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Numerical simulation of blood fluid in hemodialysis catheters and its thrombogenic potential

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ABSTRACT. The present study aimed to numerically simulate blood flow within central venous catheters of hemodialysis and its thrombogenic potential. Numerical simulation research performed through the dynamic computational program of fluids. A three-dimensional geometry of right and left internal jugular veins were built, taken from the Visible Human Project®. Catheters with obstructed and unobstructed lateral holes were constructed. For the simulation, we considered the duration of the cardiac cycle of 0.8 s with pulsatile cycle of 75 beats per minute. Shear stress, velocity and pressure increased when the catheter was within the vein and when they were obstructed. At the venous orifice of the catheter that was unobstructed, the velocity increased from 0.99 ± 0.02 m s^{-1} to 1.79 ± 0.009 m s^{-1} and the pressure from 1487 ± 0.8 Pa to 3215 ± 0.7 Pa. Blood re-circulation areas have created areas of stagnation of blood flow, making it more susceptible to the development of venous thrombi. This study may contribute to the expansion of multiprofessional partnerships between health professionals and Bioengineering fields in order to study health problems that can be verified through advanced technologies. Such technologies, such as simulation programs, detail possible adverse events based on scientific evidences which often occur silently in patients.

Keywords: hydrodynamics; vascular access devices; fibrin; diagnostic techniques and procedures.

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Introduction

Although non-tunneled Central Venous Catheter (CVC) play an important role for hemodialysis patients, they should not exceed two weeks in the vein (Peng et al., 2017; Premuzic, Perkov & Smiljanic, 2018).

In clinical practice, non-tunneled CVCs remain a minimum of two months in patients. It would be the usual time required for arteriovenous fistula maturation, however, due to the comorbidities of some patients, such as diabetes, hypertension, coagulopathies, immunological and neurological pathologies, fistulas and grafts may not heal and CVCs make the only blood access during the entire hemodialysis period (Ponce, Mendes, Silva & Oliveira, 2015; Browne, Walshe & Griffin, 2015; Pollo, Dionizio, Bucuvic, Castro & Ponce, 2016).

In the United States, CVCs are used in up to 15-20% of patients undergoing hemodialysis as a source of vascular access (Pollo et al., 2016). In addition, each year more than 110,000 new patients initiate hemodialysis, 80.2% use CVC as primary vascular access, and 68.3% of them continue to use it after 90 days of stay (Sutherland, Zhang & Charest, 2017). In Brazil, patients receiving CVC dialysis increase from 10% to 15% per year (Ponce et al., 2015).

The use of CVC may lead to delayed dialysis treatment, increased institutional cost, and the development of adverse events, such as bacterial infections and the development of thrombi with a consequent risk of pulmonary embolism, deep vein thrombosis, and vascular access limitations (Browne et al., 2015; Ponce et al., 2015; Pollo et al., 2016). Studies have indicated that the incidence of CVC occlusion due to the development of thrombi ranges from 5% to 80% in the population undergoing hemodialysis (Premuzic et al., 2018; Shin, Towbin, Zhang, Jhonson & Goldstein, 2017).

In addition, a study has shown that serum fibrinogen levels are significantly higher in patients undergoing hemodialysis and there is an increased prothrombotic state in hemodialysis patients (Premuzic et al., 2018). Added to that, there is the development of fibrin formation and thrombi that may occur within five days after insertion of the CVC (Lucas et al., 2014; Shin et al., 2017).

In this sense, despite the continued use of central access for hemodialysis, lack of understanding still prevails regarding the development of intraluminal thrombi in CVCs (Lucas et al., 2014). The hemodynamic effect of blood flow in modulating and stimulating the development of fibrin and thrombus propagation still requires investigation.

The dynamics of computational fluids allows the investigation of hemodynamic factors such as velocity, pressure and shear stress which can lead to an acceleration, modulation and progression of thrombus formation (Lucas et al., 2014; Browne et al., 2015). Numerical simulation studies evaluated the performance and necessity of lateral orifices in angiographic, thrombus-aspiration catheters and venous cannulas (Lucas et al., 2014; Dydek & Chaikof, 2016).

The need for lateral orifices, however, was not established as essential or not for the behavior of the blood fluid and its thrombogenic potential.

A computer simulation study evaluated the formation of thrombi in venous valves due to the presence of blood circulation areas that can stimulate the expression of the Tissue Factor (TF) and consequent initiation of the coagulation process (Dydek & Chaikof, 2016). It was found that, in recirculation areas, thrombin was generated and a thrombotic response was initiated (Dydek & Chaikof, 2016).

Another study simulated the presence of CVC within the jugular vein to the superior vena cava, and its influence on blood flow, however, real geometric, physical and clinical physiological parameters within the vein were not considered (Peng et al., 2017). Thus, no numerical study was found on the influence of lateral orifices on the process of thrombus formation in hemodialysis catheters.

Such data can contribute to the definition of new research methods and protocols for the evaluation of the thrombus inside the lateral orifices and for the implementation of intervention strategies in healthcare environments. In view of the above, this study aimed to numerically simulate blood flow within hemodialysis CVCs and its thrombogenic potential.

Material and methods

Type and local of study

This was a computational numerical simulation study carried out using the Swanson Analysis Systems program (ANSYS®) 18.0 (ANSYS-Fluent Inc., Lebanon, NH, USA) at the Bioengineering Laboratory of the Federal University of Minas Gerais. ANSYS is a tool commonly used by Bioengineering to evaluate computational fluid dynamics and simulate blood flow in different geometries within medical devices or human tissues.

Image processing and reconstruction of human venous tree

For the construction of the three-dimensional venous geometric models, we used images acquired from the 'Visible Human Project®' program, licensed to the Bioengineering Laboratory of the Federal University of Minas Gerais (UFMG). This is a program developed by the National Library of Medicine (NLM) in the USA, which proposed to create a base of digital images of two cadavers, one male and one female, from cross-sectional anatomical cuts, fresh and frozen x-ray tomography and magnetic resonance imaging. The anatomical axial images were 2048 pixels by 1216 pixels, where each pixel is defined by 24 bits.

To create the geometries, it was necessary to superpose the images of the cross-sectional anatomical cuts in parallel planes in the SolidWorks® program. We created plans responsible for the positioning of the images, and the spacing between them represented the physical distances between the images of the cross-sectional cuts contained in the "Visible Human Project® program.

Figure 1 shows the complete geometric solid display of the veins and the central venous catheter used in hemodialysis, taking into consideration the arterial and venous orifices.

In the hemodialysis treatment, the venous catheter orifices are the locations where the dialyzed blood reaches the patient's circulation and the arterial orifices would be the places where the patient's filtered blood is taken to the dialysis machine.

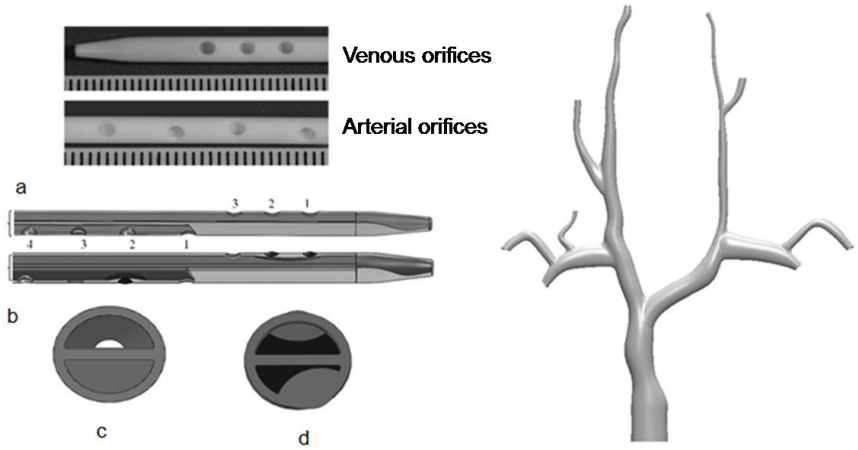

Figure 1. Three-dimensional solid display of the venous model and of the central venous catheter. Unobstructed catheter (a) and obstructed catheter (b). The numbers indicate the order of the side holes. Three venous orifices and four arterial orifices. Cross-sectional cuts made at the end of the unobstructed (c) and obstructed (d) catheter extension.
Source: Developed by the authors.

Measurement instruments

During the simulation, we obtained a numerical solution of the equations describing the fluid behavior in a certain region. In this study, the shear stress (understood as the tangential force that the blood exerts on the vessel wall) was evaluated. The shear stress is given by Equation (1):

$$\tau = \mu \frac{du}{dy} \qquad (1)$$

where: τ is the shear stress (Pascal (Pa)), μ is the dynamic viscosity (Pa.s) and *du* / *dy* is the rate of deformation (speed variation in a given displacement) (s^{-1}).

It can be said that the shear stress causes a continuous rate of deformation in the fluid. And that the viscosity represents the degree of resistance to shear stress. The Mean (M) ± Standard Deviation (SD) of the velocity, pressure and shear stress in the vein wall was also considered for this study.

In order for the simulation to become as real as possible, a complete three-dimensional geometry of the right and left inner jugular veins was constructed. We also constructed part of the right and left outer jugular veins, subclavian, suprascapular, cephalic veins and superior vena cava up to the beginning of the right atrium. Although these veins were important in assessing fluid behavior, they were not constructed as complete as the internal jugulars once we assessed the blood flow behavior when in the presence of CVC in the right internal jugular vein.

Two types of catheters were constructed: one catheter in which the lateral orifices were unobstructed and another catheter in which there was semi-obstruction in the lateral orifices. The area of the catheter without obstruction was 2.93 mm for both the arterial lumen and the venous lumen. The first two venous orifices were obstructed, resulting in an area of 2.04 mm^2, that is, a partial obstruction of 30% of the total area. The second arterial orifice was obstructed, resulting in an area of 1.33mm^2, that is, a partial obstruction of 55%. Thus, in the present study, the dynamic fluid computational analyzes were made in the venous orifice 3, in the central orifice of the tip and in the arterial orifices 1, 3 and 4, as shown in Figure 1.

Figure 1 (c) shows the cross-sectional cut of the central diameter of the unobstructed catheter and Figure 1 (d) shows the central diameter with partial obstruction in the venous and arterial orifice. The studied catheter had 0.5 mm in diameter at the distal tip and 20 cm in length. The lateral orifices were 2.0 mm in diameter and the tip orifice was 1.2 mm in diameter.

For the simulation, we considered the cardiac cycle duration of 0.8s, reaching a heart rate of 75 beats per minute. The time period for systole and diastole was 50% of the cardiac cycle. The blood was considered as a non-Newtonian fluid with numerical parameters of viscosity coming from the Carreau-Yassuda model, since, due to the large number of blood components, mainly red blood cells, there are variations of viscosity and shear stress throughout the blood circulation.

As for the time step, we used $\Delta t = 0.0005s$ with 1600 total time steps per cardiac cycle. To reach this time step, several time step values were folded and no significant difference was observed in the blood flow inside the veins. The maximum residual convergence was $1x10^{-4}$, manually set to control the accuracy of the solution of physiological relevance and approximately 1-5 interactions were required to achieve convergence at each time.

Three Intel Pentium dual-core processors 2.80 GHz 4GB RAM, three Intel Xeon Quad Core 2.67GHz 16 GB RAM and a dual-core Intel Xeon 1.60 GHz 8GB RAM, totaling 25 processing units, were used.

For the blood simulation, the real pulsatile cardiac cycle inside the veins and the atrium was considered. A polynomial curve for the input and output boundary conditions was established by Matrix Laboratory (MATLAB) version 7.4 (The Mathworks Inc., Natick, MA, USA) using cubic interpolation (Figure 2).

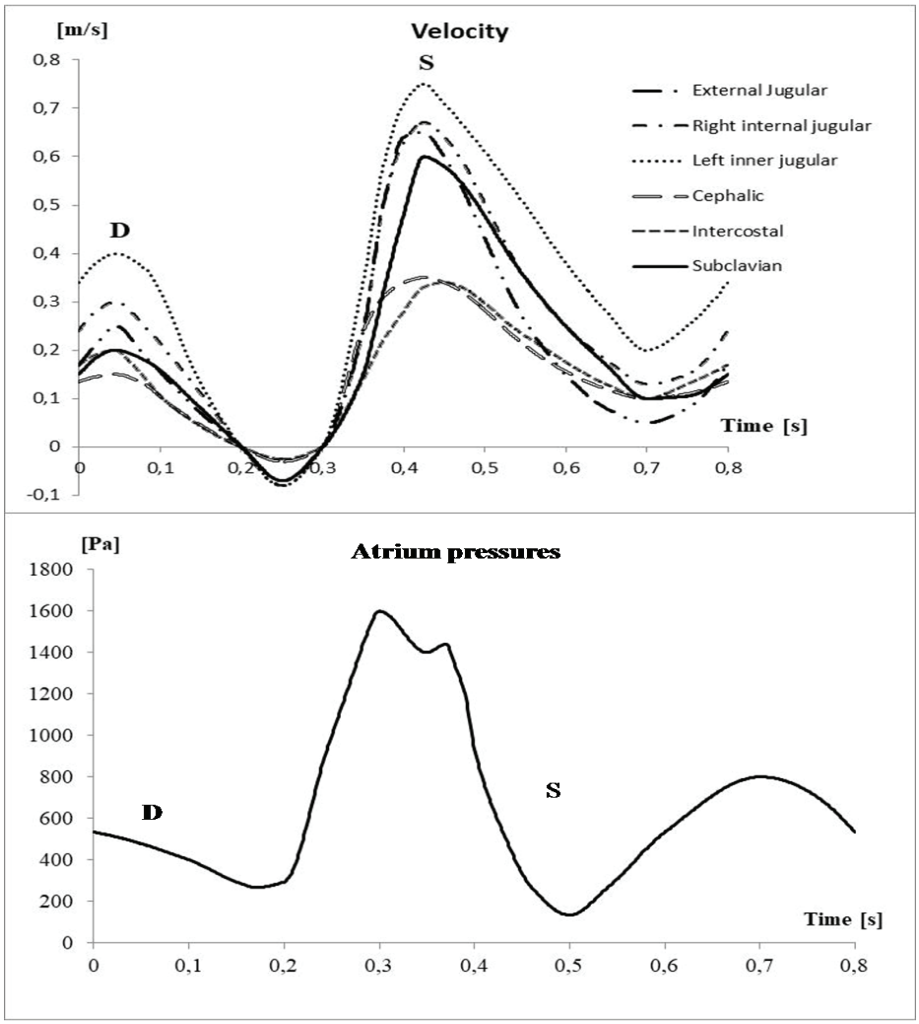

Figure 2. Distribution of velocity and pressure profile in the atrium of the veins considered as input conditions in the simulation.
Source: Developed by the authors.

We assumed a uniform velocity profile over time in the vein entries in accordance with the mean velocity of systole and diastole of each type of vein. The polynomial curves were an approximation of the curves found in the literature and in the lines obtained in color Doppler venous ultrasonography (Cronenwett & Johnston, 2014; Taute et al., 2105).

The input velocity presented a biphasic pattern within the vein, the systolic curve (indicated by the letter S) being dominant when compared to the smaller curve of the ventricular diastole (indicated by letter D).

Ethical statement

According to the policy of the Ethics Committee in Research, numerical simulation studies do not require approval from the Ethics Committee.

Results

Table 1 shows the values of shear stress, velocity and pressure in the obstructed and unobstructed catheters.

Figure 3 shows the variation in blood flow velocity within the vein and the central venous catheter. In the catheter with obstruction of the lateral orifices the flow velocity jet of the central orifice was larger.

Figure 4 shows the shear stress values of the vein geometry with and without the presence of the catheter.

Table 1. Distribution of shear stress, velocity and pressure values in the lateral orifices of obstructed and unobstructed central venous catheters. Belo Horizonte, Minas Gerais state, Brazil.

Venous Orifices of the central venous catheter	Central Venous Catheter					
	Unobstructed	Obstructed	Unobstructed	Obstructed	Unobstructed	Obstructed
	Shear Stress (Pa) (Means ±DP)		Velocity (m/s) (Means ±DP)		Pressure (PA) (Means±DP)	
Venous orifice 3	27.12 ± 0.03	35.04±0.01	0.99 ± 0.02	1.79±0.009	1487 ± 0.8	3215 ± 0.7
Arterial orifice 4	35.20 ± 0.32	37.25±0.32	0.35 ± 0.21	0.89±0.22	-247 ± 0.06	-276 ± 0.06
Arterial orifice3	13.57 ± 0.16	16.44±0.12	0.07 ± 0.02	0.17±0.02	400 ± 0.7	374 ± 0.6
Arterial orifice 1	1.30 ± 0.10	4.75±0.80	1.83 ± 0.08	1.87±0.06	525 ± 0.05	408 ± 0.03
Central orifice	10.92 ± 0.04	17.13±0.02	0.94 ± 0.04	1.67±0.02	1056 ± 0.01	2163 ± 0.02

Source: Developed by the authors.

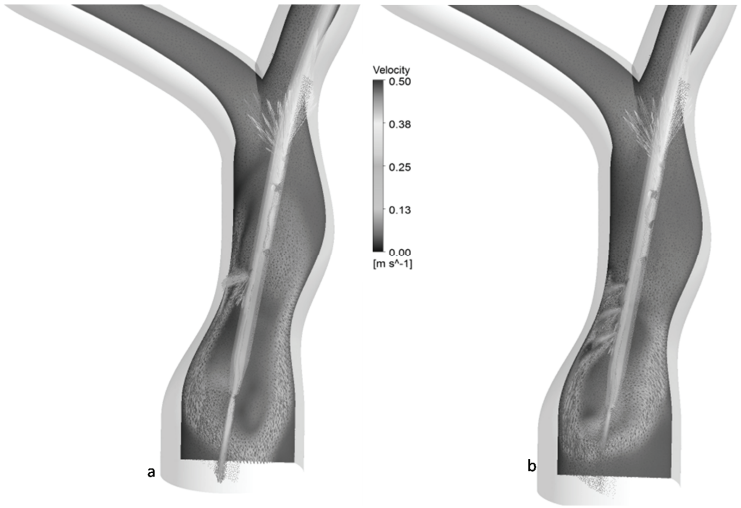

Figure 3. Variation of blood flow velocity within the vein and the central venous catheter with obstruction (a) and that in which the lateral orifices were not obstructed (b).
Source: Developed by the authors.

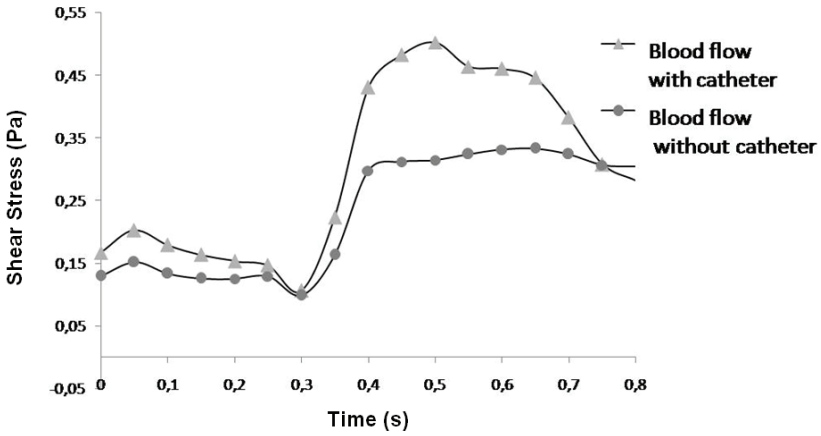

Figure 4. Distribution of shear stress values of vein geometry with and without the presence of the catheter.
Source: Developed by the authors.

Discussion

The results of this study pointed to an increase in velocity, shear stress and blood flow pressure in the vein wall when the CVC was obstructed (Table 1). It was also verified that blood flow leaving the lateral and central orifices contributed to the increase of minimum velocity and flow recirculation areas (Figure 3). Recirculation creates a variation in shear stress and velocity values and, consequently, a disorder in the direction of blood flow (Lucas et al., 2014, Peng et al., 2017). This process contributes to the progression of the coagulation cascade mediated by the endothelial cells of the vein, since it changes the morphology and functions of these cells (Sarmast, Niroomand-Oscuii, Ghalichi & Samiei, 2014; Lee et al., 2016). Between the lateral orifices, there was also the presence of vortex, circular pattern of the blood flow.

The presence of vortex, reverse blood flow, and blood circulation areas create areas of stagnation of the flow which, consequently, tends to accumulate platelets in the region near the wall and the catheter orifices, making it more susceptible to the development of venous thrombi (Browne et al., 2015). In addition, stagnation zones are associated with very low shear conditions and some parts of the vessel wall are exposed to abnormally low shear stress, which means that it tends to increase the blood cell concentration responsible for platelet activation and fibrin formation in polymer devices installed in the vessel.

The development of fibrin sheath and thrombus may occur within 24 hours after insertion of the catheter (Sutherland et al., 2017). Thrombotic accumulation in the CVC internal lumen may occlude access to blood, making the device ineffective. In the presence of thrombosis, the internal resistance to the flow increases and it may lead to a flow of less than 300 mL $min.^{-1}$, which is the recommended mean flow to circulate inside the CVC when hemodialysis occurs (Browne et al., 2015; Dydek & Chaikof, 2016). In addition, it may occur a more negative flow pressure than -250 mmHg in the arterial orifices, which is a rate considered as ideal in sites where the patient's filtered blood returns to the hemodialysis machine (Sarmast et al., 2014).

In the present study, the arterial orifice 4 also presented a more negative pressure when the CVC was obstructed (Table 1). The recirculation area in this region was thus elevated. Care should be taken when the negative pressure of the fluid increases, as it increases the resistance to blood filtration when on hemodialysis. In clinical practice, mechanical attempts to manipulate the catheter in order to improve such resistance to blood flow due to CVC dysfunction may cause a disturbance of the fibrinolytic system and promote inflammatory processes and activation of the coagulation cascade (Sarmast et al., 2014; Dydek & Chaikof, 2016).

Another factor that contributes to the activation of the coagulation factors is the increase of the blood flow shear stress when in the presence of the catheter inside the vessel (Figure 4). At high shear stress values, adhesion is controlled by the kinetic reaction of interaction between the platelet receptors and the adhesion proteins of the vessel wall (Pontone et al., 2016; García, Carrascal, Ruiz, Martin & Fernández, 2017; Li et al., 2017). As the shear stress increases, the convective transport of platelets and plasma increases and the process of adhesion to the polymer increases correspondingly. In addition, a numerical simulation and experimental comparison study of veins of patients undergoing hemodialysis showed that when the shear stress reached a value above 31.5 Pa, platelet activation automatically occurred and patients presented thrombi (Sarmast et al., 2014). In the present study, venous and arterial venous 4 also presented values above 31.5 Pa.

The shear stress is the frictional force of blood flow that acts on the vessel wall and can be detected directly in an endothelial cell on the luminal surface (Peng et al, 2017). It is fully believed that abnormal shear stress is an important reason for initiation and formation of thrombus (Peng et al., 2017; Lee et al., 2016).

A study in China that performed a numerical simulation of CVC inserted into the vein found that maintaining the catheter within the vein led to a significant increase in pressure and an abnormally high shear stress in the vessel wall (Peng et al., 2017). The term ‘abnormally high’ refers to the physiological comparison of shear stress within the vein without the CVC ranging from 0.1 to 1 Pa (Peng et al., 2017; Lee et al., 2016, Dydek, & Chaikof, 2016). However, that study did not construct the actual CVC geometry with the lateral orifices and the central division within the catheter. In addition, that study did not consider, in the three-dimensional drawing of the venous geometry, the various branches of the veins closest to the jugular to better understand the behavior of the fluid as in the present study.

In this study, on the other hand, although the shear stresses increased with the presence of the catheter, the values remained within the physiological pattern (Figure 4). In the present study, the shear stresses that

exited the lateral and central orifices were much higher than the physiological values found inside the vein (Table 1). Such high stress values contribute to the rapid occlusion of these orifices with consequent complication in the hemodialysis process.

In clinical practice, although thrombolytic agents, such as urokinase or streptokinase, can establish the patency of the catheter, fibrin and thrombus adherent to the inner wall of the catheter orifices are covalently attached and are not removed from the polymer (Lee et al., 2016).

The process may also be initiated with the posttraumatic thrombus formation associated with the insertion of the temporary double lumen catheter (Pontone et al., 2016; García et al., 2017; Li et al., 2017).The fibrin sheath forms at the point of contact between the catheter and the vessel wall and, as it advances along its entire length, it may create a one-way valve mechanism (easy-to-administer and difficult-to-aspirate solution), with consequent decreased flow in the catheter (García et al., 2017; Li et al., 2017).

The interaction process between blood proteins and CVC begins with the adsorption of the proteins on the surface of the material, which occurs in three phases: a) transport to the interface, b) adsorption reaction and c) conformational modification of the protein on this surface (Li et al., 2017). Proteins can bind to the surface of the material through electrostatic interaction between the domains of proteins and surfaces with opposing charges through hydrogen bonding or hydrophobic interactions (Sutherland et al., 2017; Li et al., 2017). The adhesion of leukocytes and platelets to the catheter occurs immediately after protein adsorption (Sutherland et al., 2017; Li et al., 2017). The contact of blood with the artificial material causes adsorption of proteins on the exposed surfaces, which assists in platelet adhesion and the initiation of an inflammatory response and coagulation pathways (Li et al., 2017).

Thus, the process of protein adsorption to the polymer may become irreversible and even with the introduction of fibrinolytic agents, tissue dissolution becomes ineffective because of strong covalent bonds between plasma proteins and the catheter wall Sutherland et al., 2017; Li et al., 2017). Complications due to the formation of thrombi in the lateral orifices of the catheters occur even with the use of anticoagulants, which reinforces the inherent thrombogenicity of polymeric materials when inserted into the bloodstream.

A prospective cohort study found that 45% of patients on fibrinolytic therapy had CVC occluded due to thrombus formation, resulting in 12 obstructions per 1,000 catheters day^{-1} (Ponce et al., 2015).

A morphologic study of the thrombus indicated that the initial process of its formation within the lateral orifices and central region of the thrombus is composed predominantly of red blood cells that can be diluted, if it is a recent thrombus, but with a limited duration (Lucas et al., 2014; Dydek & Chaikof, 2016). The restoration of the flow inside the catheter in this case is temporary since the remaining fibrin rapidly propagates to the center of the catheter orifice.

Fibrin sheath is initially composed of fibrinogen, albumin, lipoproteins and coagulation factors (Browne et al., 2015; Sutherland et al., 2017). Over time, fibrin sheath attracts platelets and coagulation factors and promotes the adhesion of leukocytes. After weeks or even months, the collagen and smooth muscle are also deposited on the catheter wall, which increases the tissue structure that is bound to the polymer and which will hardly be eliminated with anticoagulants or fibrinolytics (Pollo et al., 2016; Sutherland et al., 2017).

A Chinese numerical simulation study of CVC inserted into the vein also found an increase in pressure values at the exit of the superior vena cava that ranged from 44Pa to 69.16 Pa (Peng et al., 2017). Similar results were also observed in the present study leaving the superior vena cava (from 46 Pa to 71.2 Pa). On the other hand, in this study, pressure values leaving the lateral and central orifices of the CVCs with and without obstruction were much higher at these values (Table 1).

Such values can be qualitatively confirmed with the presence of a jet at the central outlet of the highest-pressure catheter in the wall of the endothelial cells of the vein when the catheter is obstructed (Figure 3). This change in blood hemodynamics enables endothelial cell injury that will rapidly lead to platelet adhesion and activation of coagulation factors, thus contributing to the acceleration of sheath formation around the catheter and thrombi.

A numerical simulation of venous valves performed in Boston associated chemical reactions of TF expressed in blood coagulation (Dydek & Chaikof, 2016). The results of that study identified which areas of recirculation led to the generation of thrombin and TF exposure. In addition, injury in the vessel wall due to catheter friction in the endothelium of the vein also led to the expression of TF, initiating the coagulation cascade (Lucas et al., 2014; Dydek & Chaikof, 2016). The endothelium is particularly susceptible to the activation of coagulation factors either by the CVC friction force or by the presence of recirculation and

reverse flow areas that can generate areas of stagnation and aggregation of red blood cells. As a consequence, it generates regions of hypoxia that can lead to the expression of P-selectin with a concomitant increase in local TF expression through several coagulation mechanisms (Pontone et al., 2016; García et al., 2017; Li et al., 2017).

The simulation study of venous valves further demonstrated that the variation of shear stress influences the expression density of the minimal TF to reach the threshold concentration of thrombin sufficient to propagate the coagulation cascade (Dydek & Chaikof, 2016). This finding has an important impact on the sensitivity of a given hemodynamic environment that can induce thrombin by surface-bound TF expression.

The present study had as limitation the non-performance of experimental benches for comparison with the numerical simulation and, despite the cycle-dependent pulsatile fluid, we did not evaluate the contraction and relaxation of the vein wall during systole and diastole or when the patient was standing or lying. This study, however, made it possible to understand the behavior of blood flow when in the presence of CVC and its potential for destruction of the endothelial wall and development of thrombi.

Conclusion

This study may improve the multiprofessional partnership between healthcare professionals and Bioengineering fields in order to prevent health problems through advanced technologies. New technologies can generate a greater impact both in the health area and in the scientific community and, consequently, nursing intervention might improve in the management not only of adverse events but in the direct care of hospitalized patients.

Further research is needed to prevent and treat catheter occlusion by means of new anticoagulant, thrombolytic and fibrinolytic agents. Also, lateral or catheter orifices may be developed in order to limit a disruption in blood flow.

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