Local Hemodynamics of the Vascular Access for Hemodialysis

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Key Words

Vascular access • Hemodialysis • Wall shear stress

Abstract

Vascular access is called Achilles' heel of hemodialysis because it is associated with a substantial morbidity. A permanent vascular access is created either by a direct connection of the patient's own artery and vein or by the interposition of a graft. Arteriolar beds are bypassed, which leads to a substantial increase in arterial (and venous) flow and the vessels adapt to it by a complex of interesting processes. These are reviewed together with some pathophysiological mechanisms of access complications.

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Introduction

Most end-stage renal disease (ESRD) patients are treated with hemodialysis. Such therapy needs regular entries into the blood stream, usually 2–3 times/week. Although a permanent venous catheter could be used for this purpose, its use is associated with increased morbidity and mortality due to infections [1, 2]. Therefore, a permanent vascular access (also called 'shunt') is preferred. Such access bypasses the arteriolar beds, which leads to a substantial flow increase and some interesting adaptation processes.

Vascular accesses are called 'lifelines' for patients on hemodialysis. Unfortunately, the life span of these patients is limited [3] and their management is associated with significant morbidity and costs [4, 5]. Understanding the mechanisms of access maturation and of the development of complications is necessary for proper access management. From the clinical point of view, a good vascular access should: (1) provide adequate blood flow for the hemodialysis (>300–500 ml/min); (2) have a superficial position – to be easily cannulated for dialysis; (3) have a long life span, and (4) no or a low complication rate [6].

We review the interesting hemodynamic, biochemical and clinical aspects of vascular accesses, which are overviewed in table 1.

Physiological Changes after Access Creation

The native vascular access (arteriovenous fistula, AVF) is created by the direct connection of the patient's own vein and artery. Usually an end-of-vein to side-of-artery technique is used. The most common types include radiocephalic and brachiocephalic fistulas. When patent straight superficial veins are lacking, a polytetrafluoro-

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Table 1. Overview of factors leading to access dysfunction

Site	Mechanism	Complication
Feeding artery	Endothelial dysfunction/atherosclerosis Medial calcinosis	Inadequate flow/maturation Hand ischemia
Arterial anastomosis	Wide Narrow Blood jet against venous wall	High-flow access Low-flow access Venous aneurysm/stenosis
Venous anastomosis of PTFE	Mismatch in elastic wall properties Wall shear stress changes Geometry of the adjacent vein	Neointimal hyperplasia/stenosis
Outflow vein	Jet from the anastomosis Puncture technique	Aneurysm/stenosis
Dialysis needles	Fast blood jet	Platelet activation Neointimal hyperplasia?

ethylene (PTFE) graft is used as a bridge between an artery and a superficial or deep vein; this graft is punctured during hemodialysis. Other access types are less common and include native or PTFE accesses in lower extremities, allografts, PTFE grafts at the patient's trunk, etc. [1, 7].

Just after vascular access creation, the resistant arterioles are bypassed, which leads to a sudden decrease in peripheral vascular resistance (PVR) and to a substantial increase in access flow (through the feeding artery, graft and outflow vein). While brachial artery flow is 60–120 ml/min in healthy resting individuals and even less in ERSD patients (own unpublished data), it reaches 500–2,000 ml/min in the extremity with an access. Obviously, such an increase in flow volume must lead to both local (arterial and venous) and systemic changes.

Feeding Artery

Arterial endothelial cells sense the sudden increase in arterial flow which occurs just after access creation. The endothelium responds by the increased bioavailability of nitric oxide (NO), which is the strongest endogenous arterio-dilating agent [8]. This is why this mechanism is used to test the flow-mediated dilation of the brachial artery after temporary forearm ischemia; the level of dilatation corresponds to endothelial (dys)function [9]. Physiologically, blood flow acceleration with a diameter increase occurs during physical training. The physiological purpose of the arterio-dilatation in response to the blood

flow increase is to enable perfusion of working muscles, to heal local inflammation, etc., by a decrease in PVR [10] because flow volume is directly related to cardiac output and indirectly to PVR. Naturally, the dilatation of small arterioles is mathematically and physiologically more significant for limb perfusion than dilatation of the proximal arteries.

From the hemodynamic point of view, the effect of blood on the arterial wall could be described by pressure and flow. The pressure acts perpendicularly on the arterial wall and is therefore sensed by all wall layers. This leads to wall strain, expressed by the law of Laplace. A detailed description of the blood pressure effect on the arterial wall is beyond the scope of this review [for details see 11].

Unlike blood pressure, blood flow acts only on the inner surface of the arterial wall and thus directly affects only endothelial cells and not the medial and adventitial layers. Wall shear stress (WSS) is the mathematical description of the blood flow effect on the endothelium [12, 13]. It is a force that is mathematically expressed as a vector, with direction and magnitude. The direction corresponds to the blood flow direction and its magnitude is directly proportional to wall shear rate (WSR) and blood viscosity [12, 14, 15]:

$$\text{WSS} = \sigma \cdot \text{WSR (Pa)},$$

where σ is whole blood viscosity. WSR is defined as the difference between adjacent velocities in the vascular lumen divided by their distance. Because of technical limitations, centerline blood velocity and arterial radius are

used as the approximation of WSR. As we can measure peak and mean blood velocity (e.g. by Doppler ultrasonography), we can also differentiate between peak and mean WSS – it is of particular importance in high-resistant flow. Pascal (Pa) is the official unit of WSS, but it is usually replaced by dynes per square centimeter.

In general, arterial adaptation is directed towards restoration of hemodynamic parameters to baseline physiological values [10, 16–19]. An increase in blood flow velocity leads to a rise in WSS, which is restored by arterial dilatation: a negative feedback loop [20]. A decrease in PVR in the feeding artery differs from the reaction to physical training and to local inflammation by 2 factors: it is very profound and long-term. Others [21–23] and we [24, 25] have studied WSS in the feeding artery up to 2 years after access creation. It remained supra-physiological, mainly in accesses originating from the radial artery and in diabetics. Thus, the leading force of arterio-dilatation – WSS – remains high. Indeed, the feeding artery continues to dilate within the 2nd year after access creation. On the contrary, in some animal models of AVFs, WSS normalized sooner. In an iliac AVF model in rats, WSS returned to its baseline values after 42 days [26]. Six months after the construction of an AVF between the right iliac artery and vein in monkeys, blood flow increased with a consequent twofold internal diameter increase and WSS remained unchanged [27]. Kamiya and Togawa [14] created a carotid artery to external jugular vein fistula to study the adaptation of the dog carotid artery to increased flow. They showed that the artery with high flow adapted completely by enlargement to reduce the WSS to physiological baseline values of 15 dynes/cm². Similar findings were reported by Zarins et al. [27] in a hypercholesterolemic monkey model. But the question remains: why does WSS not normalize in the human dialysis access feeding artery? We can hypothesize that (1) it takes even more time than 2 years; (2) it is due to a complex of differences in vascular physiology between human beings and animals, and (3) it is due to pathological changes associated with both ESRD and comorbidities.

Arterial dilatation in response to blood flow acceleration after access creation is mediated by NO. However, it is known that acute arterio-dilatation is limited (it could be tested by direct application of NO donors, such as nitroglycerine). On the other hand, arterial dilatation in response to chronically high blood flow continues further behind these limits. It is due to morphological changes in the arterial wall, including degradation or fenestration of the basal membrane by matrix metalloproteinases. Tronc et al. [28] documented that the matrix

metalloproteinases are directly activated by NO. Therefore, NO plays a pivotal role in both acute and chronic dilatation of the access feeding artery. As the endothelium is the only endogenous source of this molecule, endothelial dysfunction contributes to limited feeding artery dilatation. Endothelial dysfunction is associated with dyslipidemia, hypertension, diabetes mellitus, uremia, etc. [29–31]. In our previous study we observed slower long-term arterial dilatation in patients with diabetes mellitus and elevated serum cholesterol levels [24]. Of course, the magnitude of vasodilatation is also negatively related to the degree of vessel wall calcification [32, 33], which is more pronounced in diabetic patients and known as medial calcinosis [34]. It has been documented that endothelial cells sense steady and pulsatile shear stress differently [15]. The increase in mean and peak WSS after vascular access creation is not proportional: whereas mean WSS increases 4- to 6-fold, peak WSS increases only little [21–23]. It is especially due to the change in the diastolic flow pattern from high-resistant (near-to-zero diastolic flow) to low-resistant (orthograde flow during the whole cardiac cycle). After 1 year, the vasodilatation continues with persistently increased mean and peak WSS [22, 23]. Therefore, it seems that it is the peak (and not mean) WSS, which plays the main role in the arterial diameter changes directed to maintain the WSS constant [21]. In other words, the oscillatory WSS is sensed rather than mean WSS by the endothelium [23].

As a result of atherosclerosis and/or medial calcinosis, arterial stenosis could develop at any part of the extremity with vascular access. While medial calcinosis affects especially distal parts of the arterial tree, atherosclerotic plaques are predominantly located along the outer walls of bifurcations. Hemodynamically significant stenoses located proximal to the arterial anastomosis usually lead to a decrease in access flow. Hand ischemia could develop in the case of both proximal or distal arterial stenoses [35].

Arterial Anastomosis

Arterial anastomosis is the site, where the high-pressure feeding artery is connected to the low-pressure graft or native vein. Arterial anastomosis of native accesses probably plays a role in outflow vein stenosis. While in the past the side-to-side technique was sometimes used, now the preferred method is end (of vein or graft)-to-side (of the artery) [36]. The venous segment perpendicular to the artery is usually very short due to the skin cover and

due to vein fixation to surrounding tissues. Therefore, the anastomosis produces a jet of blood flow along the venous wall. Then the blood stream is turned along the outer venous wall so that some sites are exposed to low and others to high WSS. This could lead to the development of venous aneurysms, which are, sometimes, followed by stenosis. Indeed, the vast majority of native access stenoses are located within a few centimeters of the arterial anastomosis [37, 38].

Blood Flow

Generally, arterial flow is directly related to the perfusion pressure and indirectly to PVR. This mechanism is maintained in conduit arteries which supply the tissues of the extremity with access. The blood flow volume through an arteriovenous access (conduit) is related to the diameter of the fistula and anastomosis and the inflow artery. In small arteriovenous conduits, where the fistula diameter is less than 3/4 of the inflow artery, the flow is regulated mainly by the fourth power of the fistula radius. In large arteriovenous conduits, where the diameter of the anastomosis and outflow circuit is equal or greater than that of the donor artery, volume blood flow is regulated mainly by the summary resistances of the peripheral vascular bed, the donor artery and the collateral circulation, similar to that of an electric model consisting of high- and low-resistance circuits [39, 40]. Perfusion pressure is generated by the left ventricle and is augmented by pressure wave reflections [41]. Perfusion pressure drops in significant arterial stenoses.

Blood flow volumes are usually lower in distal accesses, i.e. originating from the radial artery. They range from 300–700 ml/min in native radiocephalic fistulas to 500–1,000 ml/min in distal grafts. Usual values of flow volume in accesses with the arterial anastomosis on the brachial artery are 700–1,500 ml/min [42]. So-called high-flow access is that with a flow volume of >1,800–2,000 ml/min. These values become optically higher if we compare them with the normal resting cardiac output (4–6 l/min). High-access flow could lead to heart failure (congestive or hyperkinetic) and sometimes to hand ischemia [35].

Case reports of hyperkinetic heart failure as a result of high-flow access have been published, such as that of Jin et al. [43]. More commonly, access flow contributes to the development of already present congestive heart failure either clinically silent or overt.

It has been documented that access creation leads to some significant systemic changes – to dilatation of the left ventricle, decrease in systemic blood pressure, heart rate acceleration, and increased brain natriuretic peptide, etc. [44–46]. To simplify, vascular access flow has a hemodynamic effect similar to anemia and water retention. The authors of the studies, however, usually did not measure the access flow, which makes this topic even more complicated. Moreover, these studies were limited to as little as a few months. Unfortunately, it is difficult to perform a longer study with the exclusion of potential confounding variables (such as comorbidities, progression of kidney failure), because such variables also change over time. Chemla et al. [47] documented relief of heart failure symptoms and decrease in cardiac output after surgical high-access flow reduction. Interestingly, it seems that the necessary increase in cardiac output to sustain the high-access flow must be numerically greater than the actual access flow [48].

Surprisingly, many patients tolerate high-access flow quite well. Nevertheless, we recommend examinations of the patients by echocardiography every 6–12 months to avoid pathological dilatation of the left ventricle. Patients should also be asked if they have symptoms of heart failure or hand ischemia, and brain natriuretic peptide levels should be checked.

In the clinical routine, access flow is measured by dilution techniques, such as thermodilution, ultrasound dilution or by duplex Doppler ultrasonography [49]. It is advisable to obtain reproducibility data in all hemodialysis units.

Forearm accesses are fed by both forearm arteries – e.g., radiocephalic fistula also receives blood from the ulnar artery via palmar arch. The retrograde flow in the radial artery distal to the anastomosis can easily be documented by ultrasonography and occurs in more than 99% of all forearm accesses. This is a steal phenomenon with no clinical relevance in the vast majority of patients. Ligation of the distal part of the radial artery is indicated only in some special situations of hand ischemia [50].

Outflow Vein

The normal venous wall is considerably thinner than the arterial one. After access creation, it thickens in a process sometimes called ‘arterialization’. It seems that the diameter of the outflow vein also depends on some systemic variables because various causes of ESRD are associated with different venous diameters [51]. Enormous

Fig. 1. Venous anastomosis of a PTFE vascular access. The connection of the PTFE graft to the outflow vein (OV) is shown in B-mode ultrasonography, longitudinal section. **a** The proximal end of the graft (venous anastomosis, VA) is frequently affected by neointimal hyperplasia (arrow). Neointimal hyperplasia could, however, occur also in the adjacent part of the outflow vein. **b** The flow velocity and vector (respectively wall shear stress) play a role in the development of venous neointimal hyperplasia and stenosis.

Some venous segments are exposed to very high blood velocity, which could desquamate endothelial cells and activate thrombogenic factors, such as von Willebrand factor. Other segments are exposed to slow blood flow with varying vectors. Such areas are known by the frequent development of atherosclerosis plaques in the arterial tree and probably also predispose to the development of neointimal hyperplasia. The flow characteristics depend on VA geometry.

dilatation (aneurysms) develops in some patients. The puncture technique plays a substantial role in the development of aneurysms [52, 53]. Basically, 3 methods of access cannulation are used: (1) rope ladder cannulation (changing the puncture sites along the access); (2) area puncture cannulation (punctures within a short access segment), and (3) buttonhole technique (punctures into exactly the same sites). Area punctures are most often associated with aneurysms, buttonhole technique least.

Stenoses of outflow veins usually develop close to the arterial anastomosis (see above). Some patients have central vein stenoses as a result of previously used central vein catheters.

Venous Anastomosis of PTFE Grafts

Venous anastomosis is the site where the graft is connected to the patient's own vein. It is of particular clinical importance because the majority of access stenoses develop here. They affect either the site of the graft-vein connection (venous anastomosis per se) or the adjacent part of the outflow vein. From a practical point of view, it should be mentioned that it is easy to distinguish the graft and venous wall by ultrasonography, but it is harder to do this by angiography because only filling of the vessels by a contrast agent could be seen.

Neointimal hyperplasia (NH) is responsible for the development of stenoses at the venous anastomosis. At a histological level, NH is characterized by smooth muscle

cell/myofibroblast proliferation, angiogenesis (microvessel formation), and matrix deposition [54]. This is a mechanism similar to restenosis formation after balloon angioplasty of the coronary and peripheral arteries and to NH formation in PTFE arterio-arterial grafts. However, NH in the setting of dialysis access is a far more aggressive lesion [54].

A number of studies have tried to investigate the reasons of NH formation.

(1) *Mechanical and hemodynamic factors.* Suture of the PTFE graft to the patient's vein leads to microtrauma of the venous wall, the healing of which could be the first signal for NH development. The wall of the PTFE graft has considerably different elastic properties than the natural venous wall. A mismatch in elastic properties was suggested as a cause of NH by Hofstra et al. [55]. Later research was oriented to the role of WSS in NH formation. Blood is jetted from the venous anastomosis against the floor of the outer vein wall. See figure 1 for an explanation. During the months after access creation, the outflow vein dilates and its wall thickens, while the lumen of the graft in the anastomosis remains constant or even smaller due to NH. Venous dilatation predisposes to the development of flow reversal sites (along the inner venous wall). As a result, sites with slow blood flow (and low WSS) along the venous wall develop. High blood pressure in the outflow vein prevents venous constriction in response to the WSS decrease. Sites with chronically low WSS are predisposed to the development of atherosclerotic plaques in the arterial tree and a similar effect plays

a role in the development of NH. Such effects could be studied by simulations of fluid dynamics [56, 57]. The findings of these studies stimulated the development of a vascular graft with a preformed cuff shape at the venous end to reduce the area of flow reversal.

However, as the NH develops to a significant stenosis, there is blood flow acceleration with an increase in WSS. High WSS leads to endothelial desquamation and to increased synthesis of VEGFR-1, VEGFR-2 and matrix metalloproteinase-2.

(2) *Humoral and cellular stimuli.* The PTFE graft functions as a foreign body. Indeed, the highest risk of graft thrombosis is in newer grafts prior to complete endothelialization [58]. Uremia per se and especially its frequent causes – diabetes and hypertension – are risk factors of endothelial dysfunction which could predispose to NH. As a response to the hemodynamic effects, activation of the endothelium and smooth muscle cells in the vascular intima and media develops. Smooth muscle cells and myofibroblasts migrate from the media to the intima, resulting in the formation of NH. A plethora of cytokines and inflammatory mediators have been implicated in these processes. They include intercellular adhesive molecule-I [59], P-selectin [60], osteopontin [61], matrix metalloproteinase-2 [62], hypoxia-inducible factor-1 α , etc. [54]. The molecular interactions involved in the pathogenesis of vascular access complications are intriguingly reviewed by Diskin et al. [63].

Hemodynamics of the Dialysis Needles

ESRD patients usually spend 3–5 hours three times/week on hemodialysis with 1–2 needles inserted into their access. The needles influence the hemodynamics of the access in different manners: (1) microtrauma of the puncture, and (2) changes in access blood flow velocity and pattern.

The ‘inflow’ needle takes the blood from the patient to the dialysis machine and the ‘outflow’ needle transports it back to the vascular access. Suction of the blood by the inflow needle causes a turbulent flow around this needle. Furthermore, in low-flow accesses, the majority of the access flow is removed by the inflow needle, which results in a temporary (intradialytic) decrease in blood flow velocity in the access segment between the needles. Such a decrease in blood velocity could predispose to the hypercoagulable state and to a decrease in WSS with a possible impact on NH development (see above). The outflow needle jets the blood stream against the access wall.

In in vitro models, where the needle was oriented parallel to the long axis of the PTFE graft, the velocity at the orifice is 350 cm/s at the tip of the needle with a needle flow of 300 ml/min and reaches a velocity of 80 cm/s 6 cm downstream, which approaches the velocity of normal graft flow without the needle inserted [64]. However, the needle usually does not have a parallel orientation and is oriented towards one access wall [65]. The high-velocity flow jet ‘hurts’ the wall. This leads to endothelial denudation and, potentially, to decreased NO production [66].

It has been suggested that the flow jet is a related factor towards the development of NH [54, 64]. Downstream of the ‘outflow’ needle, where the flow jet entrains the particles of the ‘normal’ flow in the vascular access, it creates a region of flow instability and turbulence. At the jet boundary regions, high-shearing forces can be observed [64] and direct platelet activation occurs under high WSR [67]. The platelets produce PDGF and other cytokines that create a proinflammatory milieu downstream at the venous anastomosis [54]. Von Willebrand factor is also activated in high WSS and contributes to the development of fibrin-platelet thrombi on PTFE surfaces. Fibrin deposition increases with rising shear rate in the presence of von Willebrand factor [68]. Thus the needle jet creates conditions for the formation of thrombi and intimal hyperplasia. We should stress that there are still very little data on the real impact of the needles on vascular access complications.

Conclusions

Creation of a permanent vascular access and its maturation leads to a complex of physiological hemodynamic changes. Extreme flow acceleration could induce endothelial denudation, activation of thrombogenic factors and cytoadhesive molecules in some sites. These factors, together with the non-physiological milieu of ESRD, contribute to the development of access complications.

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