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Feeding artery of vascular accesses for hemodialysis: model of arterial adaptation to high blood flow

PhD thesis

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Contents

Summary

Background: Arteries adapt their diameter to changing haemodynamic conditions to maintain constant wall shear stress, the force generated by flowing blood on endothelial cells. The feeding artery of haemodialysis vascular accesses is a human model of arterial adaptation to chronically high blood flow and thus to high wall shear stress. The process of arterial adaptation is endothelium dependent. Endothelial dysfunction related to End-Stage Renal Failure, diabetes mellitus, dyslipidemia may impair also the dilatation of the feeding artery of vascular accesses.

First the review of the literature presents in three parts different aspects of arterial adaptation: 1) arterial adaptation with focusing on the role of haemodynamic factors, 2) the influence of end-stage renal disease on arterial adaptation, 3) feeding artery of vascular accesses as a model of arterial response to chronic increase in blood flow.

Methods: We examined the feeding artery of radial and brachial polytetrafluoroethylene grafts shortly after and one and two years after access creation. We used duplex ultrasonography to obtain internal diameter and blood velocity in the feeding arteries. We calculated wall shear rate as 4 x blood velocity / internal diameter and used it as approximation of wall shear stress.

Results: In the first study we included 106 patients (58 non-diabetics and 48 diabetic). WSR was significantly higher in radial compared to brachial arteries independently of diabetes status. Diabetic subjects had significantly higher WSR in both radial and brachial arteries compared to non-diabetics.

In the second study we examined 75 patients. Internal diameter raise from 3.9 ± 0.1 mm after access creation to 4.4 ± 0.2 mm in the first year and to 4.6 ± 0.2 mm at the second year. Mean WSR decreased from 1806 ± 113 s-1 after access creation to 1589 ± 118 s-1 in the first year and to 1148 ± 107 s-1 at the second year. Internal diameter was negatively correlated to diabetes, cholesterol and WSR.

Conclusions:

1) The feeding arteries of vascular accesses are exposed to unusually high WSR shortly after access creation.
2) WSR is even higher in arteries of distal accesses and in diabetic subjects.
3) The dilatation of the feeding artery of vascular accesses continues at least 2 years after access creation with a continuous decrease in WSR, which however, remains highly supra-physiological.

4) Patients with diabetes have lower internal diameter and the vasodilatation of the feeding artery is delayed compared to non-diabetics.

5) Higher levels of cholesterol are probably associated with thinner arterial lumen.

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Abbreviations

AVF – arteriovenous fistula
AVG – arteriovenous graft
BA – brachial artery
CWS – circumferential wall stress
ESRD – end-stage renal disease
ID – internal diameter
pO_2 – partial tension of oxygen
pCO_2 – partial tension of carbon dioxide
PTFE – polytetrafluoroethylene
RA – radial artery
V – velocity
VSMC – vascular smooth muscle cell
vWf – von Willebrand factor
WBV – whole blood viscosity
WSR – wall shear rate
WSS – wall shear stress

1 Introduction

Arteries play an eminent role in the transportation of gases, nutrition, hormones and other signal molecules, and waste products (Ganong 1993; London et al. 2000). To assure adequate perfusion, they respond constantly to changing haemodynamic conditions. These reactions could be divided into 2 groups: acute and chronic. Acute dilatation occurs, for example, in peripheral arteries as a consequence of increased blood flow to working muscles (Miyachi et al. 1998). Examples of chronic arterial adaptation include maturation of arteriovenous malformations and natural or artificial creation of arteriovenous fistula (Girerd et al. 1996; Dammers et al. 2002; Ene-Iordache et al. 2003; Dammers et al. 2005). Acute adaptation is limited to changes of vascular smooth muscle cell (VSMC) tone. Chronic changes induce structural arterial wall remodeling (Gibbons et al. 1994; Langille 1996; Schwartz 1998; Ward et al. 2000). Both processes, acute and chronic, consist in adaptation of the arteries to different signals and thus could be named together arterial adaptation (Zakrzewicz et al. 2002).

Arterial adaptation plays a role in physiology (normal arterial growth (Prior et al. 2004), dilatation of arteries supplying working muscles (Miyachi et al. 1998)), pathology (atherosclerosis (Malek et al. 1999), aneurysm formation (Eugster et al. 2003), arteries supplying tumors (Zakrzewicz et al. 2002)) and in therapeutic interventions (by-pass grafts (Haruguchi et al. 2003), arteriovenous fistulas for haemodialysis (Girerd et al. 1996; Dammers et al. 2002; Ene-Iordache et al. 2003; Dammers et al. 2005), restenosis after angioplasty (Pasterkamp et al. 2000)).

A good model of chronic arterial adaptation to high blood flow is the feeding artery of haemodialysis vascular accesses (Girerd et al. 1996; Dammers et al. 2002; Ene-Iordache et al. 2003; Dammers et al. 2005). These accesses are used for repeated entries into the blood stream during haemodialysis procedure. After vascular access creation, i.e. creation of a shunt between feeding artery and outflow vein, sudden decrease in peripheral vascular resistance results in an increase in blood flow and vasodilatation. Chronically increased blood flow and wall shear stress in the feeding artery leads to long-term arterial adaptation (Girerd et al. 1996; Dammers et al. 2002; Ene-Iordache et al. 2003; Dammers et al. 2005).

The review of the literature consists of three parts: 1) arterial adaptation with focusing on the role of haemodynamic factors, 2) the influence of end-stage renal disease on arterial adaptation, 3) feeding artery of vascular accesses as a model of arterial response to chronic increase in blood flow.

The presentation of own results follows. It begins with hypothesis statement, through the methods and result sections. The thesis ends with the discussion of the results.

2 Review of the Literature

2.1 Arterial adaptation – general remarks

2.1.1 Arteries – structure and function

2.1.1.1 Arterial structure

Arterial wall is an active, integrated organ organized in a three-layer structure: a) external layer composed of connective tissue (adventitia), b) medial layer composed of VSMC (media) and c) inner layer composed of endothelial cells and connective tissue (intima) (Ganong 1993). Endothelial, smooth muscle, and fibroblast cells lie in a scaffold formed by the extracellular matrix and are interrelated in a complex of set of interactions, both autocrine and paracrine. The extracellular matrix is composed of collagen and elastin embedded in a mixture of glycoproteins and proteoglycans (Gibbons et al. 1994; London et al. 2000).

2.1.1.2 Vascular function

The function of each arterial segment depends on its position in the vascular system. Large elastic arteries (aorta) serve as a high pressure reservoir: they receive the pulsatile output of blood during systole and dissipate it during diastole – the dampening function. Muscular arteries, such as brachial and radial arteries, have a conduit function. These arteries serve in most cases as the feeding artery of vascular accesses. The vascular resistance is generated by arterioles. Capillaries form the milieu of oxygen, nutrients, carbon dioxide and waste product exchange between tissues and blood. Venules and veins serve as blood reservoir (Ganong 1993). To fulfill its function the vessels respond to different signals:

1) Biochemical stimuli, such as oxygen and carbon dioxide partial tensions, pH (Ganong 1993; Pries et al. 2005), hormonal signals (Ganong 1993);

2) Biomechanical (haemodynamic) stimuli:

a) Wall shear stress, created by the blood flow over the endothelial cell surface and

b) Circumferential wall stress, as a result of cyclic increase of arterial diameter with cardiac cycle (Malek et al. 1999; Paszkowiak et al. 2003; Pries et al. 2005).

2.1.2 Stimuli to arterial adaptation

2.1.2.1 Biochemical stimuli

Besides haemodynamic stimuli mature arteries respond to metabolite levels, especially partial tension of oxygen (pO_2) and carbon dioxide (pCO_2) (Pries et al. 1995; Zakrzewicz et al. 2002; Eichmann et al. 2005; Pries et al. 2005). In peripheral circulation the rise in pO_2 leads to vasoconstriction and an increase in pCO_2 and waste products to vasodilatation. This is especially the case of microvasculature, arterioles, capillaries and venules (Zakrzewicz et al. 2002). Conduit and elastic arteries respond to hormonal signals as well. Acutely, the changes in vascular tone are mediated by the action of catecholamines and natriuretic peptides (Ganong 1993). Chronically the activation of the rennin-angiotensin-aldosteron system plays an important role in vascular remodeling (Soylu et al. 2004; Yoshimoto et al. 2007). Vascular architecture in macrocirculation is controlled by haemodynamic changes, WSS and CWS (Langille 1996).

2.1.2.2 Wall shear stress

Haemodynamic changes play a pivotal role in arterial adaptation in large arteries. Arteries are subjected to blood flow and pressure. The first generates wall shear stress (WSS), the second circumferential wall stress (CWS).

Blood flow acts only on the inner surface of arterial wall and thus affects directly only endothelial cells and not media and adventitia. WSS is the mathematical description of this effect (Paszkowiak et al. 2003; Rotreklova et al. 2004; Nichols et al. 2005). It is a force that is mathematically expressed as a vector, with a direction and magnitude. The direction corresponds to the blood flow direction and the magnitude of shear stress vector is directly proportional to wall shear rate (WSR) and blood viscosity (Kamiya et al. 1980; Malek et al. 1999; Paszkowiak et al. 2003):

$$WSS = WSR \cdot WBV, \qquad (Pa)$$

where WSR is wall shear rate, WBV whole blood viscosity. WSR is defined as the difference between adjacent velocities in the vascular lumen (*Figure 1*). The ratio between the maximum velocity at the centre of the artery and the arterial radius is a common approximation of WSR (Hoeks et al. 1995; Setty et al. 2001; Setty et al. 2002). WSR is directly proportional to blood flow and indirectly proportional to arterial radius (Kamiya et al. 1980; Reneman et al. 2006):

$$WSR = \frac{(m+2) \cdot Q}{\pi \times r^3}, \qquad (s^{-1})$$

where Q is blood flow, r internal arterial radius, m = 2 for laminar flow. For ideal Newtonian fluid (non-compressible, frictionless and in rigid tube) and steady laminar pattern of flow with fully developed parabolic velocity profile this corresponds to the Poiseuille's formula (Paszkowiak et al. 2003; Reneman et al. 2006):

$$WSS = \frac{4 \cdot WBV\, Q}{\pi \cdot r^3}, \qquad \text{(Pa)}$$

where WBV is whole blood viscosity, Q blood flow, r internal arterial radius.

The SI unit for WSS is Pascal (Pa), but WSS is often expressed in dynes·cm^{-2}. The conversion between dynes·cm^{-2} and Pascal is easy: 1 Pa equals 10 dynes·cm^{-2}. Normal values of WSS are in order of 1.0 to 4.0 Pa in arteries and 0.1 to 0.6 Pa in veins (Malek et al. 1999; Reneman et al. 2006). In large and medium size arteries, WSS changes markedly during the cardiac cycle, from peak values higher than 3.0 Pa to null during diastole. Time averaged WSS is almost constant throughout all arteries, between 0.5 and 0.4 Pa (Reneman et al. 2006).

In some studies (Hoeks et al. 1995; Setty et al. 2002) WSR is used as WSS approximation. The SI unit for WSR is second^{-1}. Normal values of WSR in large arteries are in the order of 260 to 1338 s^{-1} (Reneman et al. 2006).

2.1.2.3 Circumferential wall stress

Circumferential wall stress (CWS) is generated by blood pressure with a vector perpendicular to arterial wall (*Figure 1*). Therefore, in contrast to WSS, CWS affects all the layers of arterial wall. CWS is according to the Laplace-Lamé's equation directly proportional to transmural pressure and arterial radius and indirectly proportional to arterial wall thickness (Nichols et al. 2005; Pries et al. 2005):

$$CWS = \frac{P \cdot r}{h}, \qquad \text{(Pa)}$$

where P is transmural pressure difference, r arterial radius and h arterial wall thickness.

2.1.3 Adaptation and remodeling

In large arteries arterial adaptation occurs mainly in response to changes in haemodynamic conditions (Ward et al. 2000; Reneman et al. 2006). It includes changes in arterial diameter and/or arterial wall architecture (vascular remodelling) (Gibbons et al. 1994; Schwartz 1998; Ward et al. 2000), addition of new vascular segments (angiogenesis) or elimination of redundant segments (pruning) (Zakrzewicz et al. 2002). Reviews on angiogenesis and pruning are available elsewhere (Eichmann et al. 2005). The nature of

remodeling depends on the characteristics of the haemodynamic stimuli, the duration of their action and the status of endothelium (London et al. 2000). Acute changes in haemodynamic and metabolic environment lead to transient adjustment of arterial diameter; enabled by vasomotor tone modification. Long-lasting stimuli (such as arteriovenous fistula) induce changes in arterial wall shape and composition (Girerd et al. 1996; Tedgui et al. 1999; London et al. 2002). For the description of these changes several synonyms are used: inward, negative, constrictive remodeling denotes a reduction whereas outward, positive, expansive remodeling denotes an increase in arterial size (Ward et al. 2000).

In general, arterial adaptation is directed towards restoration of haemodynamic parameters to baseline physiological values (Kamiya et al. 1984; Kassab et al. 1995; Samijo et al. 1998; Zakrzewicz et al. 2002; Wu et al. 2004). Chronic alterations in CWS (increased blood pressure) and WSS (increased blood flow) lead to modification of the arterial wall (medial hypertrophy, increased vascular lumen) that will ultimately restore basal levels of CWS and WSS – negative feed back loop (Tedgui et al. 1999).

Wall shear stress mediates acute and chronic changes of the arterial diameter by the following feedback mechanism. An example of acute adaptation to changes in WSS is one of the surrogates of endothelial function: flow-mediated dilation. After a short period of hypoxia induced by temporary artery occlusion, arterioles' smooth muscle tone decreases in order to bring more blood by the fall of peripheral arterial resistance. Once the artery is open the high flow induces an increase in WSS in the proximal arteries. Increased WSS leads to vasodilatation allowing adequate flow (Zakrzewicz et al. 2002). Similarly the feeding artery of working muscle dilates after beginning of exercise (Miyachi et al. 1998). Flow-mediated dilatation in vivo is largely mediated by shear-stress-induced generation of the vasodilators prostacyclin and nitric oxide and decreased production of the vasoconstrictor endothelin-1 by the endothelium (Raitakari et al. 2000).

Chronically increased blood flow and thus WSS leads to structural changes of the arterial wall. Thus regular aerobic leg exercise induces expansive arterial remodeling in the femoral artery of healthy men (Dinenno et al. 2001). On the contrary, in paraplegic athletes, where the blood flow to the legs is chronically decreased, the diameter of the femoral artery, is significantly lower (Schmidt-Trucksass et al. 2000). Kamiya and Togawa reported a restoration of WSR in a long time period after arteriovenous shunt creation between canine carotid artery and external jugular vein.

In contrary to WSS, according to Laplace's law, changes in arterial pressure, and thus CWS, lead to vessel wall hypertrophy therefore to normalization of CWS. The internal

diameter is not primarily affected (London 1998). Thickened arterial walls were observed in large and medium-sized arteries in hypertensive subjects (Laurent 1995).

As blood flow and blood pressure act on the arteries simultaneously, changes due to shear and circumferential stress are also interrelated. Vasodilatation in response to increased WSS leads to increased internal diameter. According to Laplace's law this is accompanied by a rise in CWS (Schwartz 1998). Increased CWS leads to hypertrophy and thus an increase in h in the Laplace's equation (London 1998; London et al. 2000). At the end, both WSS and CWS are restored to their baseline values.

2.2 Arterial adaptation in End-Stage Renal Disease

Renal failure represents a burden to the cardiovascular system (Foley et al. 2000; Parfrey 2003). All stages of renal failure and especially the end-stage (ESRD) are recognized as risk factors for the development of coronary artery disease, cardiomyopathy, and heart failure (Foley 2003). The increased cardiovascular morbidity and mortality among ESRD patients is associated with chronic pressure and volume overload as well as with several metabolic and endocrine abnormalities leading to left ventricular hypertrophy, atherosclerosis and arteriosclerosis (London et al. 2000; London et al. 2002; London 2003).

The arterial system of ESRD patients undergoes remodeling principally of central, elastic-type, capacitance arteries such as aorta or the common carotid artery, it is less pronounced in peripheral, muscular type, conduit arteries, such as the radial artery (Joannides et al. 1997; Mourad et al. 1997; London et al. 2000), where the remodeling is associated with arterial stiffening due to alterations of intrinsic properties of arterial wall material (Mourad et al. 1997; London et al. 2000).

Atherosclerosis develops rapidly in ESRD patients. Uremia produces atherogenic factors specific to uremia, as secondary form of complex dyslipidaemia (Wheeler et al. 2000; Madore 2003), calcium-phosphate alterations (London 2003; Floege et al. 2004), malnutrition, and activation of inflammation (Madore 2003). These factors are additive to the risk factors present in patients with normal renal function, such as age, hypertension, smoking, diabetes, male gender, insulin resistance (London et al. 2000; Brunner et al. 2005). Although atherosclerosis was considered the only cause of macrovascular disease (Foley et al. 2000), many vascular complications arise in ESRD patients in the absence of clinically significant atherosclerotic disease. The spectrum of arterial alterations is broader, including large artery remodeling characterized by diffuse dilatation (London et al. 2005), intima-media hypertrophy(London et al. 2003), stiffening of large elastic arteries (London et al. 2000) and diffuse calcifications of arterial wall (London 2003; London et al. 2003).

Arterial hypertrophic process and accelerated atherosclerosis in ESRD patients can be explained also by alterations in endothelial function (Glassberg et al. 2000). Flow mediated vasodilatation of the radial artery, a surrogate of endothelial function, is almost abolished in ESRD (Joannides et al. 1997). Impaired NO bioactivity was reported in ESRD patients, which include a reduction in production/release of NO, enhanced degradation of NO, overproduction of vasoconstrictors, and altered end organ sensitivity (Glassberg et al. 2000).

2.3 Arterial adaptation: the feeding artery of vascular access for haemodialysis

Vascular access for haemodialysis is created in the milieu of ESRD. When the renal failure gets to the final stage, an elimination method is needed, either peritoneal dialysis or haemodialysis. Chronic haemodialysis treatment requires repeated entries into the blood stream. Permanent vascular access is used for this purpose. On the other hand despite called “permanent”, the lifespan of the accesses is very limited (Malik et al. 2005). Regular screening duplex Doppler ultrasonography results in significantly longer PTFE graft patency due to early detection of access stenosis and, thus, more frequent elective interventions of access stenoses (Malik et al. 2005).

Native arteriovenous fistula (AVF), i.e. direct connection of superficial vein to the artery *(Figure 2)*, is usually the access of first choice because of longer patency (2001). When superficial veins are depleted, a polytetrafluoroethylene (PTFE) graft (AVG) is used *(Figure 2)*. After vascular access creation a sudden decrease in peripheral vascular resistance and consequent blood flow increase leads to WSS increase in the feeding artery. Endothelial cells sense high WSS, resulting in nitric oxide secretion. The consequent arteriodilatation lowers WSS (Girerd et al. 1996; Dammers et al. 2002; Ene-Iordache et al. 2003; Dammers et al. 2005), nevertheless WSS does not reach the baseline values and high levels persist at least to the second year after access creation. Thus the feeding artery of vascular accesses provides a good in vivo model of long-term adaptation of arteries to chronically increased blood flow and WSS.

It is known that endothelial cells sense steady and pulsatile shear stress differently (Malek et al. 1999). The increase in mean and peak WSS after vascular access creation is not proportional, whereas mean WSS increases 4-6 fold, peak WSS increases only little (Dammers et al. 2002; Ene-Iordache et al. 2003; Dammers et al. 2005). After one year the vasodilatation continues with persistently increased both mean and peak WSS (Dammers et al. 2002; Dammers et al. 2005). It seems that arteries dilate in such a way as to maintain peak WSS constant, suggesting that endothelial cells sense the maximum rather than the time-averaged wall shear stress (Ene-Iordache et al. 2003).

Conduit arteries, such as the brachial, radial and femoral arteries, maintain a low baseline WSS, allowing a large acute WSS raise, with only a minor flow-dependent diameter increase (Dammers et al. 2002).

The challenge imposed to the arterial system greatly exceeds its adaptation capacity (Dammers et al. 2005). One year is not sufficient to normalize mean WSS in the feeding artery (Dammers et al. 2005). The sustained increase in blood flow exceeds the adaptation capacity of the investigated conduit arteries.

3 Hypothesis

The adaptation to WSS is endothelium dependent. ESRD is associated with many co-morbidities representing risk factors for endothelial dysfunction: hypertension (Klahr 2001), hypercholesterolemia (Egashira et al. 1994), diabetes (Endemann et al. 2004). We conducted two studies with the aim to:

1) Describe the haemodynamic profile in the feeding arteries of various access types shortly after access creation

2) Describe the haemodynamic profile in the feeding arteries in a 2 year course.

3.1 The hypothesis we tested are as follows:

A) Feeding artery shortly after access creation:

1) WSR values in radial and brachial arteries are comparable as WSS is the leading value

2) Diabetic patients have higher WSR than non-diabetics.

B) Long-term adaptation of the feeding artery

3) The internal diameter of the feeding artery after 1 and 2 years is higher that at baseline, with a decrease in WSR

4) The internal diameter of the feeding artery is lower in patients with risk factors of endothelial dysfunction, i.e. diabetes mellitus and hypercholesterolemia.

4 Feeding artery shortly after access creation

4.1 Population and Methods

4.1.1 Population

During a four-year period (2001 - 2005) we consecutively included patients with a newly created, well functioning upper extremity PTFE-graft in General University Hospital, Prague. Basic demographic data and diabetic status were recorded (*Table 1*).

4.1.2 Ultrasonography

It is known that AVG maturates approximately within 14 days (2001), so we examined vascular accesses 14-180 days after their creation. Linear-array 3-11 MHz probe of SONOS 5500 device (Phillips, USA) was used. After careful examination of the whole access by duplex Doppler ultrasonography, as described earlier (Malik et al. 2005) the attention turned to recording the artery. Ultrasound measurements were performed at the feeding artery 1-2 cm proximal to arterial anastomosis (*Figure 3*). Centerline peak, mean and minimal velocities, and internal artery diameter (ID) were measured.

Patients with huge arterial wall calcifications making the exact assessment impossible were excluded from the study. Similarly, subjects with access complications (stenosis, thrombosis, inflammation, clinically apparent peripheral ischemia) were also excluded.

WSR was calculated using Poiseuillian parabolic model of velocity distribution across the arterial lumen based on the assumption of laminar blood flow, according to the following formula (Gnasso et al. 1996; Irace et al. 1999; Jiang et al. 2000):

$$WSR = 4*V / ID$$

where WSR is the wall shear rate (s-1), V is the blood velocity (m·s-1), and ID is the artery diameter (m). WSR was calculated separately for peak (systolic), mean and minimal (end-diastolic) blood velocity.

4.1.3 Statistical analysis

Recorded values were compared according to access types (radial vs. brachial artery) and according to diabetic status using unpaired t-test. Data are expressed as mean ± standard deviation. All calculations were performed using statistical software (STATISTICA Cz 6, StatSoft, Inc. 2003).

4.2 Results

A total of 106 patients was included into this study, 58 of them were non-diabetics and 48 diabetics. Basic demographic characteristics are listed in *Table 1*.

4.2.1 Brachial vs. radial AVG

Mean and minimal velocities were higher in radial artery, but this difference was significant only in diabetic patients. Distal (radial) accesses were characterized by significantly lower feeding artery diameter in both diabetic and non-diabetic patients. Peak, mean and minimal WSR were significantly higher in distal accesses arteries.

4.2.2 Diabetics vs. non-diabetics

Diabetic subjects had significantly higher peak and mean arterial blood velocities in radial, but not brachial AVGs. Arterial diameter was significantly lower in diabetic patients in both access types. Arterial WSR was significantly higher in diabetic patients in both radial and brachial AVGs *(Figure 4)*.

These results are summarized in *Table 2.*

5 Long term adaptation of the feeding artery

5.1 Population and Methods

5.1.1 Population

During a 5-year period (2001 – 2006) we consecutively selected patients with a newly created, well-functioning upper extremity PTFE graft in the General University Hospital, Prague. Informed consent was obtained from each patient before examination. The study was held in accordance with the Declaration of Helsinki. Together with the ultrasonography (see below), we recorded feeding artery type (brachial vs. radial), diabetic status, basic demographic and laboratory data.

5.1.2 Ultrasonography

The patients were examined within 3 months after access creation (baseline), then after 1 and 2 years. Linear-array 3-11 MHz probe of SONOS 5500 device (Phillips, USA) was used. After careful examination of the whole access by duplex Doppler ultrasonography, the attention turned to recording the artery. Ultrasound measurements were performed at the feeding artery 1-2 cm proximal to arterial anastomosis (*Figure 3*). We measured centerline peak and mean velocities, and internal arterial diameter (ID).

Patients with huge arterial wall calcifications making the exact ultrasound assessment impossible were excluded from the study. Similarly, subjects with access complications (stenosis, thrombosis, inflammation, clinically apparent peripheral ischemia, blood flow decrease) were also excluded.

We used wall shear rate (WSR) as a measure of WSS: WSS is directly proportional to the whole blood viscosity and to WSR (Malek et al. 1999). Shear rate is defined as the difference between adjacent velocities in the vascular lumen. The ratio between the maximum velocity in the centre of the artery and the vessel radius is a common approximation of WSR (Brands et al. 1995), and WSR is used as an approximation of WSS (Setty et al. 2002). WSR was calculated using Poiseuillian parabolic model of velocity distribution across the arterial lumen based on the assumption of laminar blood flow, according to the following formula (Reneman et al. 2006):

$$WSR = 4*V / ID$$

where WSR is the wall shear rate (s^{-1}), V is the blood velocity ($m \cdot s^{-1}$), and ID is the artery diameter (m). WSR was calculated separately for peak systolic (pWSR) and mean (mWSR) blood velocity.

We report the values of ID, pWSR, and mWSR for baseline, first year and second year with appendices 0, 1, 2, respectively. The difference in ID between baseline and second year ΔID_{2-0}; between baseline and first year is reported as ΔID_{1-0}, and between first and second year as ΔID_{2-1}. We use in the same manner ΔWSR_{2-0}; ΔWSR_{1-0} and ΔWSR_{2-1}, separately for pWSR and mWSR.

5.1.3 Statistical analysis

WSR was transformed using the natural logarithm to obtain its normal distribution. ID and WSR changes during the study period were tested using paired t-test. It was performed first for all subjects, then in subgroups defined by the presence/absence of diabetes and by the type of the inflow artery (radial vs. brachial). Pearson's correlation coefficients were calculated between cholesterol, triglycerides and arterial diameter and its changes.

The value of $p<0.05$ was considered significant. All calculations were performed using statistical software (STATISTICA Cz 6, StatSoft, Inc. 2003).

5.2 Results

We included 75 patients aged 61 ± 2 years, 20 were males and 33 had diabetes mellitus.

Values of ID, pWSR and mWSR are presented in *Table 3*. Internal diameter increased significantly during the study, with a concomitant decrease in pWSR and mWSR.

5.2.1 Brachial vs. radial AVG comparison

Mean and minimal velocities were higher in radial artery, but this difference was significant only in diabetic patients. Distal (radial) accesses were characterized by significantly lower feeding artery diameter in both diabetic and non-diabetic patients. Peak, mean and minimal WSR were significantly higher in distal accesses arteries.

5.2.2 Diabetes

Patients with diabetes mellitus had smaller diameters than non-diabetics. During the first year, the feeding artery of non-diabetics dilated significantly by 19% compared to 7% in diabetics, despite the latter had higher WSR. In diabetics, WSR begun to decrease significantly later than in non-diabetics: during the second year of access age. These results are in *Table 3* and *Figure 5*.

5.2.3 Cholesterol

In the whole group of subjects, cholesterol correlated with ID_0 (r=-0.24, p=0.043), ID_1 (r=-0.30, p=0.009) (*Figure 6)*, ID_2 (r=-0.34, p=0,028) but not with ΔID. Triglycerides correlated significantly only with ΔID_{1-0} (r=-0.23, p=0.046). Interestingly, these correlations were similar

in the subgroup of radial artery accesses, but disappeared in the subgroup of brachial artery accesses.

6 Discussion

6.1 Feeding artery shortly after access creation

The first study has shown that feeding arteries of vascular accesses are exposed to unusually high WSR. WSR is even higher in arteries of distal accesses and in diabetic subjects.

Physiologically, WSS controls the relation between arterial diameter and blood flow. An increase in the blood flow leads to higher WSS, which, in turn, is followed by arteriodilatation and decrease of WSS. Similarly a decrease in blood flow leads to vasoconstriction (Malek et al. 1999). The adaptation of the vessel diameter represents an important feedback mechanism to keep WSS within a narrow, so-called physiological range (Malek et al. 1999; Kubis et al. 2001). The adaptation has two steps: 1) rapid dilation within minutes as seen in flow-mediated vasodilatation (Gnasso et al. 2001) and 2) long-term structural adaptation of vessel wall (Girerd et al. 1996; Ene-Iordache et al. 2003). Rapid adaptation to the blood flow changes is mediated by changes in vascular smooth muscle tone, which is endothelium-dependent (e.g. flow mediated vasodilatation) (Bevan 1997; Sellke et al. 1997). Arterial remodelling is a long-term, partly endothelium-dependent structural adaptation of the vessel wall (Ene-Iordache et al. 2003).

Little differences in blood velocities do not explain substantial differences in arterial WSR in radial and brachial AVGs; this is rather the result of different internal diameter of these arteries and their capability to dilate. Brachial artery has a greater diameter than radial artery already before access creation (Konner 2000). Furthermore the vessel wall response to increased blood flow could be limited by structural changes of the vessel wall, such as calcification. Arterial medial calcification is more pronounced in diabetic patients, but uraemia per se also contributes to their development (Floege et al. 2004).

Konner reported that the arterial calcification was less pronounced in the elbow than in the wrist region (Konner 2000). In diabetic patients atherosclerotic and calcified radial arteries do not undergo adaptive flow-mediated vasodilatation to deliver sufficient fistula blood flow (Konner 2000). In these patients decreased vasodilatation ability is probably a result of both endothelium dysfunction linked to hyperglycaemia (Boyle et al. 1997) and structural vessel wall changes (Floege et al. 2004). Distal arterial diabetic involvement probably explains higher WSR in feeding arteries of diabetic subjects.

Early thrombosis and low access flow are major causes of graft failure in haemodialysed patients and especially in diabetics (Konner 2000). Subjects with diabetes mellitus have increased levels of von Willebrand factor (vWf) and decreased levels of tissue plasminogen

activator (Boyle et al. 1997). vWf plays a critical role in thrombus formation on PTFE surfaces. This is particularly efficient under conditions of high shear rate (Cho et al. 1995). At such conditions vWf is directly activated, it binds to an exposed subendothelium and activates platelet accumulation. Pathologically high shear rates (around 8000 s^{-1}), such as those at atherosclerotic stenosis, may directly activate platelet aggregation (Setty et al. 2002). Fibrin deposition increases also with increasing shear rate (Cho et al. 1995). All these pathological events lead to a local hypercoagulable state. High WSR in accesses of haemodialysed patients, and diabetic in particular, may play a role in access thrombosis and possibly also in hand ischemia.

6.2 Long term adaptation of the feeding artery

The main findings of the second study are as follows: 1) The dilatation of the feeding artery of vascular accesses continues at least 2 years after access creation with a continuous decrease in WSR, which however, remains highly supra-physiological. 2) Patients with diabetes have lower internal diameter and the vasodilatation of the feeding artery is delayed compared to non-diabetics. 3) Cholesterol is associated with lower internal diameter of the feeding artery however it does not influence its annual changes.

During the observation period, internal diameter continuously increased with a simultaneous decrease in WSR. These findings are in accordance with the theory of constant WSS, that states that the vessels tend to maintain WSS in physiological range by means of changes of internal diameter (Malek et al. 1999). However, even after 2 years neither pWSR nor mWSR reached normal values. The response to chronic blood flow increase requires structural adaptation associated with vascular cells growth and modification of vessel wall matrix, metalloproteinase's activation being necessary for this process (Tronc et al. 2000). Moreover, the feeding artery is subjected to supra-physiologically high WSR and the time to its normalization may be much longer than two years. However both acute and chronic increase of arterial diameter has probably its limits (Reneman et al. 2006) and it is possible that WSR will not normalize either after longer period.

The role of the feeding artery on the internal diameter results in naturally smaller internal diameter of the radial artery and higher normal values of pWSR and mWSR than brachial artery already before access creation (Reneman et al. 2006) and also shortly after access creation (Tuka et al. 2006). Nevertheless, the annual percentual diameter changes were comparable in radial and brachial arteries, suggesting that the ability to dilate of both arteries are similar.

Already in our previous study we have reported lower internal diameter and higher WSR in diabetic patients shortly after access creation (Tuka et al. 2006). Vasodilatation and long-term vessel wall adaptation to increased blood flow is endothelium dependent (Langille 1996) and can be thus prevented by factors associated with endothelial dysfunction, such as diabetes. The magnitude of vasodilatation is negatively related to the degree of vessel wall calcification (Huang et al. 2005), which is more pronounced in diabetic patients and known as mediocalcinosis (Edmonds 2000). Moreover, hyperglycaemia in diabetic patients leads to changes in endothelial cells phenotype, which is associated with vasoconstriction (Creager et al. 2003) and impaired vasodilatation (Endemann et al. 2004). Yet, the vessel adaptation to increased blood flow in diabetic patients is preserved, nevertheless progresses in a slower fashion that in patients without diabetes.

Higher WSR in the feeding artery of patients with diabetes may be both the cause and the consequence of lower diameter. The cause, if we assume that high WSR causes direct injury to endothelial cells (Boyle et al. 1997) and that high WSR is the reason for impaired vasodilatation and thus lower diameter. High WSR may be thus the consequence of lower diameter; and the lower diameter the consequence of impaired vasodilatation related to endothelial dysfunction, which is the consequence of diabetes. On the other hand, WSR is inversely related to internal diameter and the value of internal diameter was used to WSR calculation.

Our results suggest that the internal diameter is inversely related to cholesterolaemia in the radial artery but not in the brachial artery. On the other hand the relative annual change of internal diameter does not depend on cholesterolaemia. Hypercholesterolemia by itself causes endothelial dysfunction by decreasing nitric oxide synthase activity and thus the vessel potential to dilate both acutely and chronically via NO-dependent metalloproteinases activation (Tronc et al. 2000). The first measurement at baseline is already under the high flow load conditions suggesting that the first acute adaptation has already taken place. The subsequent chronic dilatation under such high WSR does not further depend on cholesterol.

6.3 Limitations

A possible limitation of our study is the use of WSR measurement as an estimation of WSS, because endothelial cells sense directly WSS and not WSR. WSS depends linearly on WSR and on blood viscosity. Some papers (Girerd et al. 1996; Gnasso et al. 2001) focus on WSS as a more accurate index of blood flow influence on endothelial cells. Nevertheless, to obtain the exact value of WSS one needs to know blood viscosity. Some authors (Girerd et al. 1996) use an arbitrary value for blood viscosity to estimate shear stress or use viscosimetry to measure it (Gnasso et al. 1996; Irace et al. 1999; Jiang et al. 2000; Gnasso

et al. 2001). It was shown that even actual measurements of viscosity must not lead to real values of shear stress (Setty et al. 2002). The use of an arbitrary value of blood viscosity would not change statistical significance of the results. Moreover, the variables affecting whole blood viscosity, such as haemoglobin level, haematocrit, plasma proteins, fibrinogen where not significantly different between groups (data not shown), suggesting that also viscosity was similar between groups. Thus, the comparison of WSR between groups can give the same results as for WSS with computed whole blood viscosity. For these reasons, we used WSR measurement.

7 Conclusions

We can conclude that feeding arteries of dialysis vascular accesses are exposed to supra-physiological values of WSR shortly after access creation. High WSR may play a role in development of access complications. Further research should reveal if long time exposition to high WSS is able do normalize or at least lower WSR.

The feeding artery continues to dilate to the second year after access creation, with a simultaneous WSR decrease. This process is dampened in patients with diabetes mellitus and hypercholesterolemia.

8 Tables

Table 1: Group characteristics at baseline

	DM[a]		Non DM	
	Radial artery	Brachial artery	Radial artery	Brachial artery
Number (%)	27 (47%)	21 (43%)	30 (53%)	28 (57%)
Age (mean ± SD) (years)	68 ± 10	66 ± 10	62 ± 17	64 ± 12
Men/women	6/21	7/14	10/20	7/21
Number of previous accesses (median)	0	2	1	2

[a] DM = diabetes mellitus There were no significant differences in age and sex distribution between groups.

Table 2: Haemodynamic parameters in feeding arteries

	DM		Non DM		Radial artery	Brachial artery
	Radial artery	Brachial artery	Radial artery	Brachial artery	p-value DM vs. Non DM	p-value DM vs. Non DM
Number	27	21	30	28		
V_{peak}[b] ($cm \cdot s^{-1}$)	235 ± 73	206 ± 57	181 ± 70	178 ± 48	0.006	0.062
V_{mean} ($cm \cdot s^{-1}$)	179 ± 55	149 ± 46*)	145 ± 55	133 ± 33	0.021	0.167
V_{min} ($cm \cdot s^{-1}$)	139 ± 46	108 ± 40*)	118 ± 46	103 ± 23	0.100	0.537
ID[c] (mm)	2.7 ± 0.8	4.1 ± 0.8***)	3.3 ± 0.8	5.0 ± 0.8***)	0.012	0.0004
WSR_{peak}[d] (s^{-1})	4040 ± 2889	2070 ± 670***)	2512 ± 1623	1477 ± 582**]	0.002	0.001
WSR_{mean} (s^{-1})	3043 ± 2041	1490 ± 528***)	1985 ± 1169	1103 ± 401***)	0.003	0.009
WSR_{min} (s^{-1})	2313 ± 1384	1075 ± 422***)	1606 ± 913	848 ± 278***)	0.008	0.069

Values are means ± SD.

Statistical significance of the difference between radial and brachial arteries is expressed by the stars in the particular column: *)p < 0.05, **) p<0.001, ***) p< 10-4

P-values comparing subjects with and without diabetes are listed at the right of the table separately for radial and brachial artery.

[a] DM = diabetes mellitus, [b] V = blood velocity (peak, mean, minimal), [c] ID = internal diameter of the artery, d WSR = wall shear rate (peak, mean, minimal)

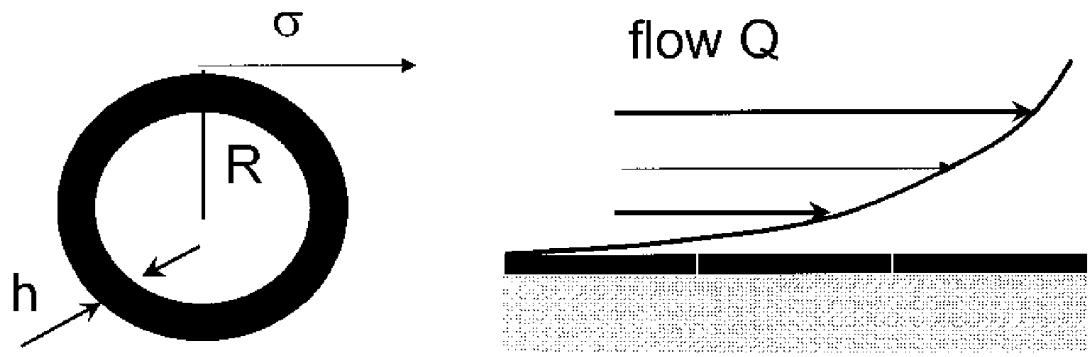
Table 3. Haemodynamic variables at baseline, first and second year after acces creation, according to the feeding artery type and diabetic status.

	All patients	Feeding artery		Diabetes mellitus	
		Brachial	Radial	No	Yes
Number of subjects (year 1/year 2)	75/41	33/19	42/22	42/24	33/17
ID_0	3.9 ± 0.1	4.7 ± 0.2***	3.3 ± 0.1***	4.1 ± 0.2*	3.6 ± 0.2*
ID_1	4.4 ± 0.2 (14%)	5.3 ± 0.2 (14%)***	3.6 ± 0.2 (14%)***	4.8 ± 0.2 (19%)**	3.9 ± 0.2 (7%)**
ID_2	4.6 ± 0.2 (5%)	5.4 ± 0.3 (-1%)***	4.0 ± 0.3 (11%)***	4.9 ± 0.3 (5%)	4.2 ± 0.4 (6%)
$pWSR_0$	2366±1290	1860±785**	2764±1468**	2016±1010**	2812±1475**
$pWSR_1$	2108±1389	1584±842**	2521±1592**	1491±783***	2894±1594***
$pWSR_2$	1517±955	1279±715	1723±1096	1180±544**	1994±1200**
$mWSR_0$	1806 ± 113	1382 ± 99***	2140 ± 170***	1565 ± 121*	2114 ± 194*
$mWSR_1$	1589 ± 118	1144 ± 95 ***	1939 ± 180 ***	1154 ± 83 ***	2143 ± 212 ***
$mWSR_2$	1148 ± 107	963 ± 116	1308 ± 168	929 ± 81 *	1457 ± 214 *

ID for internal diameter (mm), pWSR for peak wall shear rate (s-1), mWSR for mean wall shear rate (s^{-1}), data are expressed as mean ± SE.
In parenthesis percents of change between baseline and first year and between first and second year are shown. Statistical significance (unpaired t-test) is shown for the comparison between feeding artery type and between patients with and without diabetes. *for p<0,05; ** for p<0,01; *** for p<0,001

9 Figures

Figure 1: Schematic representation of haemodynamic stresses in blood vessels. (from (London et al. 2002)



Circumferential wall stress

$$\sigma = \frac{P \times R}{h}$$

Fluid shear stress

$$\tau = \frac{4 \mu Q}{\pi R^3}$$

Figure 2: Native arteriovenous fistula and PTFE arteriovenous graft.

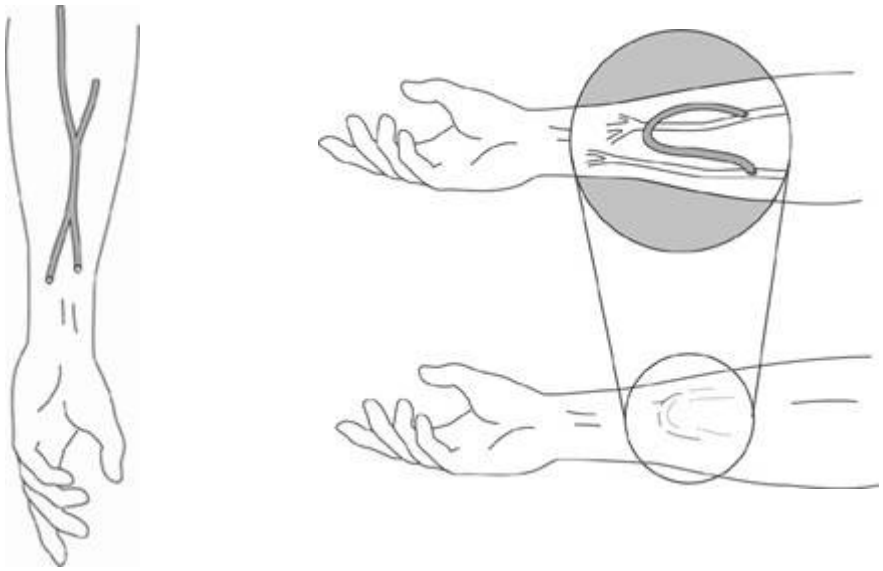


Figure 3: Ultrasonography assessment of internal diameter and velocity profile in the feeding artery

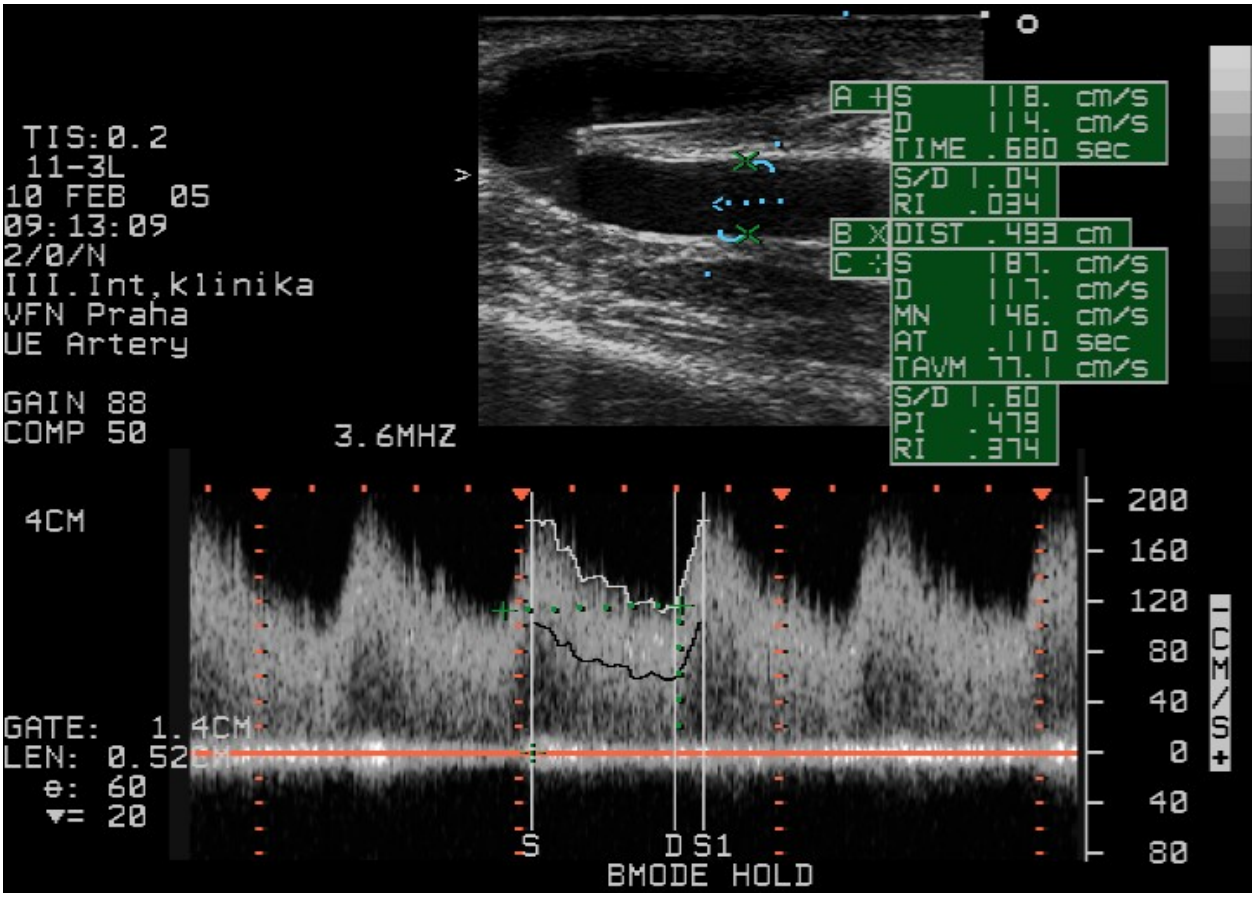


Figure 4: Comparison between WSR mean according to diabetic status; separately for radial and brachial artery

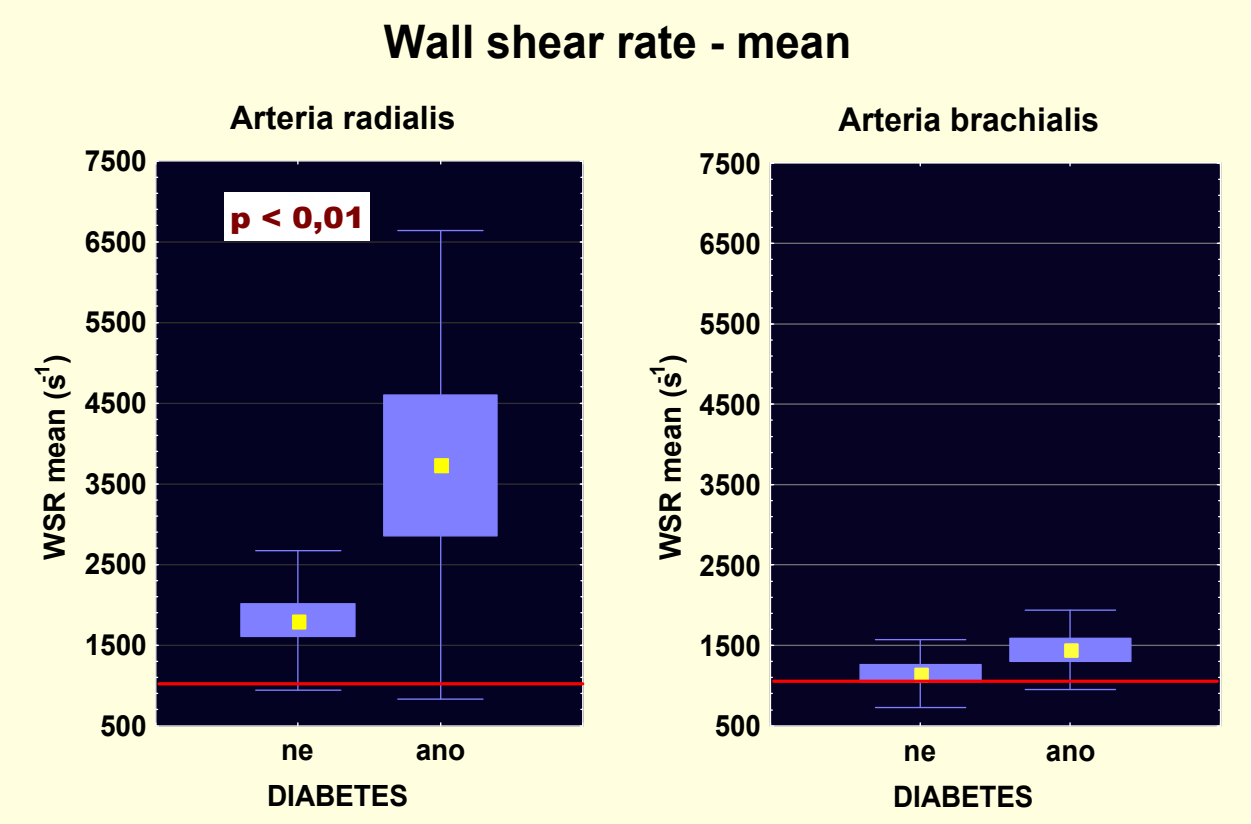
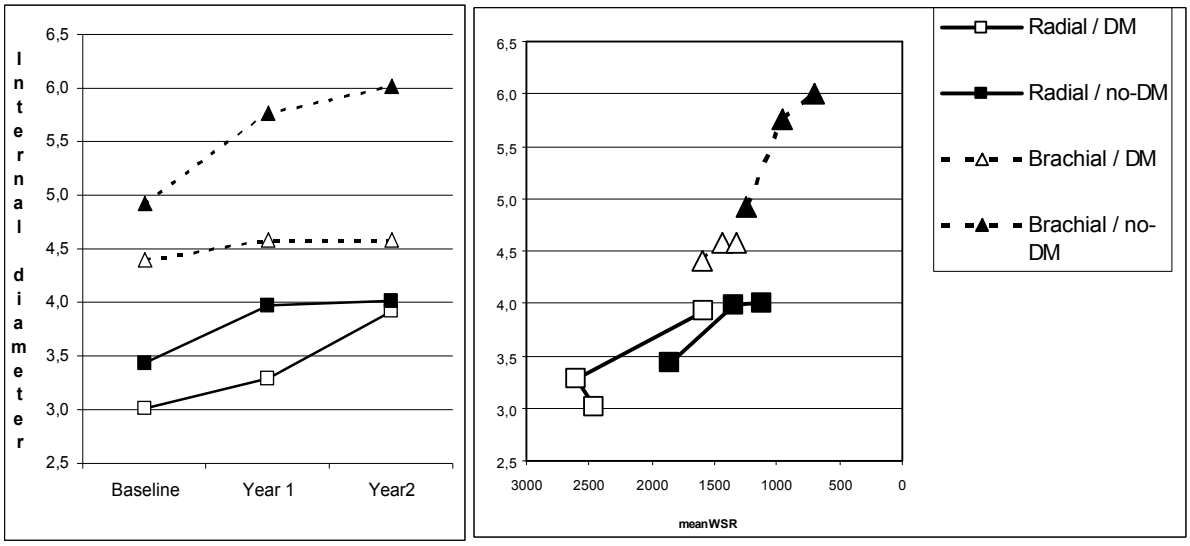
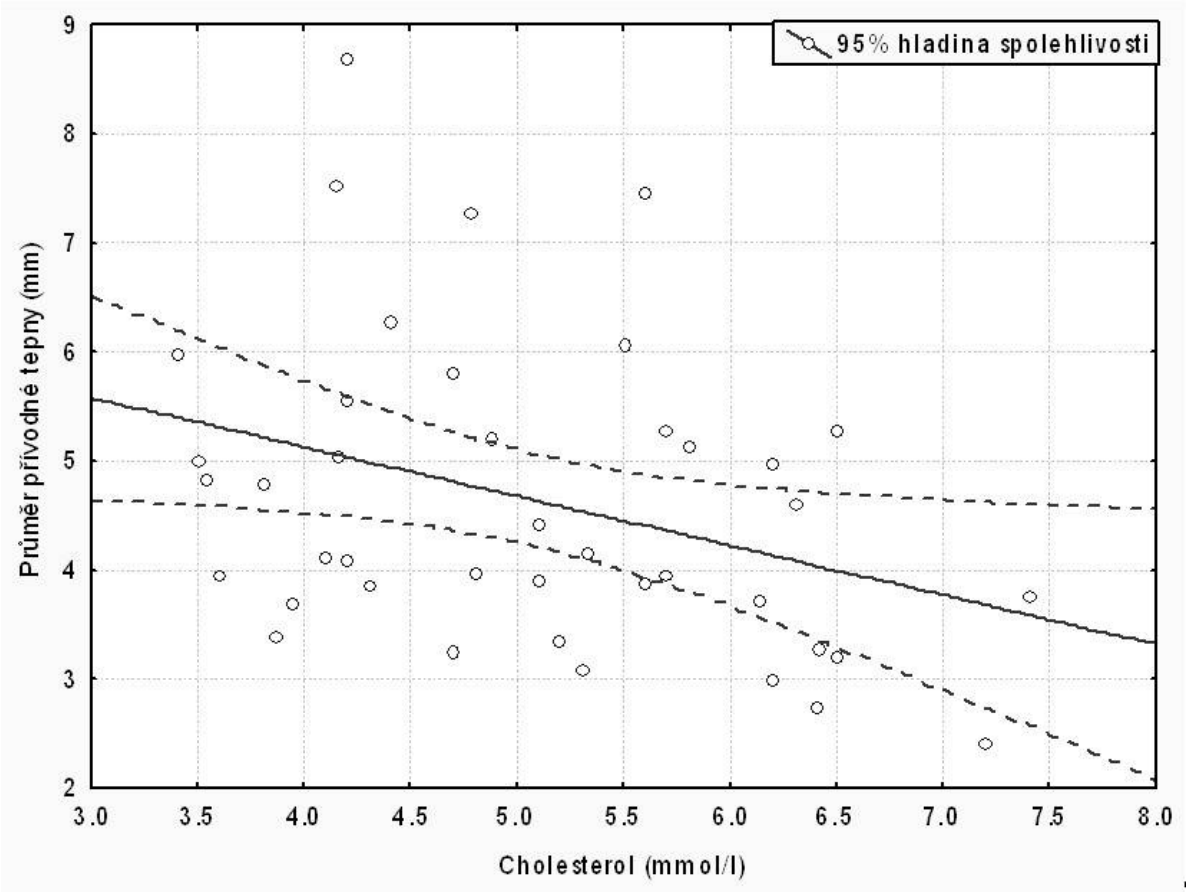


Figure 5: Mean wall shear rate and internal diameter in radial and brachial arteries; separately for diabetic and no-diabetic patients



DM – diabetes mellitus; meanWSR – mean wall shear rate

Figure 6. Correlation between cholesterol and internal diameter in year 1 (r=-0.30, p=0.009)



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