

VASCULAR HETEROGRAFTS FOR HEMODIALYSIS ACCESS: ANALYSIS OF ELASTIC AND VISCOUS MATCHING FACTOR BETWEEN HUMAN AND OVINE VESSELS

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Abstract— Long-term vascular accesses are usually performed in patients submitted to renal replacement therapy using autologous vessels. When arterio-venous fistula creation is impossible, animal conduits have been used in order to obtain high patency rates. Bovine vessel heterograft has been introduced as a substitute for the construction of arterio-venous fistulas. However, when experimental research of graft failure is focused to vascular wall properties, the ovine model is one of the more frequently utilized instead of the study of bovine vessels. Biomechanical vessel wall properties study is very important, since the viscoelastic mismatch among the fistulae conduits has been pointed out as a determinant of intimal hyperplasia, a cause of access dysfunction.

In this work we have analyzed viscoelastic properties of arteries and veins harvested from human donors in brain death condition and healthy sheep. The elastic mismatch calculus revealed that the human brachial artery and the ovine jugular veins exhibit the best coupling accompanied by an optimal viscous matching.

Keywords— hemodialysis access, arterial elasticity, venous elasticity, vascular viscosity, elastic mismatch.

I. INTRODUCTION

Renal replacement therapy is currently performed in uremic patients through long term vascular accesses usually confectioned using autologous vessels. Another choice is the used of synthetic conduits, such as expanded polytetrafluoroethylene (ePTFE), to obtain high patency rates of hemodialysis fistula. However this option is limited by the high degree of elastic mismatch, between the native vessel and the graft, an important determinant of intimal hyperplasia development. Intimal hyperplasia decreases the intra vascular lumen causing severe access dysfunction (Haruguchi and Teraoka, 2003; Hofstra *et al.*, 1995).

As was previously described, mechanical characteri-

zation of biomechanical wall properties of arteries, veins and prostheses is very important and usually performed in animal models. The ovine model is considered to be useful and widely used to mimic the human access function allowing the development of new graft designs and therapies (Kohler and Kirman, 1999; Flester *et al.*, 2004; Gleed *et al.*, 1997; Bia *et al.*, 2006a,b; Bia *et al.*, 2007; Zócalo *et al.*, 2006).

Animal heterograft has been introduced in clinical practice in order to provide of an adequate arterio venous fistula in patients in which a vascular access using native vessels is impossible. However, in the reported series the heterograft is harvested from bovine animals and, to the best of our knowledge, no ovine vessels have been recently employed to hemodialysis access in patients with end-stage renal failure (Haimov and Jacobson, 1974; Hatzibaloglou *et al.*, 2004).

Since the ovine model has been widely utilized to study arterio-venous performance, in this work we analyzed the viscoelastic properties of arteries and veins harvested from human donors and healthy sheep. Besides a comparative study using calculated values of elastic and viscous mismatch was performed.

II. METHODS

A. *In Vitro* Studies

Human and animal vessel procurements were performed according to the Guides of the transplant program of the National Organ and Tissue Bank of Uruguay and the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication N° 85-23, revised 1996); respectively.

Saphenous vein, Brachial and Femoral arteries were procured from 7 donors in brain death condition. Human donors age was 23-45 years (Mean = 29.6 years). All segments were removed and washed with saline solution and stored at 4°C. Each vessel was non-traumatically mounted on a circulating loop that mimics the human circulatory system and immersed and perfuse with a thermally regulated (37°C) and oxygenated Ty-

rode's solution, with pH=7.4. The mock circulating loop consists in a line of polyethylene tube and a Windkessel chamber, powered by a pneumatic pump. Pump rate, flow, resistances and waveform of pressures were regulated by a console that allowed fine adjustments (Cabrera Fischer *et al.*, 2002; Bia *et al.*, 2005a, b; Zócalo *et al.*, 2006).

Vessels from eight Corriedale sheep, weighing 25 to 35 kg, aged between 30 and 45 months old were chosen to be in vitro analyzed in this work. During 15 days before surgery, the animals were appropriately cared, feed and vaccinated. All animals were operated under general anesthesia induced by thiopental sodium (20 mg/kg, i.v.) and maintained with 2.5% enflurane in pure oxygen (4 L/min) through a Bain tube connected to a Bird Mark VIII respirator. Segments of Jugular vein, Femoral vein, Anterior and Posterior Cava vein, Ascending Aorta artery, Descending Aorta, and Common Carotid artery were removed and washed with saline solution and non-traumatically mounted in the circulating loop as was above described (Zócalo *et al.*, 2006). In these segments pressure and frequency levels similar to those of human vessels were ensured, in order to obtain isobaric and isofrequency recordings (Cabrera Fischer *et al.*, 2002; Bia *et al.*, 2005a, b, c; Zócalo *et al.*, 2006).

B. Data Acquisition

Both, human and animal conduits were dynamically studied in the circulating loop following a routine that has been previously reported (Cabrera Fischer *et al.*, 2002).

In all conduits mounted in the circulating loop, the intraluminal pressure was measured using a Konigsberg microtransducer (1200 Hz frequency response) and the external diameter was assessed using a pair of ultrasonic crystals (5 MHz, 2 mm diameter), according the technique largely used by our group (Cabrera Fischer *et al.*, 2002; Bia *et al.*, 2005a,b).

Similar dynamic study was followed in all conduits, in order to characterize their mechanical properties. Once the arteries or veins were mounted in the circulating loop, the segments were allowed to equilibrate for a period of 10 minutes, in which a mean pressure of approximately 85 mmHg and a stretching rate of 80 beats/min (1.34 Hz) were maintained.

Both, diameter and pressure signals were measured under dynamic conditions and displayed in real time. All signals were digitized every 5 ms and stored in the computer hard disk. Approximately 20 consecutive beats were sampled for off-line analysis.

C. Data Analysis

A computerized procedure was used to obtain a pressure-diameter loop that was employed to calculate biomechanical parameters using specific software developed with this purpose (Armentano *et al.*, 1995).

Viscoelastic properties of arteries and veins in vitro analyzed were studied assuming a Kelvin-Voigt viscoelastic model (spring-dashpot). According to this as-

sumption, pressure (P) developed in the conduit wall (P_{total}) can be divided in two components: an elastic ($P_{elastic}$) and a viscous component ($P_{viscous}$) (Armentano *et al.*, 1995; Bia *et al.*, 2005a, b; Bia *et al.*, 2006a; Bia *et al.*, 2007).

$$P_{Total} = P_{Elastic} + P_{Viscous} \quad (1)$$

As the viscous component is proportional to the first derivative of diameter (D) with respect to time (dD/dt) the $P_{Elastic}$ can be expressed as:

$$P_{Elastic} = P_{Total} - \eta \cdot dD/dt \quad (2)$$

In which η is the viscous index of the studied vessel. Calculus of the elastic P component can be performed subtracting the viscous term from the P_{total} . The procedure followed consisted in minimizing the area of the P-D hysteretic loop always preserving the clockwise direction of the loop. Quantification of the elastic component of P_{Total} , allowed the elastic index (E) calculation by means of the slope of the linear regression curve, evaluated at the mean prevailing pressure recorded (Armentano *et al.*, 1995).

Viscous and elastic mismatch between human and ovine segments were calculated as (Bia *et al.*, 2006b):

$$MatchingFactor = \frac{(SheepValue - HumanValue)}{(SheepValue + HumanValue)}$$

The matching factor value would be between +1 and -1. A value = 0 indicate optimal matching, while values different from 0 indicate mismatch

D. Statistical Analysis

Values reported are expressed as mean±standard deviation (MV±SD). Comparison among groups was performed using ANOVA followed by a Bonferroni test. A value of $p < 0.05$ was adopted as a limit for statistical differences.

III. RESULTS

No animal deaths or technical mistakes occurred during the course of any surgery or anesthesia induction. Specimens harvested from human donors were obtained without troubles.

Both, animal and human conduits were submitted to the same hemodynamic parameters, as can be seen in Table 1. No statistically significant differences were observed in diastolic, systolic, pulse and mean pressure values of all vessels ($P > 0.05$). As was expected several differences in mean external diameter values were observed both in sheep and human vessels ($P < 0.05$). See Table 1.

The highest E value was observed in the group of Human Saphenous veins and the lowest in the ovine Ascending Aorta.

The dynamic study of human vessels showed that the Brachial artery calculated E value was lower than that observed in the Saphenous veins and Femoral arteries ($P < 0.05$). See Table 2.

Values of η calculated in ovine Carotid arteries were the highest of both, human and animal vessels, on the contrary sheep Ascending Aorta showed the lowest values ($P < 0.05$). See Table 2.

TABLE 1: HEMODYNAMIC PARAMETERS

	SP	DP	PP	MP	MD
Sheep Vessels					
Jugular vein	137.4 ± 4.2	63.8 ± 2.6	71.2 ± 4.9	86.5 ± 3.1	13.92 ± 0.93
Anterior Cava vein	139.4 ± 5.0	64.6 ± 5.4	73.2 ± 4.7	88.0 ± 5.3	16.91 ± 1.11 ^a
Posterior Cava vein	140.3 ± 5.2	65.7 ± 4.3	74.0 ± 4.0	88.4 ± 3.2	21.19 ± 1.14 ^{a,b}
Femoral vein	139.6 ± 3.3	66.4 ± 4.5	71.4 ± 4.0	92.0 ± 4.0	6.39 ± 0.61 ^{a,b,c}
Carotid artery	136.4 ± 5.3	63.5 ± 4.3	73.3 ± 5.1	85.6 ± 5.2	6.37 ± 0.30 ^{a,b,c}
Ascending Aorta	137.9 ± 4.7	66.1 ± 4.4	72.6 ± 5.1	89.1 ± 4.2	22.26 ± 1.10 ^{a,b,d,e}
Distal Aorta	139.1 ± 4.5	67.9 ± 4.9	73.5 ± 4.8	87.9 ± 4.3	15.76 ± 0.93 ^{c,d,e,f}
Human Vessels					
Saphenous vein	141.0 ± 4.8	65.2 ± 5.0	75.2 ± 4.3	89.1 ± 4.9	6.89 ± 0.92 ^{a,b,c,f,g}
Brachial artery	138.2 ± 4.9	67.4 ± 4.3	70.9 ± 4.9	90.0 ± 4.2	6.00 ± 0.71 ^{a,b,c,f,g}
Femoral artery	142.4 ± 4.7	65.5 ± 5.0	74.4 ± 4.3	91.4 ± 5.0	7.33 ± 0.54 ^{a,b,c,d,e,f,g,i}

VM±SD. SP, DP PP and MP: systolic, diastolic, pulse and mean pressure, respectively (mmHg). MD: mean diameter (mm). P values determined by the one-way analysis of variance (ANOVA) with a Bonferroni test. ^a p<.05 respect to jugular; ^b p<.05 respect to anterior cava; ^c p<.05 respect to posterior cava; ^d p<.05 respect to femoral vein; ^e p<.05 respect to carotid; ^f p<.05 respect to ascending aorta; ^g p<.05 respect to distal aorta; ^h p<.05 respect to saphenous veins; ⁱ p<.05 respect to brachial artery.

TABLE 2: BIOMECHANICAL PARAMETERS

	E	η
Sheep Vessels		
Jugular vein	420.2 ± 22.5	12.82 ± 1.13
Anterior Cava vein	394.6 ± 31.1	11.95 ± 1.24
Posterior Cava vein	658.0 ± 26.2 ^{a,b}	19.43 ± 1.24 ^{a,b}
Femoral vein	692.3 ± 30.4 ^{a,b}	20.53 ± 1.06 ^{a,b}
Carotid artery	553.1 ± 19.0 ^{a,b,d}	25.76 ± 1.13 ^{a,b,c,d}
Ascending Aorta	26.1 ± 2.7 ^{a,b,c,d,e}	1.30 ± 0.39 ^{a,b,c,d,e}
Distal Aorta	130.4 ± 9.8 ^{a,b,c,d,e,f}	5.63 ± 0.87 ^{a,b,c,d,e,f}
Human Vessels		
Saphenous vein	958.45 ± 75.31 ^{a,b,c,d,e,f,g}	4.17 ± 0.52 ^{a,b,c,d,e,f,g}
Brachial artery	417.23 ± 36.21 ^{c,d,e,f,g,h}	12.01 ± 1.44 ^{c,d,e,f,g,h}
Femoral artery	629.34 ± 164.23 ^{a,b,e,f,g,h,i}	18.63 ± 3.43 ^{a,b,e,f,g,h,i}

Values are mean ± SD. E: elastic index (mmHg/mm). η: viscous index (mmHg.s/mm). ^a p<.05 respect to jugular; ^b p<.05 respect to anterior cava; ^c p<.05 respect to posterior cava; ^d p<.05 respect to femoral vein; ^e p<.05 respect to carotid; ^f p<.05 respect to ascending aorta; ^g p<.05 respect to distal aorta; ^h p<.05 respect to saphenous veins; ⁱ p<.05 respect to brachial artery.

TABLE 3: MATCHING BETWEEN HUMAN AND SHEEP VESSELS

	Human vessels						
	Saphenous vein		Brachial artery		Femoral artery		
	E	η	E	η	E	η	
Sheep vessels	Jugular vein	-0.39	0.51	0.00	0.03	-0.20	-0.19
	Anterior Cava vein	-0.42	0.48	-0.03	-0.01	-0.23	-0.22
	Posterior Cava vein	-0.18	0.65	0.22	0.23	0.03	0.02
	Femoral vein	-0.16	0.66	0.25	0.26	0.05	0.05
	Carotid artery	-0.27	0.73	0.14	0.38	-0.06	0.18
	Ascending Aorta	-0.95	-0.52	-0.88	-0.81	-0.92	-0.87
	Distal Aorta	-0.76	0.16	-0.52	-0.36	-0.65	-0.53

E and η: elastic and viscous index. The matching factor values are between +1 and -1; a value equal 0 indicate optimal matching.

The study of η in human vessels showed that values of Brachial artery group exhibit an intermediate value between Saphenous vein and the Femoral artery. Moreover, statistical differences were observed between the three groups ($P < 0.05$). See Table 2.

The elastic matching factor revealed that the best coupling was that observed between human Brachial artery and ovine Jugular vein. This finding was accompanied by a value of viscous matching near zero (0.03). See Table 3.

Elastic and Viscous matching factor calculated between human Femoral arteries and ovine Femoral veins showed a very good coupling, since both were near zero. Interestingly, Elastic and Viscous matching obtained between human Femoral arteries and ovine Posterior Cava veins were better. See Table 3.

The elastic matching between Human Saphenous veins and the ovine Femoral vein was the best (-0.16), on the contrary the coupling with the ovine Ascending Aorta was the worst. See Table 3.

IV. CONCLUSIONS AND COMMENTS

The aim of this study was to characterize the mechanical properties of both, ovine and human vessels submitted to systemic pressure levels. Besides, the viscous and elastic matching among ovine and human conduits (veins and arteries) was analyzed.

The most relevant finding obtained was that ovine Jugular veins exhibit the best viscous and elastic matching with human Brachial arteries. As was widely described, human brachial arteries are usually utilized in the arterio venous hemodialysis access confection (Hatzibaloglou *et al.*, 2004).

The in vitro model employed in this dynamic study has been previously utilized to analyze arterio-venous performance. We opted for vascular segments instead of the most used strips or rings (Mavrilas and Tsapikouni, 2002; Silver *et al.*, 2003), because the former are better to reproduce the in vivo hemodynamic conditions, and to preserve the shape and integrity of vascular/graft wall. In this study all conduits were studied under systemic isobaric levels of pressure, in order to adequately analyze the coupling between ovine and human vessels (Cabrera Fischer *et al.*, 2005; Bia *et al.*, 2006a).

The main functions of arteries are to serve as conduits (conduit function) and to smooth out the pulsatility caused by the ventricular ejection (buffer function). These functions depend on the cross-sectional area and mechanical properties of the arteries, which in turn are related to the structural components of the vascular wall. From a functional point of view, the elasticity and viscosity are the main mechanical properties of the vascular wall (Bia *et al.*, 2006a; Cabrera Fischer *et al.*, 2005; Armentano *et al.*, 2006).

The “elasticity” of the arterial wall allows the wall distension during systole and storage of part of the mechanical energy given by the heart, which is restored in diastole. This behavior is important in optimizing the heart–vessel coupling, smoothing out the pressure and

flow pulsatility and ensuring a continuous flow toward the tissues. Additionally, it avoids over-distention of walls due to pressure, giving structural security to the vascular segment.

Vascular wall elasticity has been ascribed mainly to elastin and collagen fibers, and to the smooth muscle cells. The disparity in the behavior of vessels obtained from different regions of human and sheep cardiovascular systems (Table 2), and between veins and arteries would be related to differences in the relative quantity, arrangement, and functional role of smooth muscle cells and elastic fibers among the vessel.

The “viscosity” of the vascular wall, usually associated to an energy dissipation term (Bia *et al.*, 2005a, b; Bia *et al.*, 2006a, Bia *et al.*, 2007), helps to attenuate traveling pressure pulses along the arteries and prevents reflected pressure waves from resonating in the arterial system.

Passive theories propose that viscosity is a property of the vascular wall constituents, and recognize the smooth muscle as the main determinant (Armentano *et al.*, 1995). In contrast, the active theory explains wall viscosity taking into account the force-generating mechanism of the muscle as well as the myogenic response to stretching (Armentano *et al.*, 1995). Additionally, collagen-dependent vascular viscosity should be considered because collagen fibers, particularly type III (which is present in the vascular wall), when loading have shown not only an elastic energy storage by the stretching of flexible molecular domains, but also an energy dissipation due to fiber slippage (Silver *et al.*, 2003). Therefore, it is comprehensible that several factors could be responsible for vascular wall viscosity and that the differences among the behaviors of veins and arteries, from human and sheep (Table 2) could be related not only to the relative amount, but also to the arrangement of different structural constituents of the vascular wall.

Viscous and elastic values obtained in this work in both, ovine and human conduits, are similar to those previously reported (Zócalo *et al.*, 2006; Bia *et al.*, 2006a, Armentano *et al.*, 2006; Cabrera Fischer *et al.*, 2005). These results allowed the calculi of all possible couples among them. To the best of our knowledge this analysis has been never performed.

Our results are relevant because ovine vessels have been employed as vascular substitutes for hemodialysis access construction in humans several years ago (Enzler *et al.*, 1996; Wang and Chu, 1996; Berardinelli, 2006). Furthermore, the elastic vessel wall values appear to play a major role in the pathogenesis of intimal hyperplasia of the vascular access, and the elastic mismatch per se has been involved in the genesis of intimal hyperplasia (Cabrera Fischer *et al.*, 2005; Hofstra *et al.*, 1994; Lemson *et al.*, 2000). Consequently, reduction of elastic mismatch using conduits with similar elastic properties could ameliorate the long-term access viability.

In this study we included a viscous analysis because previous reports have pointed out that conduit such as ePTFE, whose employment results in a high rate of intimal hyperplasia development, shows low values of wall viscosity (Armentano *et al.*, 2006; Bia *et al.*, 2006a, Cabrera Fischer *et al.*, 2005).

The knowledge of the basic biomechanical behavior of the different vascular heterograft would be crucial at the time of selecting a graft for a vascular access, in order to minimize the mechanical mismatch. In this context, this dynamic study identified the ovine vessels that exhibit the best viscous and elastic matching with human arteries and veins currently used in the hemodialysis access confection.

Finally, we want to point out that ovine vessels used as arterio-venous bridging graft for hemodialysis access, at present are being replaced by another substitute: bovine bioprosthesis (Berardinelli, 2006). More studies would be necessary to identify the best bovine vessels to be used in arterio venous fistulae in patients submitted to hemodialysis.

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