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Pathophysiology of Arteriovenous Fistula

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ABSTRACT

Literary data about the basic hemodynamic effects resulting from arteriovenous fistula construction in different times of functioning.

KEYWORDS: *arteriovenous fistula, vessels, blood flow, hemodynamic*

The first classical description of arteriovenous fistula (AVF) in 1757 was made by William Hunter, a Scottish physician and anatomist [1]. Much of what we understand today by the physiological effects of AVF was described in the works of Emile Frederic Holman [2]. Emile Holman (1890 – 1977) was associated with Stanford University (California, USA) for more than 70 years, from his student days to the chief surgeon, professor. Dr. Holman is best known as the first experimental researcher of the physiology of arteriovenous compounds. His first publication on this topic dates back to 1923 [3] and the last – to 1971, a total of more than 40 works. His main monograph is entitled "Arthriovenous aneurysm: Abnormal connections between arterial and venous circulation", published in 1937, was awarded the Samuel Gross Prize of the Philadelphia Academy of Surgery. Samuel David Gross (1805-1884) was a famous American surgeon, the "Nestor" of American surgery. A bronze statue of him is installed in Philadelphia. The study of AVF of various sizes and configurations on different limbs of animals allowed Emile Holman to draw conclusions about the variety of factors affecting blood flow after the formation of AVF. His conclusions were confirmed in studies of hemodynamic changes in the formation of AVF at the present stage. The effects of AVF, from the point of view of hemodynamics, can be divided into local and systemic. Since the diameter and other parameters of the vessels involved in the formation of AVF change within a few weeks and months after the creation of AVF, we can talk about immediate hemodynamic changes in the newly created AVF ("acute AVF") and distant hemodynamic effects in the already "mature" AVF ("chronic AVF"). The AVF with anastomosis between an artery and a vein "side to side" can be divided into four parts, through which blood flows. Local hemodynamic effects following the creation of AVF, hemodynamic changes in the proximal artery (PA) after the formation of AVF are similar to the effect of the formation of a "hole in the dam". Normally, there is a minimal pressure gradient between adjacent segments of the artery. After forming the AVF, the pressure gradient is significant. increases due to the large difference in pressure between the artery and vein. The blood flow in the PA increases sharply in response to a sudden decrease in the outflow pressure in the fistula [2]. The direction of blood flow in the PA remains antegrade, "from the heart". Thus, with AVF at the forearm, the blood flow in the brachial artery increases 5-10 times compared to the blood flow before the creation of the fistula. One of the factors affecting the amount of blood flow in the PA is the diameter of the anastomosis. As the size of the AVF increases, the blood flow in the PA also increases until the diameter of the anastomosis exceeds 75% of the diameter of the PA. When studying femoral AVF in dogs, it was found that an increase in the size of the diameter of the anastomosis from 1.5 to 3 times larger than the diameter of the PA leads to an increase in the total blood flow along the fistula from 5.6 to 8.4 times higher from the basal level, respectively. Thus, an increase in the diameter of the anastomosis above the level of 75% of the diameter of the PA already affects the PA and the general blood flow in the fistula to a lesser extent [2]. The situation with the distal artery (YES) is more complicated. If the diameter of the anastomosis is small, the blood flow through the DA remains antegrade, "from the heart". As the size of the fistula increases, the blood flow in the DA decreases until the diameter of the anastomosis becomes the same as the diameter of the PA. After the formation of AVF, the pressure of the antegrade blood flow approaches the pressure of the peripheral vascular bed during systole. This leads to the appearance of retrograde blood flow during diastole through the anastomosis into the venous segment. As the diameter of the anastomosis increases in comparison with the diameter of the PA, the reverse blood flow in the DA also increases until it exceeds the antegrade blood flow in the DA [4, 5-7]. Thus, in radiocephalic fistulas, retrograde blood flow in DA is determined in 75-80%. Normal reverse blood flow is 1/4–1/3 of antegrade blood flow in PA. The blood flow in the venous parts of the fistula depends on the presence or absence of valves in the veins. In the distal AVF (for example, on the forearm), immediately after its formation, almost all blood flow through the fistula goes directly to the heart through the proximal vein (PV) - retrograde in the distal vein (DV) is minimized due to the presence of venous valves. In proximal AVF involving central veins without valves. The difference between systolic and diastolic pressure (pulse pressure) in the PA increases closer to the fistula due to low resistance in it [8]. The pressure in the anastomosis center corresponds to the difference between arterial and venous pressure. Immediately after the formation of AVF, the pressure in the PV is highest directly near the anastomosis, but it decreases rapidly with the movement of blood to the heart. As the blood flow in the AVF increases, the pressure gradient forming the flow becomes sufficient to create a flow above the Reynolds number. The number, or more correctly, the Reynolds criterion, determines the laminar or turbulent fluid flow. For each type of flow there is a critical Reynolds number, which determines the transition from laminar to turbulent flow. If it is below the critical, then the flow is laminar, if higher – turbulent. Liquids are characterized by two main types of flow: laminar and turbulent. Laminar is the flow of a liquid in the form of parallel layers that do not mix with each other. An example of a laminar flowing fluid is a calm plain river. Turbulent flow is a turbulent flow accompanied by the formation of vortices, funnels and mutual mixing of liquid layers. Turbulence in the diverting vein or at the site of anastomosis is indicated by tremors and noises. The absence of turbulence may indicate a decrease in flow due to stenosis of the incoming artery or the diverting vein by the Venturi effect [9]. The Venturi effect consists in a pressure drop when the fluid flow passes through the narrowed part. This effect is named after the Italian physicist Giovanni Venturi (1746-1822). In the DV, valves usually protect against retrograde blood flow, so the pressure in the DV is increased near the anastomosis and approaches arterial. Several factors affect the amount of blood flow in the newly created AVF.

Firstly, the location of the vessels in relation to the distance from the heart. The blood flow in the fistula between the aorta and the vena cava or other major vessels is significantly larger compared to the blood flow in more peripheral vessels with comparable anastomosis sizes. Secondly, as mentioned earlier, the diameter of the anastomosis affects the blood flow non-linearly. As long as the diameter of the anastomosis does not exceed 20% of the diameter of the PA, the blood flow in the AVF will be relatively small. With an increase in the anastomosis to 75% of the diameter of the PA, the blood flow in the AVF increases significantly. With the size of the anastomosis above 75% of the PA diameter, a further but moderate increase in the total flow in the fistula occurs, including due to an increase in retrograde blood flow along the DA[10]. Due to the fact that small AVFs have an increased risk of thrombosis or insufficient blood flow rate, the diameter of the anastomosis is usually formed equal to the diameter of the bearing artery. An exception may be large arteries used to create a fistula, such as, for example, the axillary. In this case, the size of the anastomosis is deliberately reduced due to the danger of causing excessively large blood flow through the fistula, which will lead to the development of heart failure. The blood flow rate in the AVF obeys Poiseuille's law. Poiseuille's law determines the flow rate of a liquid with a steady flow of a viscous incompressible liquid in a thin cylindrical tube of circular cross-section. According to the law, the second volume flow rate of the liquid is directly proportional to the pressure gradient in the tube and the fourth degree of the tube radius and inversely proportional to the length of the tube and the viscosity of the liquid. Thus, due to the fact that the flow velocity is directly proportional to the fourth power of the vessel radius, this factor is of paramount importance. The blood pressure factor should not be underestimated. It has been shown that the blood flow rate increases linearly in hemodialysis patients with an increase in blood pressure [6, 11]. Of course, a clinically significant factor is the diameter of the artery and vein involved in the formation of AVF. Clinical data show that with small veins up to 3 mm in diameter, low blood flow is noted immediately after the formation of radiocephalic fistulas. The same is observed when the diameter of the artery is less than 1.6 mm, which increases the risk of early dysfunction of vascular access [12]. Another factor affecting blood flow is blood viscosity, primarily dependent on hematocrit [6]. Normally, the blood flow in the brachial artery in humans is 85 ml/min. After the formation of AVF, the blood flow rate in the artery increases 5-10 times [13, 14]. The measurement of blood flow velocity immediately after surgery does not always accurately reflect the actual blood flow velocity in the fistula due to vascular spasm. Intraoperative measurement of blood flow velocity, performed immediately after the formation of radio cephalic AVF, is more often about 300 ml/min [12, 15, 16]. In the brachial or femoral AVF, blood flow may be higher and reach 700-1000 ml/min. Normally, blood flow to the AVF increases by 50-100% a few weeks after its formation as the vessels dilate [17, 18]. The desired blood flow rate for HD should be 350 ml/min or higher, otherwise the effectiveness of dialysis is reduced due to the circulation in access [19]. It should be taken into account that the resistance of both the peripheral vascular bed and the arterial collateral circulation affects the hemodynamics immediately after the formation of the fistula. The pressure in the DA decreases to a minimum near the anastomosis and increases with increasing distance from the fistula due to the bringing blood flow from the arterial collaterals. Low resistance in the peripheral vascular bed supports antegrade blood flow in DA. High resistance in the peripheral vascular bed contributes to retrograde blood flow in the DA towards the fistula. If the resistance of the arterial collaterals is low, then more blood will flow into the YES, which contributes to the reverse flow. On the contrary, if arterial collaterals are poorly developed or there is high resistance in them, this contributes to antegrade blood flow in DA [2]. Reverse blood flow to the DA leads to a change in the direction of blood flow in the distal vascular bed, for example, the brush in the radiocephalic fistula. Such a phenomenon underlies the justification of the ligation of DA or the construction of a radiocephalic fistula end of the artery-to-side vein to prevent retrograde blood flow to DA in the syndrome of stealing. This syndrome develops more often in all constructions of AVF side-to-side artery-to-side vein with a large diameter of anastomosis [2]. In a fistula using brachial artery, reverse blood flow can be created in both the radial and ulnar arteries, which leads to a high risk of severe robbing syndrome. In the case of AVF formation using the radial artery with dominant blood flow through the ulnar artery, retrograde radial blood flow will be carried out through the palmar arch [20, 21]. Hemodynamic properties of vascular branches of AVF are easier to assess when studying the effects of their temporary occlusion. In the newly created peripheral AVF, PV occlusion has essentially the same effect as a non-functioning fistula. This is due to a sharp restriction of the outgoing blood flow through the DV with good functioning of the venous valves. For the same reason, DV occlusion has minimal effect in acute AVF. With occlusion, the blood flow in the fresh fistula decreases moderately (by 20-30%), because the main blood flow to the AVF goes through the PA. At the same time, there is an increase in blood flow in the peripheral vascular bed, thus, the "stealing" of the peripheral area (brush) decreases. This mechanism is used in one of the surgical methods of treating the syndrome of theft. On the contrary, occlusion of PA with open DA leads to a decrease in blood flow both in the AVF and in the peripheral vascular bed. The blood flow in the fistula with PA occlusion decreases to a lesser extent than with PV occlusion, since the open DA supports blood flow to the fistula. The same mechanism is accompanied by the fact that isolated occlusion of PA causes a greater decrease in peripheral blood flow than a combination of occlusion of PA and DA [2]. Interesting conclusions were made by the Italian authors in computer modeling using a non-Newtonian fluid. Liquids are divided into Newtonian and non-Newtonian, i.e. into those systems that obey and do not obey Newton's law. Newton's law describes the dependence of the gradient of the flow velocity on the magnitude of the shear stress. If in a moving fluid its viscosity depends only on its nature and temperature and does not depend on the velocity gradient, then such liquids are called Newtonian. Plasma, water are practically Newtonian liquids. If the liquid is inhomogeneous, then when it moves, the viscosity depends on the velocity gradient, i.e. the viscosity increases with a decrease in the velocity of the liquid. Such liquids are called non-Newtonian. It has been established that the most frequent places of stenosis formation in AVF are places that have undergone hemodynamic wall shear stress. This is exactly what is the starting mechanism for remodeling the vascular wall with intimal hyperplasia and atherosclerotic changes [22] (Fig. 2). In conditions of physiological rest, laminar, i.e. layered blood flow is observed in almost all parts of the circulatory system, without vortices and mixing of layers. A plasma layer is located near the vessel wall, the speed of movement of which is limited by the fixed surface of the vessel wall, along the axis a layer of red blood cells moves at high speed. The layers slide relative to each other. A shear stress occurs between the layers, inhibiting the movement of the faster layer. Shear stress means the force acting on the unit surface of the vessel in the direction tangential to the surface and is measured in din/ cm2. The shear stress is defined as 4ήQ/πr3, where ή is the viscosity of the blood, Q is the blood flow in ml/min, r is the radius of the vessel. Shear stress causes deformation of endothelial cells, which leads to the release of nitric oxide, which dilates blood vessels. This is an expedient reaction, due to which the diameter of the upstream vessels increases every time the blood flow in the downstream vessels increases. It has been shown that the asymmetric pattern of blood flow in the anastomosis area leads to the appearance of zones with high and low wall shear stress [23]. In the classical AVF Cimino, the magnitude of the parietal shear stress ranges from 20 to 36 din/cm2 in the direct section of the bearing radial artery. Whereas on the inner surface in the bending zone it increases to 350 din/ cm2 . Systemic hemodynamic effects caused by the formation of AVF The immediate effect after the formation of a fistula is a change in the direction of blood flow from the peripheral circulation to the area of the lowest resistance, from the left circle of circulation to the right, i.e. there is a non-physiological redirection of blood flow [25]. In this case, the compensatory response is an increase in cardiac output due to an increase in heart rate and an increase in stroke volume. An increase in cardiac output is associated with a decrease in peripheral resistance and increased activity of the sympathetic nervous system (increased myocardial contractility, increased shock volume and increased heart rate) [26, 27]. This mechanism is aimed at maintaining blood pressure. These changes are minimal in AVF with low blood flow and increase as the blood flow in the fistula increases. In addition to an increase in the blood flow rate in the fistular radial artery with ECHO-KG during the first 14 days after surgery, an increase in the final diastolic volume of the left ventricle, an increase in cardiac output is noted [28]. The mass of the left ventricle also increases with time [29]. Studies on experimental animals have shown that in fistulas with a blood flow of 20% or lower from the initial cardiac output index, the magnitude of the increase in cardiac output immediately after the formation of the fistula is equal to the blood flow according to AVF. When the blood flow in the fistula is more than 20% of the initial value of cardiac output, the increasing peripheral resistance directs the blood flow in the opposite direction, from the peripheral circulation to the fistula circuit.

Such a reaction is an acute effect, leading to acute theft of peripheral circulation. Subsequently, as the chronic adaptation to the existing fistula progresses, peripheral resistance returns to its basic level [30]. The central venous pressure and pulmonary pressure in normal animals increases slightly due to the large capacity of the venous part of the circulation. Pulmonary hypertension may develop or worsen in dialysis patients. Pulmonary hypertension is defined as a steady increase in pressure in the pulmonary artery greater than 25 mmHg at rest and more than 30 mmHg under load. Recently, 40-50% of patients starting dialysis through AVF have pulmonary hypertension. This is due to inadequate pulmonary vasodilation in response to increased blood flow associated with AVF, possibly due to non-optimal NO production [31].

Currently, there is no clear definition of AVF with high blood flow. The ratio of blood flow velocity in access to cardiac output is used, which is called cardiopulmonary recirculation (CPR). S. Pandeya, R.M. Lindsay in their study in stable hemodialysis patients showed that the average blood flow velocity in the AVF was 1.6 l/min and the average cardiac output was 7.2 l/min, thus, the average The CPR was 22% [33]. The recommendations of the Vascular Access Society define AVF with high blood flow at a blood flow rate of more than 1-1.5 l/min and a CPR of more than 20% [34]. An increase in cardiac output does not occur in parallel with an increase in the blood flow rate in the AVF. In the work of C. Basile et al. [25] it has been shown that cardiac output changes slightly at a blood flow rate ranging from 0.95 to 2.2 l/min. The reason for this phenomenon is not entirely clear, presumably, it is connected with the possibilities of adaptation and myocardial reserve. In addition to the diameter of the fistula, the proximity of its location to the heart also has a great importance on hemodynamics. A relatively small fistula (1 cm) between the aorta and the vena cava (i.e. located close to the heart) can cause shock and death in dogs [35]. AVF of the same diameter on the vessels of the limb leads to a significantly smaller change in cardiac output and small or transient changes in blood pressure and pulse rate. Temporary compression of the AVF or prosthesis can cause a decrease in heart rate and an increase in blood pressure (Nicoladoni-Branham symptom) [2]. However, this symptom is uninformative in fistulas with a low blood flow rate. The formation of experimental AVF in animals leads to salt and water retention as compensation for hypovolemia. In addition, after the formation of vascular access, the level of atrial and cerebral natriuretic peptide increases in patients with a peak level on the 10th day after surgery [28]. The increase in circulating blood volume is due to an increase in plasma volume, not erythrocytes. In patients with renal insufficiency, such compensatory mechanisms may be insufficient, therefore, as a preoperative preparation, it is necessary to replenish intravascular volume, especially in patients with brachial or femoral AVF with a high volume of blood flow. Large fistulas, such as aortocaval due to syphilitic aortitis, atherosclerotic abdominal aneurysm or trauma, lead to very serious changes in the cardiovascular system. The first symptom may be angina pectoris due to an increase in the work of the myocardium and a decrease in coronary perfusion associated with a drop in diastolic pressure [2]. Thus, acute large central AVF is similar to shock for both peripheral blood flow and intravascular volume due to switching to fistular blood flow. On the contrary, a large chronic fistula is more often associated with heart failure with high cardiac output.

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