HEMODIALYSIS ACCESS FAILURE: VISCOELASTIC VASCULAR PROPERTIES AND INTIMAL HYPERPLASIA DEVELOPMENT

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***Abstract* — Intimal hyperplasia development is largely the most important cause of vascular access failure in patients submitted to hemodialysis.**

Differences in the biomechanical properties between the vascular substitutes and the native vessels have been related to the development of intimal hyperplasia. This work aim was to characterize the biomechanical behavior of arteries, veins, cryopreserved arteries and ePTFE prostheses.

Fresh and cryopreserved human arteries and veins and ePTFE conduits were in-vitro studied in order to analyze their viscoelastic properties.

Our results show that ePTFE has an elastic index, which is significantly different from that of the other conduits. This determines a high elastic mismatch that has been involved as a cause of intimal hyperplasia development.

We conclude that the biomechanical study of tubular segments to be used as vascular accesses demonstrate viscoelastic differences that could be an important determinant of access viability.

***Keywords* — vascular access, biomechanical study, ePTFE, intimal hyperplasia, cryopreserved arteries and veins.**

I. INTRODUCTION

The introduction of hemodialysis has determined a prolonged survival in patients with end stage renal disease. However, maintenance of permanent vascular access has limited the adequate use of chronic renal replacement therapy.

An ideal vascular access must be able to withstand a considerable flow to allow the hemodialysis procedure, cause minimal complications and have a high patency rate (Rodriguez *et al.*, 2000). Many techniques have been employed for the vascular access therapy. Among the most used are the native (Brescia-Cimino) fistula, and those that use synthetic prosthesis (Cernadas *et al.*, 2003). Nevertheless, up to date, none of the synthetic or biologic conduits used fulfills the ideal vascular access properties (Cinat *et al.*, 1999).

Vascular accesses have a high incidence of complications, in particular thrombotic occlusion, which determines the vascular access failure. The development of intimal hyperplasia at the arteriovenous anastomosis, graft vein anastomosis or outflow vein have been described as a major cause of thrombosis (Tordoir *et al.*, 2004).

The development of intimal hyperplasia has been related, among other factors, to differences in viscoelasticity between the native vessels and the vascular substitutes. This work's aim was to analyze the elastic properties (E), viscous behavior (V) and pulse wave velocity (PWV) of synthetic conduits of ePTFE, and of human fresh and cryopreserved arteries and veins. Additionally, the intimal hyperplasia process, and its relationship with vascular accesses' mechanical behavior are described.

II. VASCULAR ACCESS

In end stage renal disease patients, the effort must be directed to obtain an arteriovenous fistula (AVF), while the use of grafts would be left as a second choice (Rodriguez *et al.*, 2000).

The common surgical procedure for the creation of a fistula consists in the anastomosis of the radial artery and cephalic vein in the forearm (Zarin *et al.*, 2004). This AVF is the vascular access of choice since it determines the lowest risk of dysfunction, infection, thrombosis and the longest patency rate (Añel *et al.*, 2003; Canaud, 2004). Additionally, problems concerning vascular steal syndrome and high output cardiac failure are least frequent in AVF performed in the forearm position. Finally, it preserves proximal vessels for future vascular accesses (Rodriguez *et al.*, 2000; Tordoir *et al.*, 2004).

Many patients do not have adequate veins to use for AVF. In these cases the use of an arteriovenous graft (AVG) is a valid alternative. The AVG, which consists of a prosthetic material in between the native artery and vein, should remain as a secondary option (Canaud, 2004). In these cases, the expanded polytetrafluoroethylene (ePTFE) is one of the materials used and its performance is lower than that of the AVF (Cinat *et al.*, 1999; Rodriguez *et al.*, 2000). However, those who prefer the AVG rather than the AVF usually point out that the AVG is easier to needle and has a faster maturation period (Young *et al.*, 2002) and that it is easily obtained in different diameters, making it an available tool at hand for a diverse number of vessel sizes (Cinat *et al.*,

1999). On the other hand, thrombosis is more easily treated in AVGs than in AVFs (Khosla and Ahya, 2002). Nevertheless, as it was reported, they show a lower patency rate when compared to AVF, as well as a higher incidence of infection (Ezzahiri *et al.*, 1999; Cernadas *et al.*, 2003).

An important factor that must be considered in end stage renal failure is the patient characteristics. For instance age, sex and diabetes have been shown to modify the access duration. For instance, the mean age of patients that need hemodialysis is increasing, which means that the probability that they have adequate endogenous vessels to use for an AVF is decreasing (Ezzahiri *et al.*, 1999).

In summary, the need of vascular access is increasing, but the alternatives available nowadays are far from the ideal. Therefore potential new vascular accesses must be considered. In this context, cryopreserved vessels should be considered and studied for their possible use in end stage renal failure patients (Ezzahiri *et al.*, 1999; Cernadas *et al.*, 2003; Zarin *et al.*, 2004; Young *et al.*, 2002).

III. INTIMAL HYPERPLASIA

Intimal hyperplasia has been thoroughly studied during the past years; despite the fact that a consensus has not been reached regarding the mechanisms that take place for it to develop. There is evidence to support the fact that intimal hyperplasia has a complex etiology and pathobiology which necessitates further study (Sivanesan *et al.*, 1999).

It has been observed that intimal hyperplasia in vascular accesses is the consequence of high flow rates (Kohler and Kirkman, 1999). AVFs and AVGs are currently traversed by high blood flows. As a consequence of the flow disturbances, there is a proliferation of the cells, and the extracellular matrix. These tend to move into the lumen of the graft, making an obstacle to blood passing towards the outflow vein and sometimes causing thrombi (Cernadas *et al.*, 2003; Sivanesan *et al.*, 1999). See Fig. 1. Since the precursor of thrombosis is stenosis, it is important to control the AVG evolution, in order to detect stenosis before thrombosis appears (Vassalotti *et al.*, 2004; Khosla and Ahya, 2002). In fact, the use of a stent can be helpful when applying it to a stenosed native fistula or synthetic graft (Turmel-Rodrigues, 2004) while several pharmacological drugs are needed, on the other hand, to treat thrombosis (Turmel-Rodrigues, 2004).

Two other main factors, related to flow, that affect the development of intimal hyperplasia are compliance mismatch between the native vessel and the graft (Haruguchi and Teraoka, 2003; Hofstra *et al.*, 1995), and the wall shear stress, which is characterized by the chances that blood elements, like platelets and leucocytes adhere to the vessel wall. In particular, inordinately high shear stress might provoke the denudation of endothelial cells that promotes the passage of smooth muscle cells into the intima (Haruguchi and Teraoka, 2003).

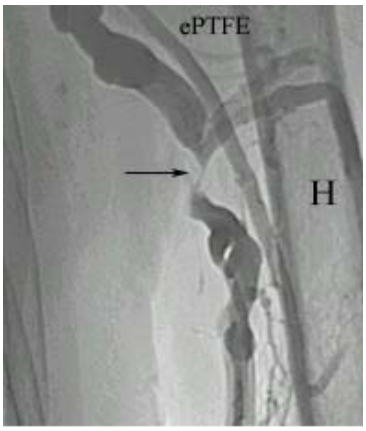

Figure1. The angiogram shows a stenotic venous tract (straight arrow) in a vascular access performed in the left arm of a chronically dialyzed patient. Between the humerus and the diseased vein a patent ePTFE prosthesis is visualized.

While veins often present high levels of intimal hyperplasia, this is not observed in arteries (Johnson *et al.*, 2001). Since veins have a thinner wall, they might be more prone to being damaged by flow (Kohler *et al.*, 1999). There exist other differences in the outcome of intimal hyperplasia in these two segments. For example, the vein presents a relatively poor demarcation of its elastic laminae, thereby easing the passage of smooth muscle cells from the tunica media to the intima as a consequence of an elevated degree of shear stress (Roy-Chaudhury *et al.*, 2002). The low nitric oxide and high numbers of fibroblast growth factors receptors in the vein might also predispose this vessel to a more frequent occurrence of stenosis and thrombosis (Roy-Chaudhury *et al.*, 2002).

According to all the aforementioned possible causes of intimal hyperplasia, it would be desirable the use of conduits with mechanical properties similar to those of the native vessels when performing a vascular access procedure.

IV. DYNAMIC STUDY OF VASCULAR ACCESSES

We have designed a circulating loop that is utilized to evaluate the mechanical properties of synthetic prosthesis (ePTFE) and fresh and cryopreserved vessels. In the circulation mock, the segments can be studied while submitted to diverse ranges of intraluminal pressure and stretching rate values. (Cabrera Fischer *et al.*, 2002; Cabrera Fischer *et al.*, 2005).

The in vitro system is constituted of a pneumatic pump which propels a liquid (*i.e.* blood) throughout the circulating loop. The pump generates the pulsatile flow to the circuit and is connected to a perfusion line that finds an organ chamber in its closed loop, where there is Tyrode's solution kept at 37ºC with a pH of 7.4 bubbled with 100% oxygen. The resistance modulator can be regulated to mimic the human circulatory system. The direction of flow is as shown in Fig. 2.

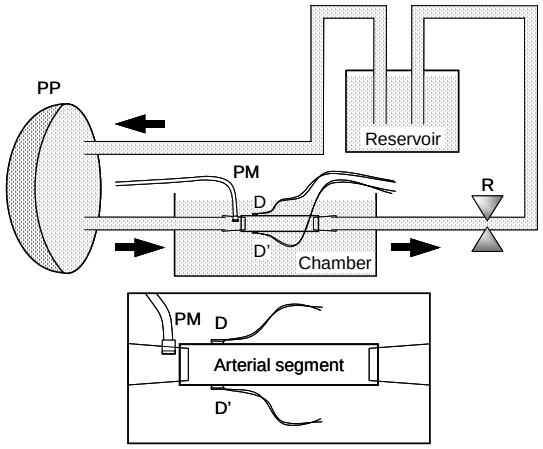

Figure 2. Circulating Loop. PP: pneumatic pump, R: Resistance modulator, DD': ultrasonic crystals measuring the diameter of the vascular segment under study. PM: pressure microtransducer. Arrows indicate flow direction.

The intraluminal pressure was measured using a Konigsberg P7 or P2.5 microtransducer (1200 Hz frequency response) while the external diameter was assessed using a pair of ultrasonic crystals (5 MHz, 2 mm diameter); as has been previously reported (Bia *et al.*, 2005; Cabrera Fischer *et al.*, 2002).

Segments of 5 cm ePTFE were placed and studied in the perfusion line immersed in the organ chamber as can be seen in Fig. 2. Human vessels procurement was done following the rules of the Guides of the National Organ and Tissue Bank transplant program from Uruguay. The processing of arteries and veins included the written consent and was carried out according to the ethics and safety standards for therapeutic use. Exclusion criteria was determined following the International Standards for Tissue Bank guidelines.

In situ measurements of 5 cm were performed on the adventitia tissue of the right and left femoral arteries and saphenous veins of 9 human donors in brain death condition. Vessel segments were excised and those to be used as fresh were sent to the biomechanical laboratory, while the rest were submitted to the cryopreservation protocol.

Fresh and cryopreserved defrosted venous and arterial segments were mounted in the organ chamber as can be seen in Fig. 2.

The pressure and diameter signals recorded were digitized using a specific program developed in our laboratory and stored for later analysis. This analysis consisted in the calculation of the stress-strain plot once the wall thickness was obtained and the evaluation of incremental elastic index (E), viscosity index (V). We also calculated the pulse wave velocity (PWV) so as to obtain a mechanical index used in clinics (Armentano *et al.*, 1991; Bia *et al.*, 2005).

V. RESULTS OF BIOMECHANICAL STUDY

Fresh femoral artery (n=9), cryopreserved femoral artery (n=9), fresh saphenous vein (n=9), cryopreserved saphenous vein (n=9) and ePTFE (n=9) were in-vitro analyzed. All segments were submitted to systemic levels of pressure (see Table 1).

The same methodological protocol was employed to characterize the dynamic mechanical properties of the vessels and synthetic prostheses. After positioning the segment in the organ chamber (in between the perfusion line), the segments were allowed to stabilize for a period of 15 minutes under a steady state of flow (150 ml/min) and a mean pressure of 93 mmHg, at a stretching rate of 80 beats/min (1.34 Hz).

The elastic and viscous indexes were derived from the pressure-diameter loop calculated according to previous works (Armentano *et al.*, 1991). The PWV values (see Table 2) were obtained according to the methodology previously reported (Bia *et al.*, 2005).

Table 1 shows that the experiments were done at isobaric and isofrequency conditions. Moreover, the mean diameter among the segments (four vessels and 1 synthetic prosthesis) was not significantly different from each another.

The elastic index (E) calculated for all vessels was similar ($p > 0.05$). The ePTFE elastic index was significantly higher than that of all the vascular segments (Table 2).

Regarding the viscous index (V), fresh and cryopreserved femoral arteries showed non-significantly different values. A similar trend was followed by the fresh and cryopreserved saphenous veins. However, viscous index differences between venous and arterial conduits were statistically significative. The viscous index for the ePTFE was almost zero and was significantly different from all the vessels studied (Table 2).

Table 1: Hemodynamic Measurements

	FFA (n=9)	CFA (n=9)	FSV (n=9)	CSV (n=9)	EPTFE (n=9)
PP	40.9 ± 4.3	42.7 ± 3.5	46.7 ± 5.3	44.5 ± 4.2	45.3 ± 4.5
MP	75.2 ± 3.2	76.4 ± 3.1	76.8 ± 3.4	75.4 ± 3.2	77.6 ± 1.1
MD	6.82 ± 0.37	6.81 ± 0.72	7.09 ± 1.06	7.05 ± 1.02	6.06 ± 0.01
PR	81±3	81±4	82±4	81±3	81±2

MV±SD. FFA and CFA: fresh and cryopreserved/defrosted femoral artery. FSV and CSF: fresh and cryopreserved/defrosted saphenous vein. ePTFE: expanded polytetrafluoroethylene segments. PP and MP: pulse and mean pressure (mmHg). MD: mean diameter (mm). PR: pump rate (b.p.m). ANOVA followed by Bonferroni test. a ,b ,c and d: $p<0.05$ with respect to FFA, CFA, FSV and CSV, respectively. No significative differences were found.

Table 2: Mechanical Parameters

	FFA (n=9)	CFA (n=9)	FSV (n=9)	CSV (n=9)	EPTFE (n=9)
E	680.2±753	675.5±78.6	700.8±65.5	698.8±70.2	$987.6\pm190.0^{a,b,c,d}$
V	17.1±3	16.2±2.5	$2.0\pm0.4^{a,b}$	$2.1\pm0.5^{a,b}$	$0.01\pm0.01^{a,b,c,d}$
PWV	1864±123	1869±92	1801±105	1807±98	$8567\pm78^{a,b,c,d}$

MV±SD. FFA y CFA: fresh and cryopreserved/defrosted femoral artery. FSV and CSF: fresh and cryopreserved/defrosted saphenous vein. ePTFE: expanded polytetrafluoroethylene segments. E: elastic index (mmHg/mm). V: viscous index (mmHg.s/mm). PWV: pulse wave velocity (cm/s). ANOVA followed by Bonferroni test. a ,b ,c and d: $p<0.05$ with respect to FFA, CFA, FSV and CSV, respectively.

The pulse wave velocity (PWV), a clinical parameter used as an indicator of elasticity, was similar among the vessels, while the ePTFE showed the highest PWV, as it was expected, taking into account its high elastic index (Table 2).

VII. DISCUSSION

Biomechanical properties of veins, arteries and synthetic prostheses have been associated with intimal hyperplasia development. More specifically, it has been suggested that an increment in compliance mismatch might induce this proliferative vascular stenosis (Haruguchi and Teraoka, 2003).

Our results demonstrated that both, elastic index and PWV have similar values for the fresh and cryopreserved arteries and veins. On the contrary, the ePTFE studied segments were stiffer than the vascular segments evaluated. These findings suggest that AVG performed using this material will have a higher elastic mismatch than that obtained with the AVF. Additionally, the ePTFE showed a negligible viscosity value, while fresh and cryopreserved human vessels showed a viscoelastic behaviour.

As was shown above, ePTFE, the synthetic prosthesis mostly used in vascular access surgical procedures has very different viscoelastic properties than those observed in the biological conduits analyzed in this work. This has to do with the high levels of intimal hyperplasia observed in the literature. We conclude that cryopreserved veins and arteries show similar biomechanical behavior than that observed in fresh vessels. In this sense, cryopreserved vessels could be considered as an alternative in the construction of AVG.

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