S.E.	P	OR	95.0% C.I. for OR	
					Lower	Upper
Age	0.05	0.04	0.13	1.06	0.98	1.13
Glycaemia	0.01	0.01	0.08	1.01	1.00	1.03
Total cholesterol	-0.03	0.01	0.01	0.97	0.95	0.99
Atherosclerosis	1.66	0.85	0.05	5.24	0.99	27.62
Delayed maturation	2.47	1.37	0.07	11.81	0.81	172.12
Statin treatment	-0.72	1.35	0.59	0.49	0.03	6.91
Erythropoietin	1.41	0.90	0.12	4.10	0.71	23.75
Diastolic blood pressure	-0.07	0.03	0.03	0.93	0.88	0.99
Constant	***3.42***	***3.67***	***0.35***	***30.71***		

B – unstandardized coefficient B, S.E. – standard error, OR – odds ratio, C.I.- confidence interval.

Table III. Comparison between consequences of stenosis according severity of stenosis defined by different criteria: vessel diameter, blood flow and resitivity index in the brachial artery.

	>= 3 mm	< 3 mm	p	BF >= 500 ml/min	BF <500 ml/min	p	RI < 0.6	RI >= 0.6	p
	n = 10	n = 43		n = 41	n = 12		n = 35	n = 18	
Kt/V	1.84 ± 0.25	1.54 ± 0.32	0.02	1.57 (1.40-1.80)	1.69 (1.30-2.00)	0.63	1.65 (1.40-2.00)	1.57 (1.52-1.80)	0.60
Pre-dialysis urea (mg/dl)	123.79 ± 37.97	150.71 ± 37.15	0.06	145.25 ± 37.74	147.83 ± 35.70	0.86	147.49 ± 31.98	148.42 ± 47.48	0.96
Phosphorus (mg/dl)	4.43 ± 1.07	5.28 ± 1.51	0.12	5.15 ± 1.61	5.19 ± 1.44	0.95	4.59 ± 1.10	5.19 ± 1.82	0.36
Creatinine (mg/dl)	8.19 ± 2.53	10.47 ± 2.32	0.01	10.29 ± 2.65	9.41 ± 2.13	0.37	9.45 ± 2.55	10.44 ± 1.24	0.35

n – number of patients, HDL – high density lipoproteins, BF – blood flow, RI – Resistivity Index, AVF – arteriovenous fistula.

patients with severe stenosis compared to patients with moderate stenosis were identified. Similarly, when using as a severity criterion a threshold RI of 0.6, no differences in outcome of patients could be found. Comparison of patients with severe/moderate stenosis, according to the 3 above-mentioned criteria, is presented in table III.

Discussions

The diagnosis of stenosis relies on the PSV ratio, criterion that is also applied for AVF [12]. However, recent data accentuate the importance of measurement of the minimum diameter of the stenosed area in addition to PSV in order to differentiate true, significant, stenosis from borderline stenosis [10,11]. Based on these data, we defined stenosis as a combination of both functional and morphological criteria. Even defined as such, the prevalence of stenosis was important in our study, some degree of stenosis being present in more than half of the patients. A similar prevalence of stenosis is confirmed by other epidemiological studies [15-18].

The localisation of stenosis depends on the site of arteriovenous anastomoses with an impact on fistulas' primary and secondary patency [19]. In our study the juxta-anastomotic localisation of stenosis was found in the majority of cases, in the forearm and in the upper arm AVF equally. These results are not entirely in accord with angiographic studies, in which the juxta-anastomotic localisation of stenosis is predominant in forearm fistulas, but proximal stenoses (e.g. at the end of the superficialisation area) are dominant in the upper arm AVF [19].

We assessed various clinical and laboratory data which could be either risk factors or consequences of stenoses. The risk factors for stenosis identified by our study were largely in accordance to known pathogenic mechanisms and data in the literature. Low values of diastolic blood pressure seem to be a risk factor for stenosis in our group, similarly to previous data [20-22]. The association of lower cholesterol with stenosis is somewhat counterintuitive; however, in the stenosis group, statin treatment was more prominent and prevalence of previous atherosclerosis related cardiovascular events was significantly higher. Both statin treatment and lower cholesterol in these patients are more likely a fortuity association, explained by the aggressive treatment of high cardiovascular risk patients. Also, increased fasting blood glucose in stenosis patients as compared to their non-stenotic counterparts is another reflection of high cardio-vascular risk profile. Similar associations have been previously reported [23,24].

Measurements of the diameter of the brachial artery, feeding artery, and anastomosis are useful especially in atherosclerotic patients and are described as risk factors for stenosis [21, 25-27]. The small calibre of these vessels was associated with the presence of stenosis also in our study.

Delayed maturation is associated with a late fistula failure, the mechanism of which might be related to a small vessel diameter; if other factors intervene it is not determined [11,12]. We found however increased prevalence of delayed maturation in stenosis patients, suggesting stenosis to be a major player in the pejorative outcome of AVF with delayed maturation.

In what concerns the possible consequences of stenosis, with the exception of puncture site incidents, the mere presence of stenosis did not cause differences in dialysis efficacy between patients. Therefore, the positive diagnosis of AVF stenosis according to current US criteria may not be reason enough for invasive therapy. The same argument is advocated by other authors who suggest a distinction between significant (severe) stenosis, which should be treated and stenosis without severity criteria [10].

We aimed to compare the usefulness of the relative simple measure of severity of stenosis represented by the diameter of the vessel to other more complex and time-consuming methods (such as the flow of the brachial artery or RI) by assessing whether these different methods have clinical relevance. When defining severity of stenosis according to vessel diameter differences we found that patients with severe stenosis have decreased dialysis efficacy as measured by Kt/V and predialysis parameters. This could have potential consequences in the patient's survival [28] and assessing severity of stenosis by this method could identify clinical significant stenosis and prompt therapeutic intervention. We did not find differences in outcome, when using the flow of the brachial artery or the RI to compare patients with severe versus less severe stenosis. As flow in the brachial artery and RI are more difficult to measure than diameter of stenosis and do not contribute to the identification of patients at risk for adverse dialysis outcomes, they do not seem to be mandatory in assessing severity of stenosis. A prospective study of our patients could evaluate if there is an association between these two functional parameters and the loss of vascular access over time.

The limitation of our study was the relatively low number of patients of a single centre, future multicentric studies have to be conducted in order to confirm our results. This would facilitate inclusion of a sufficient number of patients for stratified analysis according to the location of AVF, location of the stenosis and comorbidities such as diabetes mellitus or age. The transversal nature of our study does not allow to rule on the predictive value

of stenosis for AVF failure, a further prospective study being necessary. A further shortcoming of the study is the lack of inter-observer and intra-observer agreement, which could be a source of technical errors in the measurement of some ultrasonographic parameters.

Conclusions

Prevalence of stenosis was high in our cohort, more than half of patients having some degree of stenosis. Risk factors for stenosis are those related to atherosclerosis, including its risk factors and treatment, low diastolic blood pressure, and delayed maturation of AVF. Diameter of stenosis was the most useful marker in appreciation of the severity of the stenosis. Severe stenosis results in lower dialysis efficacy.

Conflict of interest: none

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