

Original Article

Low-pressure environment and remodelling of the forearm vein in Brescia–Cimino haemodialysis access

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Background. The aim of the study was to determine which, and to what extent, haemodynamic parameters contribute to the remodelling of the venous limb of the Brescia–Cimino haemodialysis access.

Methods. The dimensions of the radial artery and the venous limb of the haemodialysis access were measured by an echo-tracking technique. In six ESRD patients undergoing primary arteriovenous fistula (AVF) formation, vessel diameter, wall thickness, blood pressure and blood flow were measured after the operation, and at 1 and 3 months follow-up. The contralateral forearm vessels in their native position served as baseline values for comparison.

Results. The diameter of the proximal antecubital vein progressively increased over the study period without reaching significant differences (4430, 5041 and 6620 μm at weeks 1, 4 and 12 respectively), whereas the intima-media thickness remained unchanged. The venous dilatation was associated with a reduction of the mean shear stress that culminated after the operation and progressively returned to normal venous values at 3 months (24.5 vs 10.4 dyne/cm^2 , $P < 0.043$). Thus the venous limb of the AVF undergoes eccentric hypertrophy as demonstrated by the increase in wall cross-sectional area (4.42 vs 6.32 mm^2 at week 1 vs week 12, $P < 0.028$). At the time of the operation, the blood pressure in the AVF was $151 \pm 14/92.4 \pm 11$ mmHg vs $49 \pm 19/24.5 \pm 6$ mmHg (means \pm SEM) for the radial artery and the venous limb of the vascular access, respectively. One year after the operation the blood pressure in the venous limb had not changed: $42 \pm 14/25.3 \pm 7$ mmHg (means \pm SEM). Under these conditions, the systolo-diastolic diameter changes observed in the radial artery and the antecubital vein were within a similar range at all time points: 56 ± 17 vs 90 ± 26 μm (means \pm SEM) at week 12.

Conclusions. The increased circumferential stress resulting from the flow-mediated dilatation rather than the elevation of blood pressure appears to represent the main contributing factor to the eccentric hypertrophy of the venous limb of Brescia–Cimino haemodialysis access.

Keywords: arteriovenous fistula; blood pressure; Brescia–Cimino access; haemodialysis; remodelling; vein

Introduction

The modification of haemodynamic factors plays a crucial role in vessel wall remodelling. Experimental models have been developed to study the effects of changes in chronic blood pressure [1,2] and blood flow [3–5] on conduit arteries, and on venous segments [6] used for bypass surgery. For methodological reasons only very limited information is available regarding vascular wall remodelling under acute or chronic changes of haemodynamic factors in humans with the exception of hypertension or related conditions [7–10]. The formation of an arteriovenous fistula (AVF) for haemodialysis in patients with end-stage renal disease (ESRD) represents a unique model to study the relationship and the time course between the development of vascular geometry changes with respect to the antecubital vein, and the haemodynamic alterations following the formation of an AVF. Recent work by Girerd *et al.* [11] has shown that remodelling of the radial artery in patients with ESRD and AVF is not accompanied by arterial hypertrophy despite a 1.4-fold increase in diameter following a sixfold increase in blood flow. However, neither qualitative nor quantitative estimation of the venous remodelling of AVF has been assessed so far.

Late failure of the AVF in ESRD patients is usually due to intimal hyperplasia and impaired outflow following reduction of peripheral flow. Although most of the intimal hyperplasia lesions occur at the

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anastomosis, thrombotic events also occur along the venous segment of the AVF where punctures are performed during haemodialysis.

It is known that in lower-limb vein grafts from artery to artery intimal thickening develops along the full length of the vein. It is not known what happens in the venous side of the AVF. Whether vascular remodelling or uncontrolled vascular growth along this segment contributes to the prognosis for long-term patency remains to be determined. Due to the limited distensibility reserve of the vein exposed to a new haemodynamic environment in AVF, characterized by high blood flow and increased blood pressure levels, a greater circumferential wall stress may contribute to vascular wall hypertrophy and subsequent thrombotic complications [6].

The present study was designed to assess the modifications of the geometric and mechanical properties of the antecubital vein in relation to the changes in blood flow and blood pressure following the formation of an AVF according to the Brescia–Cimino technique. The measurement of the structural parameters, the haemodynamics and the time course of the changes may help identify the strongest determinant of remodelling in the haemodialysis access.

Subjects and methods

Subjects

Six patients (all males) with stable ESRD and no previous AVF, aged 30–73 years were included in this study and examined 1, 4 and 12 weeks after formation of the AV haemodialysis access according to the Brescia–Cimino technique. Causes of renal failure were nephroangiosclerosis in three patients, polycystic renal disease in two and chronic glomerulonephritis in one patient. Pre-operative systolic blood pressure was 144.8 ± 17.9 mmHg and diastolic blood pressure was 88.6 ± 8.3 mmHg (means \pm SEM).

Among the six patients, four received antihypertensive therapy, calcium antagonist alone in one or in combination with angiotensin-converting enzyme inhibitors in two. One patient received a combination of three medications (β -blocking agent, calcium antagonist plus angiotensin-converting enzyme inhibitor).

The study was approved by the Ethics Committee of the CHUV Hospital, and all patients gave oral informed consent.

Measurement of vascular parameters

Investigations were performed in a controlled environment at 21°C. Each patient was studied in the supine position after at least 10 min of rest. Systolic and diastolic pressures were determined automatically every 3 min at the non-operated arm with an Omron oscillometric BP recorder. Systolic and diastolic pressures were determined as the average of three measurements. At the completion of the operation, blood pressure was recorded using an arterial line in the radial artery and in the antecubital vein 2 cm away from the anastomosis. Intravascular blood pressures were measured again in all patients 2 cm distal from the anastomosis, and between 11 and 14 months after the formation of the AVF.

The internal diameter of the radial artery and of the antecubital vein were recorded simultaneously using a high resolution echo-tracking system that was developed in house and described in detail in the past [12]. A skin mark was identified and recorded for subsequent measurements. The combination of diameter changes in relation to pressure modification allows the computation of compliance and distensibility of the vessel.

The high-resolution ultrasound system used in the present study (NIUS 02) has been previously described [11,12] and validated for the measurement of artery internal diameter and systolic–diastolic variations as well as measurement of vessel wall thickness in experimental and clinical applications [13–15]. A pulse echo-tracking device was used to acquire back-scattered radiofrequency data from the radial artery and the antecubital vein 2 cm proximal to the anastomosis on the wrist. The probe consisted of a 10-MHz highly focused piezoelectric transducer (6 mm diameter, 11 mm focal length) operated in the pulse-echo mode (Figure 1). The -10 dB beam width is 0.3 mm at the focal point, and the depth of field at -10 dB is 5 mm. A stereotactic arm permits motion of the transducer in x , y , and z co-ordinates with micrometric steps for placement of the probe perpendicular to the arterial axis in its largest cross-sectional dimension. The transducer is positioned so that its focal zone is located in the centre of the artery, and the back-scattered echoes from both the anterior and posterior walls can be visualized on the computer screen. Vessel diameter and posterior wall thicknesses are measured when a radiofrequency ultrasound signal composed of two high-amplitude peaks, delineating the anterior and posterior walls, is obtained. These signals are visible only as the ultrasound beam crosses the centre of the vessel in a perpendicular way.

For the measurement of internal diameter and intima-media wall thickness of the posterior wall, electronic trackers are automatically positioned on the outer radiofrequency line of the second peak of the anterior wall, and on the inner radiofrequency lines of the first and second peaks of the posterior wall. Their movements are electronically tracked for 10 s, sampled at 100 MHz over 8 bits, and stored at a 50-Hz repetition frequency. Data are determined by computing the analytical signal according to methods previously described and based on Fourier transformation. The pulse length of this 10-MHz ultrasound system was $0.1 \mu\text{s}$ at 6 dB and corresponded to a practical axial resolution of 0.16 mm for absolute internal diameter or wall thickness measurements, and 0.0025 mm for these parameters during systolic–diastolic changes. Systolic–diastolic variations in internal diameter and posterior wall thickness were recorded. For data analysis, each patient was described by the average of recordings of mean wall thickness (millimetres), calculated by integrating the time course of the systolic–diastolic variations, and diastolic internal diameter (millimetres), over several cardiac cycles. Because wall thickness is influenced by the changes in distending BP (hence internal diameter), wall cross-sectional area (WCSA) is more appropriate for detecting vascular wall hypertrophy. Because of the incompressibility of the arterial mass [13] WCSA (mm^2) can be calculated as $\pi \times (R_e^2 - R_i^2)$, where R_e and R_i are the values of internal and external radii respectively.

Blood flow in the AVF was measured by echo-Doppler using a 7.5-MHz linear array probe (System Five, GE) where diameter of the vein was recorded simultaneously with time-averaged mean blood-flow velocity during five cardiac cycles. AVF blood flow was determined as the average of five measurements. Mean shear stress was calculated using the

Echotracking

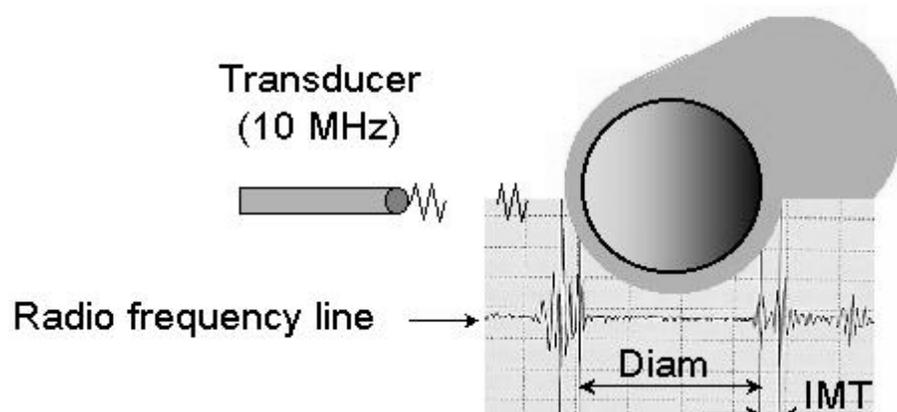


Fig. 1. Arterial diameter determination by A-mode echo-tracking system (NIUS-02). Electronic tracers automatically focus on the echogenic interfaces delineating wall lumen.

Poiseuille equation, $\sigma = 4\eta Q/\pi r^3$; considering blood viscosity (η) to be identical and constant throughout the study period in the six patients.

The contralateral radial artery and cephalic vein, which were left intact, were measured respectively with the high-resolution echo-tracking system and the echo-Doppler and served as reference values for comparison with the AVF. Indeed, due to low blood-flow velocity in the intact cephalic vein, the echo-tracking system does not permit the accurate positioning and measurement of venous dimensions. Therefore, the cephalic vein diameter was measured with B-mode imaging (10-MHz probe) following inflation of a cuff to 60 mmHg at the arm level to obtain complete vein distension. The resolution of the B-mode imaging does not allow precise venous-wall thickness measurements, therefore wall cross-sectional area of the native vein was not computed at that stage.

Statistical analysis

All values are expressed as means \pm SEM for blood pressure values and as median/range for haemodynamic and geometric values. Statistical significance was defined as a probability value <0.05 . Because of the limited sample non-parametric analysis was used to analyse results of haemodynamic or geometric measurements (Wilcoxon).

Results

None of the patients suffered acute AVF complication following formation, and haemodialysis was begun between weeks 4 and 6 after the operation. Antihypertensive treatments remained unaltered throughout the examination period.

Reference values for geometry and haemodynamics measured at the contralateral forearm are summarized in Table 1. Table 2 summarizes the haemodynamic parameters of the study population at the three measurement periods. No significant changes in blood pressure or blood flow in the AVF were

Table 1. Geometric and haemodynamic characteristics of the vessels of the non-operated forearm. Mean \pm SEM; median (range)

Radial artery systolic blood pressure (mmHg)	143 \pm 16
Radial artery diameter (μ m)	2415 (2401–2845)
Radial artery thickness (μ m)	299 (277–370)
Radial artery flow (ml/min)	12.5 (12.0–17.6)
Venous diameter (μ m)	2370 (2000–3660)

Table 2. Temporal trend of the haemodynamics

Week	Radial artery sys. pressure (mmHg)	Blood flow (ml/min)	Mean shear stress (dynes/cm ²)
1	144 \pm 18	539 (325–990)	24.5 (5.3–132)
4	138 \pm 18	640 (393–980)	18.1 (7.3–51.8)
12	145 \pm 14	750 (275–1000)	10.4 (2.45–14.8)*

Blood pressure values are means \pm SEM; blood flow and shear stress are median (range); * $P < 0.043$, week 1 vs week 12.

observed during the 3-month observation. The systolic and diastolic pressures recorded during the operation 2 cm away from the anastomosis were $151 \pm 14/92.4 \pm 11$ mmHg vs $49 \pm 19/24.5 \pm 6$ mmHg (means \pm SEM) for the radial artery respectively the venous limb of the Brescia–Cimino fistula. At 13 months after the formation of the AVF, blood pressures in the venous limb 2 cm distal from the anastomosis remained unchanged: $42 \pm 17/25.3 \pm 7$ mmHg (means \pm SEM). None of the dialysis patients suffered haemodynamic complications at follow-up.

The changes in the geometric parameters of the arteriovenous segments of the AVF are shown in Table 3. The internal diameter of the artery did not change significantly during the 3-month period, reflecting the stabilization of the blood flow increase in the AVF shortly after the operation. On the

contrary, the internal diameter of the proximal segment of the antecubital vein progressively increased over the study period, whereas the intima-media thickness of the venous wall remained unchanged. The dilatation of the venous segment was accompanied by a reduction of the calculated mean venous shear stress that reached a near normal value for venous flow at 3 months [17]. Overall the dilatation of the venous segment together with a constant wall thickness induced a significant increase in wall cross sectional area (WCSA); 4.42 mm^2 (4.01–6.40) *vs* 6.32 mm^2 (4.90–7.11) at week 1 *vs* week 12 respectively; $P < 0.028$. The vascular wall remodelling at 3 months can be defined as eccentric hypertrophy according to the definition proposed recently by Mulvany *et al.* [17]. There is indeed an increase in vascular mass.

The systolo-diastolic diameter changes observed in the radial artery and the antecubital vein are of similar magnitudes at all time points; 56 ± 17 *vs* $90 \pm 26 \mu\text{m}$ (means \pm SEM) at week 12 respectively (Figure 2).

Table 3. Temporal trend of the geometry of the vessels

Week	Radial artery diameter (μm)	Antecubital vein diameter (μm)	Antecubital vein WCSA (mm^2)
1	3275 (2410–4417)	4430 (3040–6140)	4.4 (4.1–6.4)
4	3555 (2845–4375)	5041 (4160–7675)	5.3 (4.3–6.9)
12	3310 (2420–4216)	6620 (3550–7140)	6.9 (4.9–7.1)*

Median (range), * $P < 0.028$, week 1 *vs* week 12.

However, the invasive blood pressure measurements obtained at the end of the operation near the anastomosis were quite different between the arterial and the venous segments. There was a greater than twofold reduction in systolic pressure immediately after the anastomosis in the antecubital vein.

Discussion

The formation of an AVF for haemodialysis in patients with ESRD represents a unique model to study the relationship between vascular remodelling and haemodynamic changes, as well as the time course of the processes following the formation of an AVF. The major findings of the present study are the following: (i) the venous segment of the Brescia–Cimino AVF is characterized by a high blood flow (20-fold increase) and a low blood pressure level; (ii) under these haemodynamic conditions and in the supine position, the vein retains a compliance reserve that preserves the vessel from developing inappropriately high wall stress; and (iii) remodelling of the venous wall is characterized by an eccentric hypertrophy that appears to result from increased circumferential wall tension due to the flow-mediated dilatation rather than from elevation of the blood-pressure level. The high flow rate is a well known haemodynamic characteristic of the Brescia–Cimino dialysis access, whereas the low blood pressure observed in the venous segment is not as familiar to doctors and nurses involved with haemodialysis.

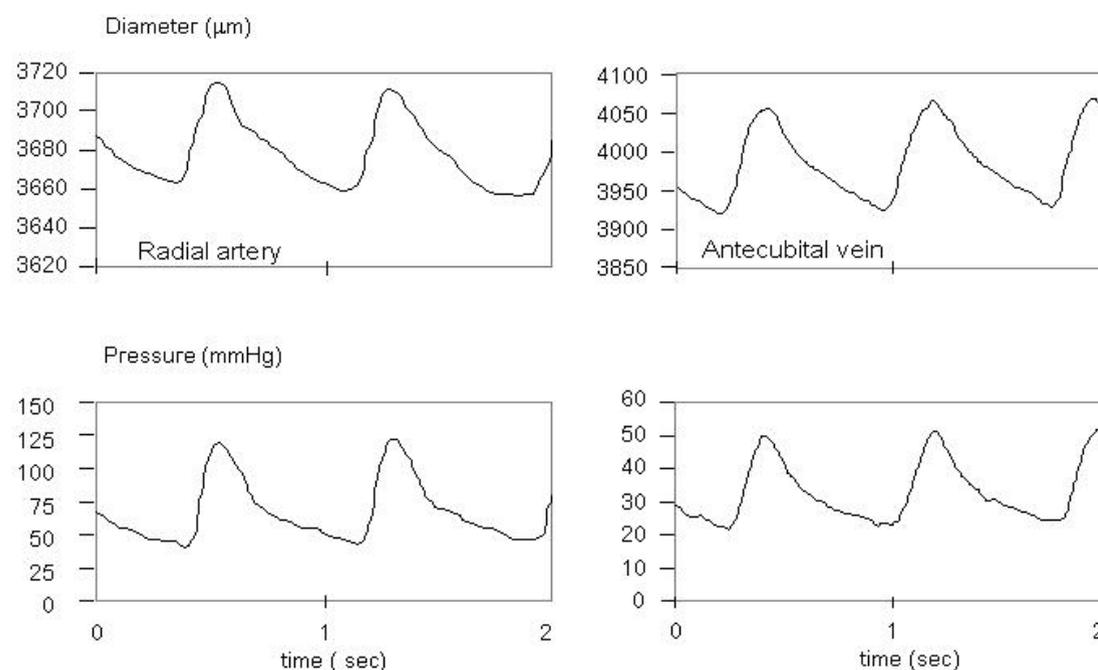


Fig. 2. Synchronized recordings of the internal diameter and blood pressure obtained at the end of the operation before intravascular catheter withdrawal.

Previous work by Dobrin *et al.* [6] have demonstrated that the compliance of the venous wall is greater than that of arteries of similar calibre at a pressure range below 50 mmHg. This apparently increased venous compliance at low pressure levels is due to the fact that the veins are more or less collapsed and that once having reached a cylindrical shape collagen fibres prevent further dilatation. Above this pressure level the vein reaches a plateau and does not distend further, whereas the artery retains a certain degree of distensibility reserve. Based on these findings we sought to assess whether and to what degree the distensibility reserve of the venous segment of the Brescia-Cimino AVF, or lack thereof, may contribute to the remodelling of the venous segment. Thrombotic complications often occur on the venous limb of the AVF and quite often at the anastomosis. Occlusion of the venous segment distal to the site of the anastomosis may in part result from inappropriate or ill-controlled remodelling of the vessel wall that may contribute to the thrombotic process. Previous data have shown that a mismatch of the elastic properties around the anastomosis may contribute to intimal hyperplasia formation via flow disturbances [18,19]. In the case of Brescia-Cimino AVF, such a mismatch does not seem to be the case, as discussed below.

It is assumed that formation of an AVF between the radial artery and an antecubital vein will considerably increase forearm blood flow for haemodialysis purpose, and that the blood pressure in the venous segment will increase accordingly. Indeed, blood pressure readily increases in the antecubital vein but not to the level that one would implicitly anticipate. The direct recording of the systolo-diastolic diameter changes demonstrates that the venous segment remains quite distensible when compared with the radial artery. Therefore, either the vein undergoes a rapid and consequent remodelling, transforming a poorly compliant structure into a vessel with biomechanical properties similar to those of the radial artery, which is quite rich in vascular smooth-muscle cells, or the vessel was indeed exposed to a much lower blood pressure level than anticipated. The first hypothesis is quite unlikely because the initial measurements were performed only a few days after formation of the AVF, much too early for the haemodialysis access graft to mature. Hypertrophy of the smooth-muscle cells via activation of early genes and/or reorganization of the extracellular matrix under the influence of proteinase activation would require a much longer period to modify the biomechanical properties of the antecubital vein so dramatically. The second hypothesis appears more likely. Indeed, when intravascular blood pressures were recorded in the AVF at the completion of the AVF operation, we observed a striking fall in pressure level millimetres away from the anastomosis along the venous limb of the haemodialysis access. The pressure difference between the two segments was due partly to the severe fluid energy loss at the anastomosis, where the circulation is characterized by a disturbed flow pattern. Therefore, in addition to

reduction in resistance within the venous system, the energy loss associated with the AV anastomosis can explain the low pressure level recorded in the venous limb of the AVF. Thus, the wide diameter changes recorded in the antecubital vein reflect the low blood pressure environment in the haemodialysis access vessel. Consequently, in the conditions under which the experiment was performed, the antecubital vein retains a distensibility reserve at the operating blood pressure range that allows buffering of the pulse pressure. Whether this reserve is solely the consequence of the venous shape or is also due to the remodelling process is not fully elucidated at this time. The cyclic deformation of the venous limb of the AVF may participate in the mechanisms that trigger the remodelling process of the vessel wall throughout the maturation phase of the haemodialysis access.

The combined effects of high flow rate in the venous segment and the augmentation in stretch due to the pulse pressure increase induces a dilatation that is in part mediated by the increase in shear stress. However, at 3 months, remodelling of the venous segment normalized the mean shear stress to values generally found in the venous system [16]. This is definitely not the case in the radial artery, which does not seem to possess remodelling reserve, as a possible consequence of irreversible alterations of the vessel wall components due to chronic uraemia. Whether the endothelium is a crucial mediator in transducing mechanical forces to the venous wall components remains to be more thoroughly evaluated. Indeed, endothelial dysfunction has been reported in patient with ESRD [20,21]. However, other forms of mechano-transduction mechanisms have been suggested to communicate the information generated by haemodynamic modifications at the surface of the endothelium to the subendothelial wall compartments [22,23]. Under chronic haemodynamic flow alteration, the vascular system will tend towards normalization of circumferential wall stress and shear rate. In the case of AVF according to the Brescia-Cimino technique, the remodelling of the venous limb as demonstrated here takes the form of an eccentric hypertrophy, resulting in an increase in vascular mass [17]. The latter is most probably the consequence of the conjugated effects of the flow-mediated dilatation following the formation of an AVF that increases circumferential wall stress according to Laplace's law, than the result of an increased blood pressure level. Indeed, clinical experience has taught us that failure of maturation of the AVF is usually linked to the lack of high blood-flow development as frequently encountered in patients with previous catheterization of the proximal veins and subsequent thrombotic events. In those particular cases, venous pressure reaches much higher levels than in the functioning AVF but blood flow is dramatically reduced, thus impeding venous dilatation and maturation.

Local flow disturbances at puncture sites with activation of haemostasis and coagulation processes may, in concert with ongoing remodelling mechanisms,

contribute to accelerate venous wall alteration and thrombotic complications.

In conclusion, this study shows that the venous limb of the AVF according to the Brescia–Cimino technique is subjected to a high blood-flow and a low blood-pressure environment and that the venous wall undergoes eccentric hypertrophy as a result of increased circumferential stress due to higher shear forces. The contribution of the slight elevation of blood pressure remains to be investigated further but seems to play only a minor role, as suggested by the lack of vessel enlargement in absence of flow development.

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