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Bio-tribology of Vascular Devices: A Review of Tissue/Device Friction Research

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Abstract:

Vascular medical devices, such as stents, catheters and more advanced devices inevitably interact with surfaces within the human body. These interactions and the underlying biological and tribological (friction) mechanisms and resulting implications are not well understood, currently. For the further optimisation of these devices and the development of new and safer devices, a deeper understanding of vascular biotribology is required. Studies about this topic are scarce and no review is available. This review paper introduces vascular physiology relevant to interaction with medical devices and highlights where tribological effects may come into play. Furthermore, implications with existing medical devices are investigated in the context of biotribology and relevant studies are discussed. The different approaches to study the interactions are compared, and the current state of the field is reviewed. The aim of this paper is to provide an introduction to this interdisciplinary field, for both researchers with an engineering background and those with a biological background, and to present the current state of the field of research.

Keywords: Endothelial cells, friction, catheters, stents, cardiovascular, vascular

1. Tribology in Stent and Catheter Interactions with Vessels

Both stents and catheters, the two most common vascular medical devices, inevitably interact with blood vessels as part of their function in the body. This section shall give a general insight into where this frictional interaction takes place exactly and how it is relevant for the complication-free application of the respective devices by considering them from an engineering point of view.

1.1. Stent Interaction

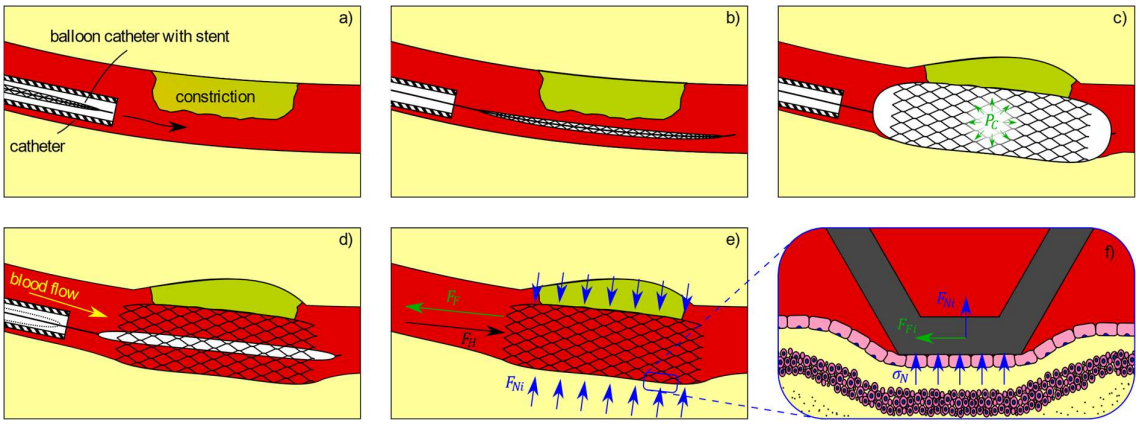

Figure 1: Schematic drawing of stenting process. a) Catheter and balloon catheter with stent are delivered to constricted vessel. b) Balloon Catheter and stent are positioned along constriction. c) Balloon is inflated with pressure P_C, widening the stent, resulting in restoration of vessel volume. d) Balloon catheter is deflated and retracted into the catheter. Blood flow is restored as stent stays in place and keeps vessel open. Blood flow direction marked in yellow. e) Forces acting on deployed stent. Normal forces F_{Ni} between vessel wall and stent struts result in friction force F_F, which keeps the stent in place by acting against hemodynamic force F_H exerted by the blood flow. f) Detail view of a single stent strut pressing against the endothelial layer with normal pressure σ_N, resulting in normal force F_{Ni} and friction force F_{Fi}.

Stents are mesh structures used to keep open a vessel that has been blocked. For example, during percutaneous coronary intervention, where a blood vessel in the heart is obstructed and needs to be revascularized. The stent is delivered with a catheter to the site of obstruction where it is expanded using a balloon catheter, as seen in Figure 1, with balloon pressure P_C between 8 and 20 atm [1]. Then, the balloon catheter is deflated and flow is restored; the vessel is revascularized. The catheter and balloon catheter are then removed, whilst the stent stays in place ensuring the vessel stays open.

Tribology is relevant during both the deployment and the deployed phase. In the deployment phase, it is important not to cause excessive damage to the tissue, as this may necessitate further intervention. The possible friction related complications caused by stent intervention are covered later.

When the stent is deployed, the possibility of stent migration presents a major complication. It means that the stent is being “washed” downstream under the hemodynamic force exerted on it by the blood flow, causing it to migrate away from its original deployment site. Stent migration can be attributed to an unfavourable ratio of friction to hemodynamic force. Considering this from an engineering point of view (free body force diagram, Figure 1 e), only

a few forces are exerted on the stent: the hemodynamic force $\mathrm{F_{H(t)}}$, normal forces $\mathrm{F_{Ni}}$, and friction force $\mathrm{F_F}$. $\mathrm{F_{H(t)}}$ is caused by blood flow, making it highly time dependent due to the cardiac cycle. Normal force $\mathrm{F_{Ni}}$ is the contact force the vessel wall exerts on the ith stent strut due to the contact pressure σ_N and is related to it by the surface integral of the normal pressure σ_N over the apparent contacting surface $A_{Contact,i}$:

$$\mathrm{F_{Ni}} = \oiint^{A_{Contact,i}} \sigma_\mathrm{N}\, dA$$

This interaction causes a friction force which is determined by the static friction coefficient μ_S. The static and not the dynamic friction coefficient should be considered because the stent should not move. Using Amonton's law on the infinitesimally small area dA, the friction force for the ith strut is:

$$F_{Fi} = \oiint^{A_{Contact,i}} \mu_s \sigma_\mathrm{N}\, dA$$

Together, those partial friction forces exerted on the stent, which has n struts, make up the total friction force acting on the stent F_F:

$$F_F = \sum_{i=1}^{n} F_{Fi} = \sum_{i=1}^{n} \oiint^{A_{Contact,i}} \mu_s \sigma_\mathrm{N}\, dA \qquad \text{Eq. I}$$

Returning to the free body force diagram, the only forces acting along the vessel direction are F_H and F_F which act against each other. When the maximum hemodynamic force exceeds the friction force, the stent can be flushed away and migrate, hence the condition to avoid stent migration is: $\mathrm{F_{H,max}} \leq F_F$ and with Eq. I:

$$\mathrm{F_{H,max}} \leq F_F = \sum_{i=1}^{n} \oiint^{A_{Contact,i}} \mu_s \sigma_\mathrm{N}\, dA$$

From this equation, there are several ways to decrease likelihood of stent migration: the first is to increase the normal pressure. This has been done for many years and is known as stent oversizing. It means that the stent is chosen to be bigger than the vessel and hence a larger normal pressure can be achieved. However, this comes with the disadvantage of possibly damaging the artery as bigger oversizing means more strain to the vessel. Other options to decrease the likelihood of stent migration are decreasing the hemodynamic force by making the stent more streamlined or increasing the contact area, either by adding more struts or by increasing the individual struts contact area. Finally, the friction coefficient could be

increased, and this is where tribology comes into play. As stents are inflated very slowly (over ~ 30 s, [2][3]) and hereafter supposed to be static, they can be assumed to be in a permanent state of boundary lubrication. While theoretically blood is an available lubricant and should be considered as such, in practice it probably cannot provide sufficient lubrication during stent application. This is due to the high contact pressure and the low speeds in conjunction with blood's relatively low viscosity. Therefore, chemical and physical properties of the materials are the major factors driving the interaction. Chemical bonds, Van der Waals forces, capillary attraction and electrostatic effects may play important roles governing the friction between stent and vessel wall, contributing to the adhesion force F_{Adh} occurring over the real contact area, $A_{Contact,real}$ (i.e: actual contact area on a microscopic level where surface asperities interact), through interfacial shear stress, τ:

$$F_{Adh} = \oiint_{A_{Contact,real}} \tau \, dA$$

and through F_{Adh} influence the static friction coefficient.

1.2. Catheter Interaction

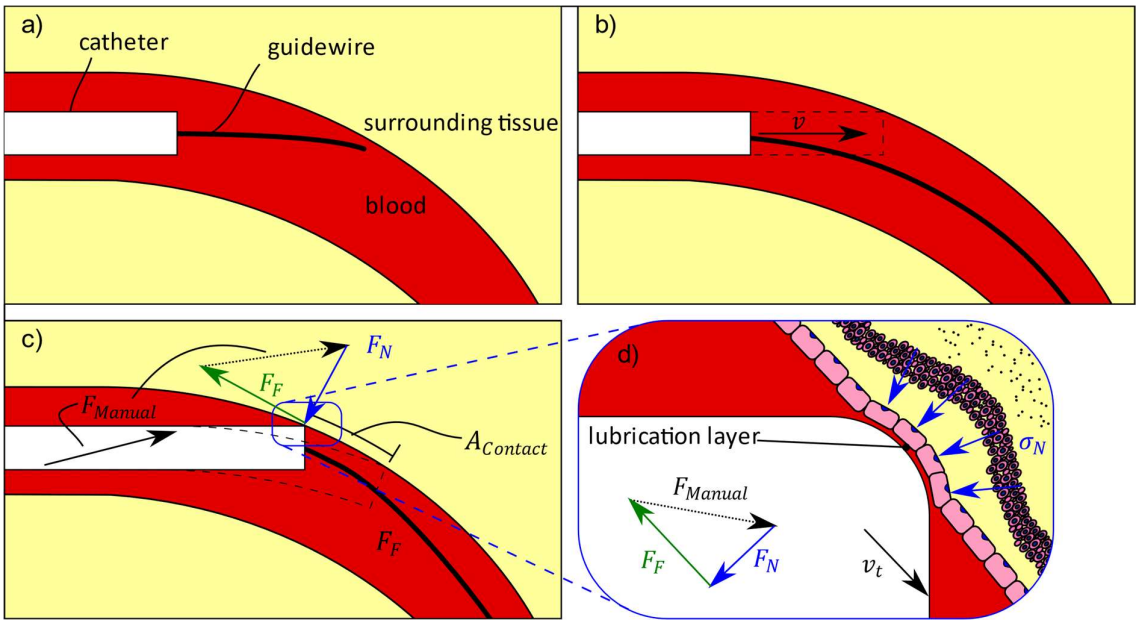

Figure 2: Schematic cross-section view of insertion of a catheter into a blood vessel. a) advancing guidewire into vessel b) Movement of catheter through artery with speed v (initial contact of catheter and artery marked by dotted catheter outline). c) Catheter inserted further (final position marked by dotted catheter outline) causing contact and consequent friction at contact area $A_{Contact}$. Parallelogram of forces F_N and F_F determines manual force F_{Manual} required for insertion of catheter. d) Detailed view of contact between catheter and artery. Normal pressure between endothelial cells and catheter σ_N under tangential speed v_t with formation of lubrication layer.

Catheters are tubes usually made from a soft polymer which are inserted into vessels, for example to deliver drugs or medical devices, such as stents. During vascular surgery,

guidewires are inserted and advanced through the vessels to guide the catheter to the correct position in the body. This interaction can cause damage to the vessel wall which contributes to the success of the intervention. Contrary to a stent's stationary application in the body, the application of guidewires and catheters is of a dynamic nature. They move through the body, touching the vessel walls under relative motion. This is schematically shown in Figure 2. After advancing the guidewire into the vessel (Figure 2 a), the catheter is pushed into the vessel, guided by the guidewire (Figure 2 b) and as the vessel goes around the corner, the catheter touches it along contact area $A_{Contact}$ as shown in Figure 2 c). Like the stent, the catheter experiences a normal pressure σ_N by the vessel wall resulting in a normal force F_N and a friction force F_F through the respective surface integrals, but in this case there is only one contact area (Eq. I, $i = 1$). Hemodynamic effects are neglected in this drawing. Contact forces can be expected in the range of 0 N to more than 1.5 N, with forces bigger than 1 N considered critical [4].

F_{Manual} is the force applied by the person carrying out the insertion operation. This force is determined by the parallelogram of forces F_N and F_F. Hence, a higher friction force causes a higher resistance. This resistance could be reduced through the application of friction and lubrication knowledge. In addition to hindering the intervention, the contact between endothelial layer and catheter means risk of damage to the endothelial cells (wear). This could be prevented by using advanced materials.

As catheters are supposed to move relative to the vessel surface most of the time, lubrication will play a more important role for these medical devices than with stents. Good lubrication may make the procedure easier by enabling lower friction. It may also improve safety by reducing the likelihood of complications, as good lubrication is generally associated with wear reduction. Lubrication regimes are described by the Stribeck Curve which connects friction with sliding speed, lubricant viscosity and normal load. While deployed stent friction takes place in the boundary lubrication regime (mostly direct contact of surfaces) due to low speeds, catheters could be pushed into mixed (still surface contact but thin film lubrication is present) or even hydrodynamic (full separation of surfaces by lubricant film) lubrication during movement. Soft tissue contact mechanics govern the interaction between the soft vessel surface and the harder medical device material. Models to describe the contact include: the fundamental Hertzian contact theory [5], the JKR model, the Winkler foundation model and the Derjaguin Muller Toporov model [6]. Modelling the contact could prove essential to determine pressures and understand the interaction better.

2. Cardiovascular Physiology Related to Biotribology

When entering the field of vascular biotribology, it is crucial for tribologists to familiarise themselves with the biological aspects of this field of research to understand the possible connection between friction and disease. The following section shall be an introduction in vascular tissue and its cell structure and functions with a focus on tribologically relevant parts.

2.1. Overall Structure of Blood Vessels: Arteries

Arteries are comprised of three layers where the tunica externa is the outermost layer of the blood vessel (see Figure 3). The tunica externa consists of collagen fibres and scattered elastic fibres. It is responsible for connecting the vessel with the surrounding tissue. The tunica media is the middle layer which contains smooth muscle cells, generally orientated in a concentric pattern, that enables contraction or dilation of the vessel as required. The tunica media is separated from the tunica externa by a band of elastic fibres and connected to the tunica interna by collagen fibres. The tunica interna is the innermost layer. It consists of a thick layer of elastic fibres on the outer perimeter, connective tissue and an endothelial cell monolayer on the inside [7]. The endothelial layer probably plays the main role in tribological interaction with a medical device as it is in direct contact with the medical device surface.

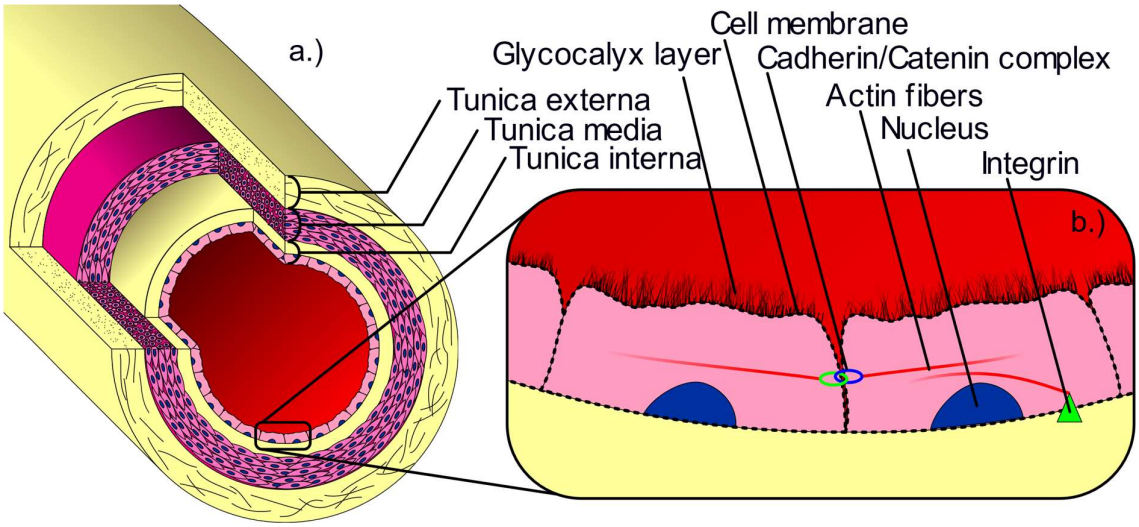

Figure 3: (a) Schematic cross-section view of blood vessel and (b) endothelial cell structure. Not to scale.

2.2. Inner Lining of Blood Vessels: The Endothelium

The endothelial layer is the interface between tissue and blood and permits the exchange of cells, oxygen and other molecules between these entities whilst containing and controlling blood flow. It is composed of a uniform monolayer of endothelial cells, which senses a number of flow characteristics (shear stress magnitude, directionality, frequency) and converts this information into biochemical responses [8][9][10]. For example, the endothelial layer can manipulate the vascular tone of blood vessels by releasing contracting and relaxing factors, depending on the flow's intensity. This vascular tone defines the resistance of blood vessel to flow [11], and regulates overall blood flow and supply to organs. This ability to control blood flow is one of the attributes that make the endothelium a critical component for the proper functioning of the cardiovascular machinery.

The endothelium also plays a key role in maintaining blood flow by controlling blood fluidity. The surface of a healthy endothelial layer is both antithrombotic (limits the ability of blood to clot) and anti-inflammatory (limits the response of the body to an injury, infection or death of tissue usually accompanied by local pain, heat, redness and swelling). These properties are achieved by the emission of molecules that regulate blood coagulation and platelet functions

[12]. When the endothelium becomes diseased or damaged, it shifts towards the emission of procoagulant and prothrombotic molecules [13]. Thus, a diseased endothelium develops blood-clot-promoting features instead of its usual blood-clot-inhibiting features. Therefore, an endothelium that is damaged during procedures involving catheters or stents creates an environment where blood clots could be more likely to form. In the context of stenting, an impaired re-endothelialisation can lead to stent thrombosis, [14].

2.3. The Individual Unit of the Endothelium: The Endothelial Cell

The endothelial layer consists of endothelial cells arranged in a monolayer. An endothelial cell is shown schematically in Figure 3b.

The cellular membrane is vital to the proper function of cells, as it protects the contents of the cell. The cell membrane is made of a phospholipid bilayer. This forms an effective barrier for water and solutes [7]. Specialised components can be integrated into the cell membrane, such as receptors for adhesion to specific ligands, or gate proteins for active/passive migration of molecules. The membrane also connects to the cytoskeleton to give the cell its structural integrity and allow it to withstand external forces.

In the cell membrane, apart from the phospholipid bilayer, relevant components to biotribology include the family of cell adhesion molecules (CAMs), specifically cadherins [15] (anchors between cells) and integrins (anchors to the extracellular matrix). Both Cadherin/catenin [16] and Integrin [17] complexes can connect to actin fibres. Actin fibres are part of the cytoskeleton; the framework of the cell. The cytoskeleton is not only responsible for structural integrity, but it can also be manipulated to allow the cell to migrate by rearranging actin fibres. Integrins act as a receptor mediating mechanical and chemical signals [18][17][8]. Apart from cadherin and integrin, cell adhesion molecules (CAMs) also include selectins and immunoglobulins [19]. Selectins allow tethering of leukocytes to the endothelium, which is necessary to allow leukocyte migration to the relevant site [12]. Adhesion is an important frictional mechanism capable of damage and high friction. As the CAM's purpose is adhesion, and they are the direct interface of the cell to the surrounding environment, they could play a major role in frictional interaction and should be considered when investigating vascular tribology. Any bond or stimulus created by a contacting medical device will affect friction forces and damage inflicted to the cell.

Together, the ECs form the endothelium; a specialised, complex structure not only containing blood flow, but also responsible for the recruitment of leukocytes. Recruitment occurs via secretion of signals that enable leukocytes' adhesion and migration through the endothelial layer[20][12].

The surface of endothelial cells in contact with blood is covered with a fur-like structure called the glycocalyx. The glycocalyx consist of carbohydrates and may be imagined as hairs protruding from cells (compare electron microscope images of Reitsma et al. (Figure 4)). The carbohydrates connect to the membrane with proteoglycans and glycoproteins[21].

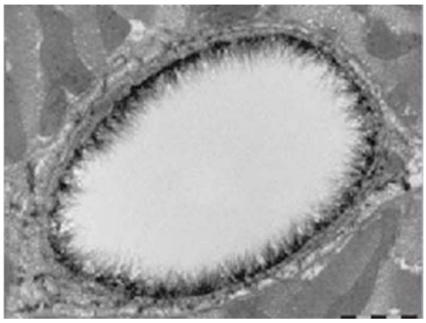

Figure 4: Electron microscopic image of glycocalyx (adapted from Reitsma et al. [21]*)*

Glycocalyx serve a variety of purposes, including determining vascular permeability, influencing blood cell-vessel wall interactions, harbouring endothelial cells adhesion molecules, while also decreasing the adhesion of leukocytes [21]. The glycocalyx are also responsible for shear-sensing and nitric oxide regulation as well as being anti-coagulant. If the glycocalyx are disrupted, this leads to increased platelet adhesion [22]. Tribological relevance of the glycocalyx has been proposed before, when Chen et al. investigated glycocalyx influence on friction [23] and in a recent study by Lin et al. [24]. Just like CAMs, glycocalyx are in direct contact with the interacting medical device. As such, they should be regarded when studying frictional interaction on a microscopic level and interpreting vascular biotribological data.

2.4. Tribology and Endothelial Cells: Friction Induced Effects on Cell Health and Behaviour

The nucleus and the cytoskeleton may be affected by tribological interaction, without being involved in the frictional contact. The process of cells sensing and reacting to external loads is called mechanotransduction. The sensors are called mechanotransductors which regulate genes that in turn affect cell behaviour. Little is known about the specifics of how endothelial cells behave under frictional load. However, studies were conducted to investigate the effects of indentation, substrate deformation, strain and (fluid) shear stress on endothelial cells, which are the main effects occurring during a frictional experiment. These studies can serve as a reference point for what to expect from a tribological interaction.

The nucleus acts as the main memory and control unit of the cell by storing DNA (the cells gene material) and controlling processes, such as protein synthesis and reproduction. In all cells, these functions are crucial for performing the intended tasks of the respective cell. The nucleus is suspected to interact bi-directionally with the cytoskeleton[25]. Tension on the cell can induce a reaction of the nucleus, such as gene expression or DNA damage [26]. Endothelial cells are designed to withstand (hemodynamic) shear stress and high (blood) pressures; in fact, endothelial cells thrive under the influence of high unidirectional shear stress. Shear stress is sensed by a number of mechanoreceptors, including VEGFR2/VE-cadherin/Pecam-1-complex, integrins, the glycocalyx and primary cilia. These receptors regulate many biological responses through signalling pathways including Krüppel-like factor 2, nuclear factor erythroid 2-related factor, nitric oxide and MAPK phosphatase-1. In general,

high unidirectional shear stress on endothelial cells leads to a protective phenotype promoting quiescence and a healthy endothelium. A low and/or oscillating shear stress can cause the endothelial cells to become pro-inflammatory, apoptotic, more proliferative, pro-thrombotic or unable to regulate vascular tone [27]. *In* vivo, these mechanisms are responsible for vascular remodelling via smooth muscle cells which are sensitive to stretch and ECs which are sensitive to stretch and shear stress [28]. However, stresses could exceed a healthy threshold during frictional interaction. Normal and shear forces affect EC cytoskeleton modelling and signalling pathways and therefore may induce functional and structural changes [29] which can result in disease. Further studies indicating that friction affects endothelial behaviour include Pitenis et al., who have shown that friction can induce inflammation (on epithelial cells) [30], and Dawson et al. who concluded that coated and uncoated catheters alike affect flow mediated dilatation [31]. Considering these studies and the close connection between a healthy shear stress and a functioning endothelium, it should be explored if and how frictional interaction directly interferes with healthy gene expressions and signalling pathways causing ECs to malfunction, linking device friction to physiopathology (connection between physiology and disease).

The cytoskeleton consists of actin fibres, microtubules and intermediate filaments. It can be imagined as a network of ropes and pipes going from one location at the cell membrane to another, enabling the cell to apply forces on the cell membrane. The cytoskeleton can be remodelled in reaction to changes in the environment.

Actin fibres are the main contributors for cell contraction. They can be imagined as ropes going from one location at the cell membrane to another. Myosin motors can move on the actin fibres to allow for cell motility. In quiescent endothelial cells, actin fibres are responsible for structural support[32][33]. When exposed to shear stress, endothelial cells remodel their actin fibres to align with the direction of shear stress to resist the external load [34][35][36]. Therefore the cytoskeleton acts as a bridge between the extracellular and the intracellular domains [37]. Hence, when the cell experiences friction induced shear stress, the external forces must be equal to the internal forces; the cytoskeleton takes the main load. If the cytoskeleton fails under that load or cannot adjust quickly enough to the change in environment, this could cause the cell to tear apart and be destroyed.

When it comes to studying the effects of tribological interactions on endothelial cells, the cytoskeleton and the nucleus should be considered as interacting units. The cytoskeleton transmits forces to the nucleus at a much faster pace than would be expected for biochemical messengers [38][39]. The nucleus then reacts to the sensed change of environment with cytoskeleton remodelling and gene expressions. This might cause ECs to dysfunction, leading to complications.

3. Relevance and Importance of Vascular Biotribology

The purpose of this review paper is to present biotribology research relevant to all endovascular medical devices such as stent retrievers and other mechanical thrombectomy

devices (devices used to remove blood clots blocking arteries) and more advanced devices like HARP, a snake-like robot that can be inserted into blood vessels [40]. The review will however, focus on research carried out on stents and catheters, as they are the most established and common devices. Stents are thin-walled pipe-shaped mesh structures whose function is to keep a vessel open (using mechanical pressure). Catheters for vascular applications are polymeric tubes of varying flexibility deployed in the body to achieve multiple functions: deliver stents or stent retrievers to a location or to remove or inject fluids like medication or blood. Despite the obvious physical interaction with blood vessels, the tribology between vascular medical devices and the human body is poorly understood up to this date.

3.1. Importance of Tribology on Stents

In vascular applications, most commonly, stents are folded around a balloon catheter which is then inflated inside the stenosed (constricted) vessel to revascularize it (re-establish flow). Other designs include self-expanding stents made from shape memory alloys. During catheter/stent deployment, these devices induce friction and radial forces, causing damage to the blood vessel in two ways: 1) the arterial wall can be overstretched and thus injured; 2) the endothelium can be damaged or removed due to friction [41]. Overstretching is caused by too high pressures while the friction damage to the endothelium is a tribological problem.

Damaged endothelium is known to be a leading cause of failure by restenosis (a re-constriction). Restenosis can necessitate a new revascularisation procedure or cause late stent thrombosis [42]. The reason for this is that the natural reaction of the body to the damage is very similar to wound healing, including steps of blood clotting, inflammation, and recruitment of new cells by proliferation [43]. Marx et al. reviewed the restenosis progress under consideration of smooth muscle cell (SMC) proliferation (multiplication) [44]. Normally, SMCs are kept in a quiescent state where they do not divide or migrate. This is important because uncontrolled growth would decrease the blood vessels lumen. However, they can be activated to switch into a proliferative and migrative mode to repair the vessel after injury. Although this is meant to be a recovery mechanism, it can be disadvantageous as, in a stented artery, this can cause restenosis. The factors that lead to the activation include growth factors, cytokines (proteins involved in cell signalling) and reduced inhibitory factors. Under normal circumstances, the healthy endothelium protects from circulating growth factors by acting like a barrier and producing factors that inhibit SMC proliferation and migration. To counter the harmful proliferation of SMCs, drug-eluting stents can be delivered using medications that inhibits intimal proliferation [44]. Cornelissen et al. reviewed the harm caused by stenting and state that the re-reendothelised tissue is often still incomplete or dysfunctional which promotes in-stent thrombosis and restenosis [45]. Therefore, damage and de-endothelisation caused by tribological interactions, must be studied with the aim to minimise or avoid damage to the endothelium. Instead of treating the symptoms, biotribology could be applied to further understand the interaction and prevent the root cause of restenosis, the destruction of the endothelium.

After the stent has been deployed, natural deformation of the vessel due to the cardiac cycle can also cause rubbing and friction between the stent and the arterial wall. This might cause further damage or irritate the endothelial cell layer. The endothelium tries to repair itself and, in the process, can cover the stent struts [46]. As the new endothelial cells may be damaged, this can lead to the formation of stent thrombi[47]. Once the endothelium is damaged, the aforementioned chain of events leading to restenosis can be activated. Furthermore, an inflamed cell layer can cause atherosclerosis [48].

As a damaged endothelial layer causes restenosis and in-stent thrombosis, these two diseases can be minimised by reducing the damage caused to the endothelial layer when the stent surface is interacting with it, both in the deployment and the deployed phase. Tribology could help to assess and minimise the wear damage caused to the endothelial layer due to the understanding of the underlying friction mechanisms these studies provide. Tribological studies will also help to develop materials that can allow to produce less invasive stents.

Another complication connected with stents is migration. Migration happens after a stent is deployed if the hemodynamic force of the pulsating blood is higher than the friction force between the stent and the vessel wall. Understanding and optimising friction could help to make stents that have less risk of migrating.

3.2. Importance of Tribology on Catheters

When a catheter is inserted into a blood vessel, it inevitably touches the vessel walls and could damage the endothelium in the process. This can disrupt the critical functions of the endothelium and could therefore lead to complications like restenosis. An enhanced catheter surface could reduce the risk of injury during insertion. Furthermore, a low-friction catheter might make the procedure simpler and therefore safer overall [49][50]. Some catheters, such as intravenous catheters, can stay at the same location after insertion. However, when the patient moves, the catheter may interact with the vessel, resulting in irritation. A recent study from Takahashi et al. investigated the effectiveness of reducing mechanical interaction between intravenous catheters and vessels in order to reduce catheter failure at peripheral intravenous applications. This study shows that reducing interaction could help to lower the risk of catheter failure [51]. Interaction between current catheter materials and blood vessels can cause problems, which can be mitigated by avoiding this interaction. However, the method outlined by Takahashi et al. required scanning and analysis of vein diameters, a procedure for which there may not always be time. An alternative approach would be to develop materials which even when contacting the artery would not cause major damage. This would eliminate the necessity for expensive and time-consuming scanning procedures and hence make the intervention cheaper, quicker, and more accessible.

3.3. Conclusion

Some of the complications caused by vascular medical devices which inherently interact with the blood vessels are of a tribological nature. This becomes obvious when looking at these complications in the context of the very basic concept of tribology: friction, lubrication and wear. The problem of stent migration and difficult catheter deployment can be traced back to an insufficient and an excessive (static) friction coefficient, respectively. Blood can be considered as lubricant in vascular tribological interactions, yet its role has not been explored sufficiently. The serious implications of restenosis are ultimately caused by damage, or wear of the arterial wall, making tribological studies necessary.

Therefore, in conclusion, it is important to source and develop methods that allow for the study of vascular biotribological interaction. A deeper understanding on both macro and microscale could then allow for quicker development and discovery of new, promising and less invasive materials, coatings or surface treatments, ultimately making the intervention with stents and catheters less invasive and safer.

4. Studying Vascular Biotribology: The Different Approaches

Friction studies on the interaction of medical devices with tissue have been conducted using a wide range of techniques with varying complexity and realism in terms of their emulation of the real system. Tribological experiments can generally be categorised into five major categories of increasing complexity. Each of these categories has advantages and disadvantages. More complex studies usually promise to have a greater significance and more representable results at the cost of reproducibility and financial and time commitments. The five categories in order of increasing complexity are models (using artificial materials as surrogate for biological tissue), *in vitro* (in a petri dish), *ex vivo* (tissue extracted from an animal), *in vivo* (in a living animal) and medical studies. Furthermore, *in silico* (on a silicon chip, computer) models can help to simulate interactions without requiring physical resources apart from a computer. This section of the review divides experiments into categories based on the environment of the testing apparatus: models, *ex vivo*, *in vitro*, *in vivo* and *ex vivo,* and *in silico*.

4.1. Models

Experiments conducted simulating the vessel tissue with a supplement such as a hydrogel but without biological components are called models in the context of this review paper. By simplifying the system that they mimic, models provide more control over the variables. Hence, experiments of this type tend to be more reproducible than the more complex ones and are better at evaluating the influence of specific components. Instead of starting with a complex system and then simplifying it until the experiment is controllable and reproducible, this type of experiment can be seen as a starting point for a different approach where complexity is added as needed. The downsides of these experiments are that it can prove difficult to find materials that match the exact behaviour of biological tissue. Also, because realistic behaviour needs to be verified, experiments involving real tissue are inevitable. One

of the biggest disadvantages of these experiments is that cell damage and behaviour cannot be investigated. However, models can be used to gain initial insights as they are cheap and quick to set-up.

Ho et. al. investigated uncoated and poly(MPC-co-BMA) coated PU catheters regarding friction against an AFM tip and surface roughness under wet and dry conditions. While no significant difference could be observed under dry conditions, significantly decreased surface roughness and friction forces were observed under wet conditions [52].

4.2. In vitro

Classically, in *in vitro* experiments, cells are cultured on polystyrene or glass. This type of experiment has the advantage of using biological components in a controllable environment, hence they are closer to reality than models. However, the mechanical parameters of the substrate (polystyrene or glass) do not match the ones of the real tissue which leads to pressures that are unrealistically high. To avoid this disadvantage, alternative, soft materials can be used as a substrate, such as hydrogels. The hydrogel approach allows an approximation of *in vivo* mechanical parameters of the ECM and thus low, more realistic pressures occur than when cells are seeded on polystyrene or glass. Those studies allow for the examination of cell damage depending on the normal pressure, as it can be estimated using Hertzian contact theory or simulations. A disadvantage of most *in vitro* experiments is that they usually do not include the use of the natural lubricant in blood vessels that is blood itself. It is known that blood is a complex suspension of cells in a liquid and has viscoelastic properties [53]. Given the major influence of the lubricants properties in tribological systems, especially in (elasto)hydrodynamic lubrication [54], it may be worth investigating further the blood's influence on vascular tribological systems to replicate the real situation. *In vitro* experiments allow researchers to investigate which parts of the cells react to friction and could possibly be exploited to fine tune friction coefficients.

In 2010, Chen et al. investigated the influence of the glycocalyx on HUVEC (human umbilical vein endothelial cells) friction[23]. Cells were treated with TGF-β_1 to increase the glycocalyx by 148 % or heparinase I to decrease the glycocalyx by 57 %. They found that heparinase I treated cells experience higher frictional stress than non-treated cells which experience higher frictional stress than TGF-β_1 treated cells. This study suggests that glycocalyx play an important role in reducing friction. While they draw the connection to friction between red blood cells squeezing through capillaries, the glycocalyx could influence friction between medical device and artery. This study is a good example of how *in vitro* experiments can be used to investigate tribological effects of different cell parts. Pitenis et al. demonstrated the potential of *in* vitro experiments to study biochemical reaction of cells to friction as they detected inflammatory markers after conducting tribology on epithelial cells *in vitro*[30]. Marshall et. al. developed a spherically capped hydrogel probe that allows the application of load independent contact pressures for low deformations [55]. While this probe shape is not suitable for all materials, this technique may be used for some catheter materials.

A lot of research has been conducted on the friction between corneal epithelial cells and hydrogel materials to improve the interaction between the human eye and contact lenses. Established techniques of this research field [56][30][57] could be applied to vascular biotribology.

4.3. Ex vivo

Ex vivo experiments are carried out on tissue that is removed from the animal and then mounted onto a tribometer allowing a precise measurement of normal and friction forces under realistic parameters. These experiments are a compromise between being close to the real tribological system while still allowing the measurement of friction and normal forces which proves difficult in *in vivo* experiments. After the experiment, the sample can be examined for cell damage. The main disadvantage of this type of experiment is that removing the substrate from the body causes relaxation due to the lack of blood pressure. Hence, the material behaviour may differ from when before the substrate is removed from the body.

Takashima et al. used an universal tester to determine friction coefficients between a porcine aorta and a steel ball [50]. The universal tester allows changes in the initial angle between the aorta surface and the horizontal plane. The study suggests that static and dynamic friction coefficient depend on this angle.

4.4. In vivo

In vivo studies are carried out by inserting a medical device into a living being and examining cell damage by removing the affected tissue after the experiment. A limitation of this approach is the difficulty to measure the exact normal and friction forces. Pull-out forces can be measured to obtain values for the friction component, but the normal component is difficult to measure.

Capron et. al. investigated the damage a balloon catheter causes to the artery during so called “soft” (inflating the balloon with 0.05 ml of water) and “hard” (0.09-0.11 ml inflation) friction, quantifying the severity of the interaction in ml injected into the balloon catheter rather than in normal pressure [58]. It was found that “hard” friction removes the whole endothelium while “soft” friction can leave parts intact. As established earlier, a dysfunctional endothelium can cause problems in the form of thrombosis or stenosis. While the approach of quantification in the form of measuring added volume is pragmatic, reporting the pressure in the catheter would allow for more comparable results.

4.5. In silico

In silico studies have been conducted to estimate friction between cells and medical devices. This approach yields the opportunity to simulate the interaction between blood vessel and materials used for medical devices with no physical testing. Rather, a computer

model/simulation is built and verified using a given data set. Then parameters for different materials can be inputted to the model and results can be obtained much quicker than with physical testing. Advanced models also include the influence of blood as lubricant. These models could possibly be developed further to estimate cell damage. Simulations rely on being verified by experiments and the availability of the mechanical properties of the material of interest. If this data exists, simulations present a quick way of predicting the experiments outcome without needing anything but a computer.

Vad et. al. approached the evaluation of the friction coefficient between a stent graft and a PDMS tube and developed a computer model to simulate the contact finding that oversizing can increase the friction coefficient and hence reduce the risk of the stent graft to migrate [59]. Prokopovich and Perni investigated the friction coefficient of catheters against sheep artery and vein tissue using a JKR theory based model they developed that predicts the friction force between tissue and biomaterials based on the material parameters and asperity density. They reported that the predicted forces agree with earlier obtained experimental values [60]. Then they developed the model further so that it can account for different asperity shapes and the presence of blood as a lubricant [61]. Prokopovich and Perni's simulated results matched well with experimental data and they found that friction between catheter and vessel is mainly dominated by adhesion effects.

While experiments simulated *in silico* are not able to reflect the real world interaction perfectly due to its complexity, they have a lot of potential and could be used to highlight promising materials that could then be tested in the real world using *in vitro*, *ex vivo*, or *in vivo* experiments.

5. Present State and Impact of Experimental Findings

This section gives an overview over the results of past vascular biotribology studies and their relevant context, as well as recommendations for future studies.

5.1. Biotribology for Catheters

For tribology on catheters, two factors should be considered. First, damage caused by frictional interaction between the surfaces on a cellular level should be avoided and secondly, the friction coefficient should be as low as possible to allow for a quicker and gentler intervention. Classically in tribology, low friction and low damage are linked and it has been shown that lower friction catheters cause less damage in rabbit arteries [62]. Higher frictional forces have been reported to cause inconvenience to the patients during the deployment of the catheter [50].

During deployment, catheters can interact with cells by dragging or removing them from the surface. Dellimore et al. [63] observed high complications with high morbidity (such as mechanical traumata) following the mechanical interaction of urinary catheter and urethra. A review by Dellimore et al. [64] has shown that transcatheter cardiovascular intervention

often results in complications that can be linked to mechanical interaction between vessel wall and catheter. Those complications include vascular trauma, haemorrhage and arterial spasm. The prevalence of those complications can be reduced by passive catheter design strategies including surface topology and material design to reduce friction. This study has shown that while some procedures, such as percutaneous coronary intervention, were very mature (i.e. plateauing or decrease of complication prevalence) at the time of the review, other types of vascular intervention, such as transcatheter aortic valve implantation and endovascular aneurism repair, still yielded potential for improvement.

Lowering friction of catheters has been investigated regarding polymerization [49], hydrogel coatings [65], and polymer coating materials [62][52]. Ho et al. also suggest a further investigation into the contact between endothelial cells and polymers with a focus on cellular adhesion molecules and damage caused to the cells [52] which is supported by Prokopovich et al. simulations suggesting that adhesion plays a major role in the interaction [60]. Niemczyk et al. investigated friction of chitosan coated catheters and compared them to commercially available coated ones using an *in vitro* system. They found that (chemically modified) chitosan coatings act as lubricous coatings - frictionally comparable to hydrogel coatings - while coming with additional advantages as they are biodegradable and antimicrobial [66].

Weiss et al. simulated catheter-vein contact to investigate thrombophlebitis (sterile inflammation with formation of a blood clot) [67], a common complication with intravenous therapy [68]. Hydrophilic-coated catheters were reported to cause less trauma than uncoated catheters and were preferred by patients according to Stensballe et al. [69]. Additionally, a recent study by Lin et al. revealed that a hydrophilic coating reduced wear to the glycocalyx [70]. The findings of Weiss et al.,Stensballe et al. and Lin et al. are particularly interesting considering the recent studies of Pitenis et. al. who found that friction can promote inflammatory gene expressions [30] as an anti-inflammatory phenotype is one of the key features of ECs. As mentioned earlier, shear stress is sensed by ECs by a number of mechanoreceptors and an inappropriate shear stress can cause endothelial cell dysfunction which can lead to more severe complications which, hitherto, seems to affect catheter physiopathology. Even modern, hydrophilic coated catheters, while coming with the advantages of increased patient comfort and reduced spasm incidence, were not found to positively influence endothelial dysfunction and radial occlusion. This suggests that the current reduce in friction alone is not enough and more in-depth understanding is required to tackle the latter two complications [71].

Dellimore et al. investigated Attenuated Total Internal Reflection Fourier Transform Infrared (ATR-FTIR) spectroscopy for quantification of catheter-induced tissue damage *in vivo* using an *ex vivo* set up on porcine aortic tissue. They found clear changes in the resulting FTIR spectra; Most notably damage to the outermost layer of the aorta changed the spectrum significantly, making ATR-FTIR a promising tool for future wear assessment of catheter induced damage. Furthermore, they recorded the friction coefficient during the controlled tissue damage testing and found that friction of catheters on aorta is a function of wear. The friction coefficient they measured was between 0.05 and 0.25, decreasing with consecutive sliding

(representing different complexities of catheter intervention) of the catheter, which was attributed to increasing wear [72].

Much work has been done to improve catheters making them safer to use and more comfortable for the patient. Future experiments to improve catheters should be carried out with the aim to be comparable, meaning that the severity of the frictional interaction should be quantified in reproducible parameters, for example by mentioning the normal pressure and relative speed between the surfaces, the frictional force and the geometry of the probe. The interaction between current catheter materials and the human body is not sufficiently understood and optimised up to this point and investigating it further could yield great potential.

5.2. Biotribology for Stents

This section reviews the insights we have gained into the tribology of stents. When discussing biotribology for stents, two phases should be considered, deployment and stationery. During the deployment phase, damage to the endothelium occurs due to interaction of vessel wall and stent, which can be so severe that the endothelium is entirely removed from that region. This is wear damage. Hence, in this phase, the wear aspect of tribology is in the focus and it is linked to in-stent thrombosis and restenosis as established earlier. The second phase is the deployed stage of the stent. While wear in form of constant irritation due to blood vessel interaction must be considered again, the friction aspect takes a significant role in this phase. This is because stent migration in its core is a (static) friction related problem. Both phases must be considered when conducting tribological experiments on stents.

During the deployment phase, wear plays a major role while the coefficient of friction is secondary. Hence, experiments that focus on cell damage/tissue damage and biological reaction are important. Franke et al. used a special apparatus to assess endothelial cell reaction on stenting *in vitro*. In their experiment, a stent mounted on a balloon catheter was pressed in between two surfaces that were cultured with endothelial cells. The balloon catheter was inflated with a pressure of 9 bar. Afterwards, the stent was removed. Nitric oxide, prostacyclin and lactate dehydrogenase were measured. A significant decrease of nitric oxide, which is responsible for down regulation of platelet aggregation, was found [73]. As increased platelet aggregation promotes thrombosis, this makes sense considering in-stent thrombosis is a common complication with stents. Dunn et al. conducted tests with a glass pin on bovine aortic endothelial cells. They drew a connection between damage to the endothelial layer caused by stent deployment and stent migration under the influence of pulsatile blood flow. Dunn et al. also found that pressures around 5 kPa were required to cause significant cell damage [74].

In the deployed phase, there could still be damage or irritation caused by long term interaction between stent and vessel wall. This is supported by a study conducted by Pitenis et al. focusing on biochemical responses during the interaction between hydrogel and epithelial cells which increased the expression of pro-inflammatory genes as observed by Pitenis et al. [30]. Although epithelial cells were used rather than the inner lining endothelial

cells, this shows that friction can cause inflammation. Similar experiments must be conducted on endothelial cells and if endothelial cells also show signs of inflammation as a reaction to friction, it should be investigated what causes the inflammation and if advanced materials could reduce it. However, as quantitative knowledge about the interaction in this phase (pressure and relative speeds) is very scarce, it has been difficult to study tribology of deployed stents up to now. Hence, before conducting such experiments, it is crucial to find reliable values for the required mechanical parameters, for example by means of finite element simulations.

However, during this stage, the CoF plays a major role. Chen et al. studied the friction between aortic stent grafts against porcine aorta, PDMS and PVA cryogels. They reported an average friction coefficient of 0.0328 to 0.0540 for a material pairing of porcine aorta/stent graft sheath [75]. McGee et al. researched the effect of calcification on tissue-stent interaction. They found that calcification significantly increased the coefficient of friction from 0.09+/- 0.05 up to 0.35 +/-0.015[76]. Dean et al. investigated friction on smooth muscle cells using Lateral Force Microscopy. They report a friction coefficient of 0.06 [77]. All of these friction coefficients are very low and increasing the friction coefficient would likely lead to a decreased likelihood of the stent migrating. According to Liffman et al., the force exerted on the stent-graft by the blood flow may exceed the force needed to displace it [78]. Certain frictional interactions, hooks and barbs and stent-graft oversizing are used assist to keep stent-grafts in position [59]. Furthermore, reliable values for the friction coefficient are required for advanced finite element modelling of stents and stent grafts [59][79].

Hence, in the context of stents, the effect of friction coefficient and damage caused must be studied very carefully. Generally, in tribology, a higher friction coefficient is associated with higher damage. On the other hand, a low friction coefficient could promote stent migration which is undesirable. Therefore, in-depth studies of the underlying friction mechanisms are necessary to find out if there is an inherent parity between damage and CoF and if not, how a sufficiently high CoF can be obtained while reducing the damage caused to the endothelial layer.

6. Conclusion

Conclusively, it can be said that vascular intervention with stents and catheters can cause significant damage on a tissue level, which can lead to severe diseases such as thrombosis and atherosclerosis. Furthermore, it can interfere with a healthy endothelium's cell mechanics and cause endothelial dyfunction. To avoid these diseases, mechanisms between endothelial cells and medical devices must be exploited to develop better materials for the future. It can also be used to improve numerical simulations of interventions. Studies have been carried out to investigate cell damage and friction coefficient, but few have quantified the damage in a comparable way and studied the contact interactions in-depth.

Many studies use a glass bead as probe, but to obtain real contact conditions and to assess friction and wear reliably, it is necessary to use real material pairings. Chemical interaction

between the two surfaces appears even more important considering the finding of Prokopovich et. al. that adhesion is the driving factor in friction between catheters and arteries. Therefore, more research should be carried out regarding cell reaction on mechanical interaction and friction using real medical device materials such as stainless steel, Nitinol and different polymers.

An optimized workflow to improve medical device materials would include an *in silico* model, as well as *in vitro*, *ex vivo* and finally *in vivo* experiments. First, a simulation, that would ideally be able to simulate cell damage, would be carried out using a material database to scout for suitable materials. Materials that are deemed to be promising could be used as probe materials in *in vitro* studies on cultured monolayers to examine their compatibility under friction. *In vitro* studies should evaluate cell viability, inflammatory markers and coefficient of friction and parameters may need to be adjusted for different applications (stents, catheters). Results need to be compared and verified with *ex vivo* and finally *in vivo* studies.

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9. Appendix

9.1. Overview of Studies Conducted

Category	Year	Study	probe material	sample material	Lubricant	measurement technique	outcome
Models	1991	Uyama et. al. [25]	Polymerized ethylene-vinyl acetate copolymer film	Glass, PVC	Water	Pullout force from PVC tube, slide against silicone elastomer sheet	Pullout force reduced to 0.5 N from 10 N by polymerization
	2003	Ho et. al. [27]	AFM tip	Coated and uncoated	Water	AFM	Coating with poly(MPC-co-BMA) significantly

				PU catheter			reduced friction and surface roughness
in vitro	2010	Chen et. al. [12]	(TGF-β_1 / heparinase I-treated) HUVEC on PNaSS gel	Glass or HUVEC on PNaSS gel	Cell media	Rheometer. Static loading, followed by constant angular speed (rotating motion)	Glycocalyx play an important role in friction and are suspected to reduce friction
	2018	Pitenis et. al. [8]	PAAG (hydrogel)	hTCEpi (corneal epithelial cells)	Growth media	Custom microtribometer (sliding motion)	μ = 0.019 ± 0.005 (low pressure), μ = 0.026 ± 0.006 (high pressure). High friction stresses increased inflammatory gene expressions
in vivo	1989	Capron and Brunev al [21]	Balloon catheter	Rat thoratic aorta	Blood	Application of a balloon catheter in "hard" and "soft" friction regimes in rats.	"Hard" friction removes whole endothelium while "soft" friction leaves parts intact
ex vivo	2007	Takashi ma et. al. [22]	Steel ball	Porcine aorta	Physiological saline solution	Universal tester and indenter assembly	Mean μ_d = 0.046.
in silico	2010	Prokop ovich et. al. [29]	Silicone elastomer and PU (Catheter materials)	Lamb aorta and vena carva	None	JKR theory based asperity model with a Monte Carlo Method.	Adhesive friction dominant (over viscous and deformational). Modelled friction coefficients agree with experimental data
	2013	Prokop ovich et. al. [30]	PVC	Pork aorta	Horse blood	JKR theory based asperity model with a Monte Carlo Method.	Extension of the model in [29]. Integration of differently shaped asperities and blood in the contact.