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Surface Coatings for Ventricular Assist Devices

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Abstract
This review focuses on the surface engineering of ventricular assist devices (VADs) for treating heart failing patients, which involves modification of the blood contacting surfaces to improve the blood compatibility (or heamocompatability) of the VADs. Following an introduction of the categorization and the complications of ventricular assist devices, this review pays attention to heamocompatability, applications, and limitations of six types of surface coatings for ventricular assist devices. The six types of surface coatings are: (1) titanium nitride (TiN) coatings, (2) diamond-like carbon (DLC) coatings, (3) 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer coatings, (4) heparin coatings, (5) textured surfaces, and (6) endothelial cell lining. In particular, diamond-like coatings and heparin coatings are more commonly used than others for VADs due to their excellent haemocompatibility, durability, and technical maturity. For high performance and long lifetime of VADs, surface modification with coatings for haemocompatibility is as important as the mechanical design of VADs.

Keywords: ventricular assist device, surface coating, haemocompatibility, heparin, textured surface, endothelial cells.

1. Introduction

Despite a great advance in cardiovascular therapies over the past decade, congestive heart failure due to left ventricular systolic dysfunction remains a significant healthcare problem [1]. For patients with end-stage heart failure, treatment options are extremely limited; cardiac transplantation is currently the treatment of choice, but it is limited by the shortage of donor supplements [2]. This shortage has led to the development of ventricular assist devices (VADs; blood pumps) as an alternative therapy to support the failing heart in seriously ill patients with the end-stage congestive heart failure [3,4]. Nevertheless, the interactions between the blood and the surfaces of the biomaterials cause complications of VADs such as thromboembolism, bleeding, and infection.

Thus, the selection of biomaterials for the blood contacting surfaces for VADs is an important factor. To improve the haemocompatibility of VADs, early efforts were in the selection of haemocompatible bulk biomaterials (not coatings). Among several available biometals,

titanium and its alloy are commonly used for VADs due to their excellent biocompatibility, fair haemocompatibility, and low cost. On the other hand, polyurethane is one of the potential polymers for blood-contacting applications as it has excellent mechanical properties and good biostability. However, currently used bulk biomaterials for blood contacting applications are far from ideal in terms of the blood compatibility and it seems that the potential for haemocompatible bulk biomaterials has been fully explored.

The limited haemocompatibility of bulk biomaterials has led to attention of surface coatings or surface engineering in order to reduce the complications such as thrombosis, infection, etc [5]. It has been shown that surface coatings on bulk biomaterials for VADs are effective for the mitigation of the complications. The surface coatings for VADs have evolved from organic/ inorganic (passive) coatings to bioactive coatings (e.g. biomolecule coatings, and cell-based coatings). Based on the commercial applications and the potential of the coatings, this review will focus on the following six types of coatings: (1) titanium nitride (TiN) coatings, (2) diamond-like carbon (DLC) coatings, (3) 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer coatings, (4) heparin coatings, (5) textured surfaces, and (6) endothelial cell lining. Obviously, type (1) and type (2) coatings are inorganic coatings, type (3) coating is an organic coating, and type (4) to type (6) coatings are bioactive coatings. The coatings of type (1) to type (5) are used for VADs by most manufacturers, whereas cell-based coatings (type (6)) are still in their early stage of research and development.

2. Ventricular assist devices

Ventricular assist devices (VADs) were born out of the need to support clinically deteriorating patients for whom organ shortage precluded immediate transplantation. Current implantable left ventricular assist devices (LVADs) (Fig. 1) adequately support the blood circulation. Miniaturized ventricular assist devices promise to offer children the same improvement in survivability and in the quality of life as adults [6]. Today, with the advance in technology and with more clinical experience, the majority of patients supported with ventricular assist devices are discharged from hospitals and approximately 70% of them survive till heart transplantation [7].

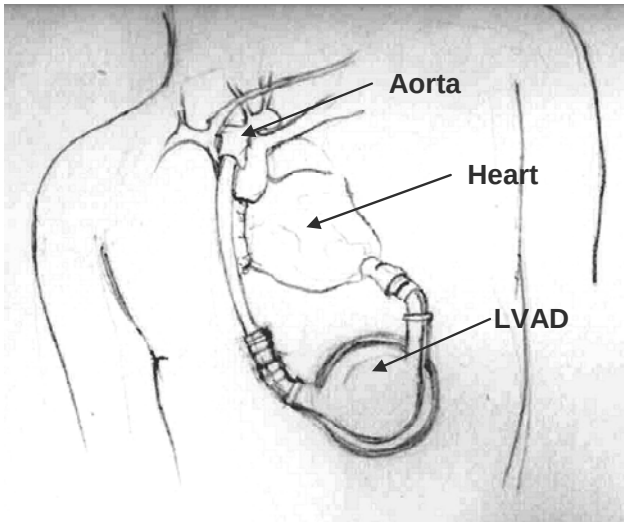

Fig. 1. An illustration of a left ventricular assist device (LVAD) [8].

The tremendous impact of heart transplantation on the development of mechanical circulatory support devices is apparent from the increasing utilization of VADs. In fact, the proportion of patients supported by mechanical devices at the time of transplantation has increased from 2% in 1990 to over 16% in 1997 [9,10]. VADs are now used to treat patients with terminal heart failure not only as a bridge to transplantation but also for a bridge to recovery in certain carefully selected patients. More recently a strategy of combining LVAD support with pharmacologic therapies has been developed to produce maximal reverse remodeling. Briks et al. [11] reported that with the use of a specific sequence of mechanical and pharmacologic therapy, approximately 75% of the patients who received a full course of the combination therapy recovered.

2.1. Classification of ventricular assist devices (VADs)

VADs can be categorized by the mechanical action (pulsatile vs. continuous flow), or by the implantation site (intracorporeal, paracorporeal or extracorporeal) [12]. Pulsatile devices were the first pumps [13] used clinically and hence are often referred to as the first generation pumps. They are large and have multiple moving parts. The second generation continuous flow pumps [14] can be miniaturized and have a single moving part. Their possible small sizes allow exclusive intracorporeal placement. The third generation pumps are magnetically levitated (bearing-less) [15] and are generally in preclinical studies [16]. However, the VentrAssist and the Incor VADs as two types of the third generation pumps are already in clinical use. The present trend in the third generation pumps is toward long-term nonpulsatile artificial hearts [17]. The characteristics of some types of VADs are outlined in Table 1, whereas the surface coatings of the VADs are also shown.

Table 1 Characteristics of some left ventricular assist devices (LVADs)

Device	Manufacturer	Mode of blood flow	Features	Blood-contacting surface	Ref.
DeBakey VAD®	MicroMed	Continuous flow	Second-generation blood pump, with an axial rotor supported by ceramic bearings	Polished titanium surface	[18]
EVAHEART® LVAD	SunMedical	Continuous flow	Second-generation blood pump, and a compact centrifugal blood pump	2-methacryloyloxyethyl phosphorylcholine (MPC) polymer coating	[19]
Heartmate® II	Thoratec	Continuous flow	Second-generation blood pump, with a rotary and axial flow	Textured/smooth surface combination	[20]
INCOR®	Berlin Heart	Continuous flow	Third-generation blood pump, with a magnetically suspended axial flow rotor	Heparin-coated surface (Carmeda® coating)	[21]
VentrAssist™ LVAD	Ventracor	Continuous flow	Third-generation blood pump, with a magnetically suspended centrifugal rotor	Diamond-like carbon (DLC) coating	[22]

As an example, the VentrAssist LVAD (Fig. 2) is a novel centrifugal pump with a hydrodynamically suspended rotor**.** This device shows promise for use in end-stage heart

failure for permanent implantation or bridge to transplantation. The design allows blood to flow through the center of the rotor and over its outer surface, thus maximizing washing of all blood-contacting surfaces without areas of stasis, flow obstruction, or retrograde flow. Thrombosis has been minimized by the application of DLC coatings on the blood contacting surfaces of the pump [22,23].

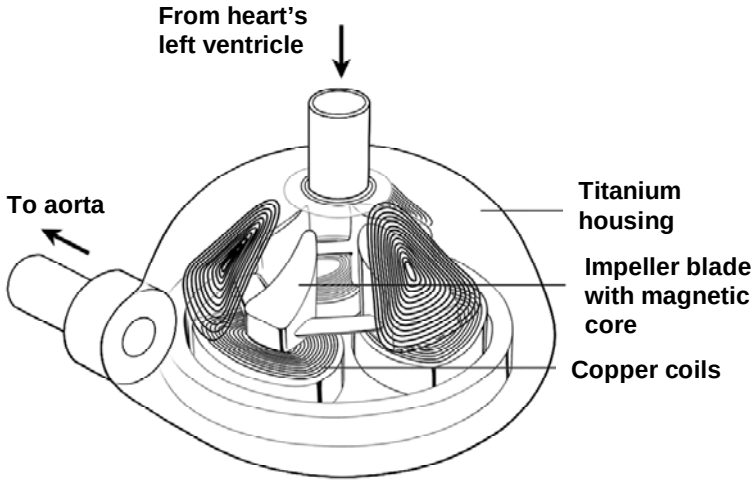

Fig. 2. VentrAssist^{TM} LVAD [22] (Permission for the use of the copyrighted material has been granted).

2.2. Complications of ventricular assist devices (VADs)

Early experience with LVADs showed that the hematologic responses of VAD recipients were affected by the contact between the blood and the foreign materials. In particular, thromboembolism, bleeding, and infection remain major complications of VADs [24,25]. Thromboembolism involves the formation of a blood clot through the activation of thrombin. Once thrombin has been activated it activates platelets that lead to a coagulation cascade of the blood. The severe thromboembolism will bring stroke or extremity ischemia, and therefore requires pharmacologic systemic anticoagulation. Hence, many heart pumps require an anticoagulant or an anti-platelet agent to prevent thrombosis. The use of a systemic anticoagulatnt for VADs is related to the incidence of bleeding complication. It is a major clinic challenge to make a safe balance between the coagulopathy and the thrombus formation. Infection is also considered by physicians and investigators to be a major and potentially devastating complication in VAD patients. Infection is directly responsible for the death of 10-15% of bridge-to-transplant VAD patients. The infection rates from drivelines, cannulas, and from the VAD pocket tend to fall in the 20-30% range [24]. A potential solution to the above complications is the development of surface coatings that are passive to thrombin and blood clot, or are able to release an anticoagulant in a controlled manner in a local site rather than through the whole human body, and/or are capable of incorporating an antibacterial agent. Although cellular coatings on VADs are less susceptible to infection [26], they are still in their early stage of research and development.

3. Haemocompatible surface coatings for VADs

Improvement in the anticoagulation behaviour can be achieved with passive or active surface coatings. Passive coatings (e.g. TiN, DLC, and MPC) serve as a barrier between the bulk

material and the blood, while active coatings (e.g. heparin coating, textured surface, and endothelial cell lining) directly interact with the blood or interfere with the process of intimal proliferation [27].

3.1. TiN coatings

Titanium and titanium alloy were originally used for bone implantation where they turned out to be superior to other metals due to the good integration into bone. With the aim of improving the fretting resistance of the titanium alloy surface by increasing the surface hardness, titanium nitride (TiN) coating was developed [28]. TiN coatings made by physical vapor deposition or chemical vapor deposition have also been widely used for industrial applications such as cutting tools for a long period of time [29]. The suitability of TiN coatings for blood-contacting applications was later realized [30] and TiN coatings have been considered for heart valves, heart assist devices and heart pumps for 15 to 20 years.

In 1993, Dion et al. [31] showed that the titanium nitride coating was well tolerated by the blood despite its surface irregularities, and appeared as a good candidate material for left ventricular assist devices based on the principle of the Maillard-Wankel rotary pump. In 1997, Montiès et al. [32] tested composite materials made of TiN coating on graphite substrate for long-term and permanent use of a CORA rotary pump as a implantable left ventricular assist device because the fine-grained graphite can be well tooled, rectified, polished to obtain a good surface state, and is corrosion resistant. In 1998, a titanium nitride-coated mixed flow blood pump was tested by being connected between the left ventricular apex and the descending aorta in an 87 kg calf [33]. All the blood-contacting surfaces of the pump were free of thrombus with the exception of crevices at the inflow cannula junction and between the leading edge of the stator blades and housing. However, it seems that TiN coatings have not been widely used for commercial VADs. One reason may be that TiN coatings are inferior to diamond-like carbon coatings in terms of haemocompatibility.

3.2. Diamond-like carbon coatings

Carbon forms a great variety of crystalline and disordered structures. Diamond-like carbon (DLC) is a metastable form of amorphous carbon (a-C) containing a combination of four-fold coordinated sp^3 (diamond-like) sites, and the three-fold coordinated sp^2 (graphitic) sites, with some of the bonds terminated by hydrogen (amorphous hydrogenated carbon, a-C). DLC films (or coatings) can be deposited easily on many substrates of a wide area at room temperature [34]. The deposition of DLC films requires both a carbon source and an energy source to create excited carbon species. The common DLC film deposition processes are cathodic arc deposition, pulsed laser deposition, direct ion beam deposition, plasma-enhanced chemical vapor deposition, ion beam sputtering, and direct current/ radio frequency sputtering.

Diamond-like carbon (DLC) coatings have many advantages including high strength, low frictional coefficient, chemical inertness, high thermal conductivity, excellent biocompatibility, as well as excellent haemocompatibility [35]. The DLC-coated surface showed the least platelet adherence compared to a range of other commonly used blood interfacing materials, including temperature isotropic carbon (LTIC), Ti alloy, TiC, oxidized

Ti (TiO), polycrystalline diamond (PCD), expanded polytetrafluoroethylene (ePTFE), etc. [36,37]. The good hemocompatibility of DLC coatings was attributed to their hydrophobicity and the surface smoothness [38].

The excellent haemocompatibility of DLC coatings has led to their use in VADs. In 1998, Yamazaki et al. [39] developed a two stage ion beam sputtering method to form a DLC film onto a titanium alloy (Ti6Al4V) surface and applied it to the blood contacting surfaces of a Sun Medical centrifugal pump (Sun Medical, Suwa City, Nagano, Japan). The entire blood contacting surface of a compact centrifugal blood pump was coated with a diamond-like carbon coating to improve blood compatibility. The pumps demonstrated excellent hemocompatibility in long-term in vivo experiments; the pumps showed trouble-free continuous function over 6 months. Later in 2003, VentrAssist™ implantable rotary blood pumps were manufactured by the VentrAssist Division, Ventracor Ltd. (Australia) and the blood contacting surfaces of the pumps were diamond-like carbon coatings on the Ti alloy substrate [40]. Recently in 2006, titanium alloy surfaces were coated with a diamond-like carbon coating and used for the EVAHEART® ventricular assist devices (SunMedical Technology Research Corp., Nagano, Japan). Twenty bovines were implanted with the EVAHEART® centrifugal VADs for durations from 30 to 196 days [41].

One of the major limitations of this coating technology is the micro-cracks possibly formed on the surfaces of the metal substrates. The DLC coatings must therefore be optimized in order to minimize the risk of film breakdown. There have been several recent attempts to improve the tribological properties of DLC coatings. A modified DLC coating with elastic features is a promising candidate coating material for VADs [42].

3.3. 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer coating

In addition to the above ceramic coatings, some polymeric coatings have also shown excellent haemocompatibility. One example is the 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer, which was developed about 20 years ago for good blood compatibility. The 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer (Fig. 3) is a phospholipid polymer, resembling the surface structure of a biomembrance. The improved blood compatibility of the MPC polymer was related to the minimized protein adsorption through an increase in the amount of free water in the MPC polymer [43]. The MPC polymer surface was able to completely suppress platelet adhesion and activation even when the MPC polymer was in contact with human blood without an anticoagulant [44]. Because of the properties of blood compatibility and no adsorption of proteins, the MPC polymer has been used for manufacturing non-thrombogenic dialysis membranes and durable glucose biosensors [43].

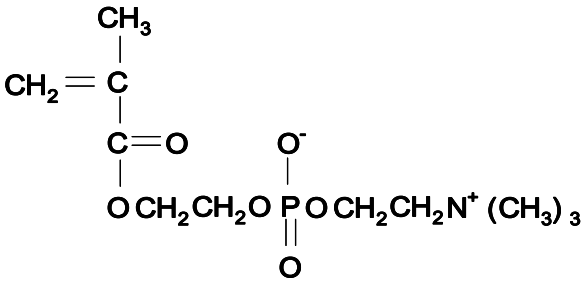

Fig. 3 Molecular formula of 2-methacryloyloxyethyl phosphorylcholine.

In particular, MPC polymer has been used for the blood compatibility of heart pumps or ventricular assist devices. In 2002, Yamazaki et al. [45] reported EVAHEART® compact centrifugal blood pumps (Sun Medical, Suwa City, Nagano, Japan) made from pure titanium and modified with 2-methacryloyloxyethyl phosphorylcholine (MPC) on the entire blood-contacting surfaces. The pumps were evaluated by implanting them in seven calves. No thrombi were found on the blood contacting surfaces with the MPC coating. It was concluded that the EVAHEART® blood pump demonstrated excellent performance in long-term in-vivo experiments.

In 2003, Kihara et al. [19] further evaluated the EVAHEART® left ventricular assist system (LVAS) coated with MPC polymer compared to a DLC coating. In the study, four calves were implanted with the MPC polymer-coated LVAS and eight calves were implanted with DLC-coated LVAS. The MPC polymer coated EVAHEART LVAS (Sun Medical, Suwa City, Nagano, Japan) seemed to have low thrombogenicity and high biocompatibility similar to the DLC coated system. However, MPC polymer coating showed greater promise for an antithrombogenic LVAS due to its ease of application, significant cost benefit, and reduction in anticoagulation therapy in acute postoperative period.

In 2004, MPC polymer was modified with butyl methacrylate and used as coatings on pure titanium for the surfaces of both the casing and the impeller in a blood pump [46]. The film was formed by dip coating the surfaces with an ethanol solution (MPC solution) containing 0.5% by weight of a copolymer of 30 mol % MPC and 70 mol % butyl methacrylate. The coated pumps were evaluated using animal experiments and results showed that it was possible for the blood pumps to operate continuously for 30 days or longer without any administration of anticoagulants.

MPC polymer seems biodegradable and thus its antithrombotic property in the MPC-coated blood pumps may have limited life time, which means that an anticoagulant will still be needed after a period of implantation. The MPC coating is also not as strong and stable as the TiN and the DLC coatings on a metallic or polymeric substrate to be used for the blood pumps [19]. Ideally, the MPC coatings should be grafted onto the blood contacting surfaces through an intermediate layer or a linker to form strong covalent bonding.

3.4. Heparin coating

The basis for heparin's anticoagulant activity in plasma is that it inactivates the formation of fibrin clots by inhibiting two principle pro-coagulant proteases, factor Xa and thrombin. Coating the surfaces with heparin can prevent platelet adhesion and activation, leading to improved blood compatibility of artificial materials [47][48]. A heparin surface was prepared

by first forming a intermediate layer of a polymeric amine, onto which a macromolecular conjugate of heparin was then irreversibly attached by covalent bonding [49]. Multilayer films consisting of polyethylenimine (PEI) and heparin were also successfully prepared on 316L stainless steel surface via electrostatic self-assembly (ESA) of PEI and heparin. In this case, the heparin was attached by the mechanism of ionic bonding rather than covalent bonding. Static platelet adhesion and clotting time experiments indicated that the PEI/heparin coated 316L stainless steel could resist the platelet adhesion and prolong the static clotting time effectively [50]. Using Carmeda® BioActive Surface technology (Carmeda, Upplands Väsby, Sweden), blood contacting surface was modified with end-point-immobilized heparin. This heparin coating can retain thromboresistant properties for periods up to several months. The Carmeda® surface has been applied to critical medical devices by U.S. and European device manufacturers [47,51]. As a new development, a multilayer polymeric coating containing surface-bound active heparin and incorporated nitric oxide (NO) was prepared to mimick the nonthrombogenic properties of the endothelial cell (EC) layer that lines the inner wall of healthy blood vessels [52]. The multilayer polymeric coating was capable of functioning by two complementary anti-thrombotic mechanisms, one being the potent anti-platelet activity of released NO, and the other the ability of the immobilized heparin.

Heparin coatings have been used for cardiovascular devices including VADs. In 2001, Koster et al. [51] tested the Berlin Heart VAD (Berlin Heart AG, Berlin, Germany) consisting of a polyurethane blood pump coated with unfractionated heparins (Carmeda® surface). They aimed to investigate whether heparin coating of the VAD surface could promote the presence of heparin/platelet factor 4 antibodies (HPF4/A) and the development of immunologic or thrombogenic reactions. There was a concern that those antibodies could be strongly associated with an increased risk of development of thromboembolic complications. Fortunately, Koster et al. [51] observed that the heparin coating of the VAD surface did not enhance the occurrence of HPF4/A-associated immunologic or thrombogenic reactions. In 2004, Hetzer et al. [21] tested all blood-contacting titanium surfaces of the Berlin Heart INCOR axial flow pumps (Berlin Heart AG, Berlin, Germany) coated with heparin by the Carmeda® process. After implantation of the heparin-coated INCOR pumps, there were no thrombosis or thromboembolic events in the coronary arteries or branches of the aortic arch.

Due to their biodegradable nature, heparin coatings have a limited life time for the effectiveness of the heparin, which is in contrast to the TiN and the DLC coatings. Heparin coatings are applied preferably through immobilization by covalent bonding, but the chemistry involved is rather complex. Additional heparin in the form of an anticoagulant will still be needed for patients with a ventricular assist device. However, prolonged postoperative use of heparin as an anticoagulant may have the complication of heparin-induced thrombocytopenia [55].

3.5. Textured surfaces

Devices that incorporate textured blood-contacting surfaces have shown improved blood compatibility. This is because the textured surfaces or surfaces with cavities entrap blood components to form a biological "neointimal" layer, which is able to minimize the thromboembolic events and reduce the need for systemic anticoagulation in patients with long-term left ventricular assist devices with a low risk of thromboembolism [53]. It is believed that the biologic lining is due to the deposition of blood-borne endothelial cells or endothelial cell precursors on the blood-contacting surfaces. However, the formation of a

stable neointimal layer is dependent on the three-dimensional topography of the blood-contacting surface.

Several methods have been used to create and evaluate the textured surfaces. For instance, a textured surface was developed from sintered titanium microspheres fused to a substrate by Thermoelectron Corporation during the 1980s [54]. The titanium microspheres sieved to 75 – 100 μm in diameter were attached to the static blood contacting device surfaces to form a continuous layer of 3-4 microspheres in thickness. The surfaces were then heated under vacuum to sinter the microspheres to form voids between the individual microspheres into which cells grew and adhered [55].

Excimer laser micro-machining was also used to make a master negative mold of patterned cavities for the manufacturing of a polyurethane textured surface by solvent casting [59]. Specifically, an approximately 1-mm wide and 1.9-mm long rectangular region could be laser machined at a time, and therefore a larger surface was machined by repeating the same process. A textured surface (Fig. 4) was produced on one side of a polyurethane sheet cast on the patterned mold. The resulting textured surface consisted of regularly spaced and tapered polyurethane micro-fibers (25, 50, or 100 μm in length), and had the same spacing (~100 μm) and base diameter (~25 μm) on the smooth base plane.

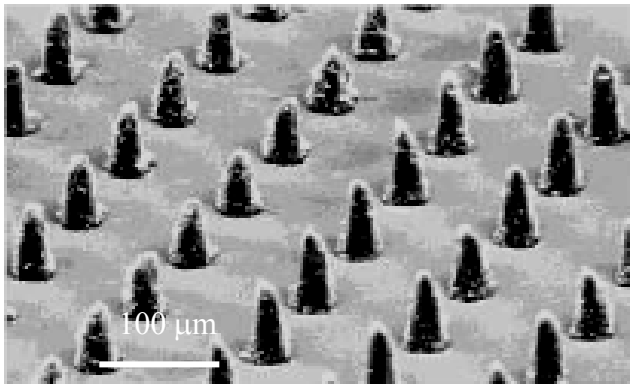

Fig. 4. Scanning electron micrograph of a polyurethane textured surface with a fiber length of 50 μm [56]. (Permission for the use of the copyrighted material has been granted).

The above textured surface consisting of the regularly spaced micro-fibres was evaluated in vivo in a subsequent study. Briefly, polyurethane vascular patches with and without the textured surface were fabricated and implanted for 1- and 3-weeks. As a result, subsequent cellular migration and tissue healing occurred more rapidly on a textured polyurethane surface in order to form the biological and thromosis-resistant coating [57].

Argon plasma etching was also used to produce micro-patterns on titanium oxide films synthesized by plasma immersion ion implantation and deposition (PIII&D) [58]. By etching for 30, 60, 90, and 120 min., the surface of the titanium oxide was made into wells containing organized arrays of square holes of different depths separated by a space of 25 μm. The resulting textured surfaces were able to influence the cell behavior. As another method, particle casting was used to form geometric features on segmented polyurethane surfaces. The surface micro-textured material was incorporated as a part of a flexible blood-contacting surface of LVADs, followed by implantation in calves. Preliminary results indicated that a stable neointimal layer could be formed upon the particle-cast surfaces. Furthermore, the cavity size of the particle-cast surfaces showed a significant effect on the neointimal adhesion

[59].

It is surprising that the concept of textured surfaces for attracting the formation of a "neointimal" layer was used about 40 years ago. In 1968, a porous matrix of Dacron fibrils, within an implantable left ventricular-aortic assist pump was utilized to permit formation of a stable autologous lining within the assist pump following implantation of the device. In vivo tests over a time period of from 6 to 120 days in 15 calves showed that a stable autologous lining was present on all the surfaces of the assist pumps in four animals [60]. It should be mentioned that textured surfaces have been used in some commercial VADs. For example, sintered titanium textured surfaces and integrally textured polyurethane lines were used in HeartMate® I LVAD (previously Thermo Cardiosystems, Inc, Woburn, MA, but now owned by Thoratec Pleasanton, CA), a pneumatic actuated pusher plate pump that has been in clinical use since 1986 [55,61,62]. It was shown that the endothelial cell precursors could colonize on textured surfaces of left ventricular assist devices with a high proliferative capacity and thus contribute to the development of a biologically nonthrombogenic neointima [63].

However, the use of textured surfaces in continuous flow pumps is controversial. For example, the HeartMate® II LVAD (Thoratec Pleasanton, CA) is a miniature axial flow pump which was initially fabricated with the same sintered microsphere coating as used with the HeartMate® I LVAD, on the stationary inner surfaces of the pump. The pump was first used in a European study that ended early due to finding severe thrombosis in a design of the HeartMate II axial flow pump. The pump was redesigned with smooth titanium stators while retaining textured titanium in the conduits, because the textured surfaces did not work in areas of pumps with very small clearances in the pump. As a result, no pump thrombosis was observed in the 30 implants that followed redesign [64].

It should be noted that not all textured surfaces lead to the formation of a layer of sole endothelial cells. Salih et al. [63] have noticed the presence of at least two cell populations on some textured surfaces: fibroblasts and smooth muscle-like cells, or 'myofibroblasts'. Thus, in addition to the textured surface morphology, proper biochemical singling (for example through growth factors) should be deposited onto the blood-contacting surfaces to induce or trigger the formation of an endothelial cell layer. To obtain a defined endothelial cell layer, the textured surfaces can also be seeded with endothelia cells followed by in vitro culture before implantation, as will be seen in the following section.

3.6. Endothelial cell lining

The growth of an endothelial cell (EC) layer on a blood-contacting surface has been suggested for a long term use and it is believed that the metabolically active endothelial lining plays a major role in preventing blood thrombosis. There have been many studies on the use of an EC layer to improve the blood compatibility of cardiovascular devices such as stents and artificial heart valves. There is also an interest in the use of an EC coating to improve the blood compatibility of VADs [65,66]. However, the application of an EC coating for VADs is still in its infancy.

Several biological substances including biomolecules and growth factors have been deposited on medical devices for the growth of EC layers. For example, polyurethane cardiovascular implants have been modified by the immobilization of proteins and peptide factors via

covalent conjugation, followed by in situ seeding of human endothelial cells [67][68][69]. Similarly, Sreerekha et al. [70] modified Dacron and polytetrafluoroethylene with biomolecules such as fibrin, fibronectin, and gelatin along with growth factors. After the modified surfaces were seeded with endothelial progenitor cells (EPCs), the EPCs could differentiate into ECs and form an EC monolayer that synthesized nitric oxide for haemocompatibility and was able to resist the shear stress involved in the cell culture environment. A textured surface was also directly coated with an EC layer. Specifically, human umbilical vein endothelial (HUVE) cells were cultured on both smooth and patterned surfaces with the latter being prepared by argon plasma etching of titanium oxide films. It was shown that the titanium oxide had good cyto-compatibility and the micro-patterns influenced the wetting-ability of the blood contacting surface and thus the cell behavior on the surface [58].

While the strategy of the EC lining seems potential, only a few studies have been reported in the application of the strategy for VADs. For instance, Nikolaychik et al. [65] have tested endothelial cell monolayers under dynamic conditions inside a beating ventricular prosthesis in vitro with the goal of producing a permanent biocompatible artificial cardiac prosthesis. An endothelial cell loss of 35% indicating denudation of the endothelial cell lining was measured. As another example, Scott-Burden et al. [66] seeded LVADs with genetically engineered smooth muscle cells to compare with endothelial cell layers. The both monolayers were exposed to the whole blood in parallel plate flow chambers and were quantified in terms of platelet-adhesion. It was noticed that the platelet deposition on the genetically modified myocyte layers was similar to that associated with the endothelial cell layers. The seeded LVADs were cultured in vitro flow loops for 18 hours before being implanted. It was found that the smooth muscle cells, transduced with the genes to optimize nitric oxide production, adhered well to the pump surfaces under in vitro and in vivo flow conditions. Finally, in vitro studies were conducted with textured polyurethane membranes, which were used in HeartMate VADs (Thoratec Corporation, Pleasanton, Calif), coated with endothelial cells. It was shown that the cell-coated textured polyurethane membranes were less susceptible to infection. Thus, cellular coating may provide a strategy for reducing the risk of infection [26].

Although a lining layer of endothelial cells (ECs) on a blood contacting surface has shown less thrombogenicity [62], ECs become less viable or partly lose their functions of endothelial-dependent relaxation and biological factor production. Another possible problem with the endothelial cell lining strategy is that the originally formed monolyer of ECs may be partially washed away by the blood flow and lead to the loss of endothelium [71]. To improve the adhesion of the endothelial cell layer, the substrate surface may need to have a micro- or nano-porosity for cell attachment. Another effective method of promoting the integration of endothelial cells onto a device would be the creation of a functional layer by immobilizing substances such as extracellular matrix (ECM) proteins and peptides that have a high affinity to the endothelial cells. Other biomolecules such as growth factors may also be essential for maintaining the functionality of the endothelial cells.

4. Conclusions

This review has paid attention to the haemocompatibility of the ventricular assist devices, which can be addressed by using different surface coatings. Diamond-like carbon (DLC) coatings are more advanced and perform better than TiN coatings. Although MPC polymer coatings are not suitable for long term or permanent implantation of VADs, they generally show better haemocompatiblity than inorganic TiN and DLC coatings. Properly textured surfaces have the ability to induce the formation of an endothelial cell layer in vivo and thus contribute to the excellent haemocompatibility. However, textured surfaces are normally difficult to produce and there is no warranty to induce the formation of the required endothelial cell layer. In spite of the potential haemocompatibility, in vitro formed endothelial cell layer has the problems of functional viability in vivo and reliability of cell attachment. Thus, all the coating strategies have their advantages and disadvantages, however, DLC coatings and heparin coatings are relatively well developed for commercial applications in VADs. One of the future trends of research will be the better understanding of the individual strategies so that an optimal combination of the strategies will be available. For all the coating types, there is a common issue of interfacial bonding, which should be better understood and ensured. Finally, for testing the haemocompatibility of coating materials intended for VADs, the whole blood rather than platelet-enriched blood should be used to evaluate the surface-coated ventricular assist devices (or heart pumps) in vitro and/or in vitro.

5. Export commentary & five-year view

Heart failure is a serious medical problem and ventricular assist devices can alleviate the problem by acting as a temporary blood pump till heart organ transplantation, or till the recovery of the failing heart or by serving as a permanent heart replacement. However, thromboemblism is a complication of the heart pumps especially if implanted for a long period of time (years not months). Conventional solution to the thromboemblism has been the use of an anticoagulant, which however has the problem of unstoppable bleeding. Thus, an alternative solution is modifying the blood contacting surfaces of the ventricular assist devices with a blood compatible coating. Fortunately, there have been some types of surface coatings developed for the ventricular assist devices.

However, there are still many challenges; the interfacial bonding between inorganic coatings (e.g. TiN and DLC) and titanium-based substrates should be guaranteed, which may require gradient and multilayered coating design. The inorganic coatings are normally dense, smooth and bioinert so that the adhesion of blood cells can be minimized. If the inorganic coatings are not smooth or the surfaces have specially designed porosity, roughness, or patterned texture, then the surfaces can attract proteins and endothelial cells to form a biological layer, which is intrinsically compatible to blood, in situ after implantation.

As an example of further development, a haemocompatible endothelial cell layer can be grown on the blood contacting surfaces of a ventricular assist device using in vitro cell culture followed by implantation. However, it is not known whether the applied endothelial cell layer can stay firmly on the blood contacting surfaces without being flushed away by the blood flow, and without the loss of its biological functions.

A foreseeable future work would be the use of a combined approach to modify the blood contacting surfaces of the ventricular assist devices. For example, a bioinert surface with a

patterned texture or topography will be created, which would be favourable for the mechanical attachment of the subsequently formed endothelial cell layer. In order to provide suitable microenvironments for the endothelial cells' growth and function, the bioinert and textured surfaces may need to contain some pores to cater for the incorporation of extracellular matrices and/or growth factors. Finally, a biodegradable membrane can be used to grow an endothelial cell sheet in vitro and the cell sheet can be applied on the textured surfaces for further cell attachment and growth. Finally, while biological coatings (or cell-based coatings) of VADs represent scientifically a step further compared to the conventional inorganic coatings, their potentials and final commercial values are still pending for exploration.

6. Key issues

• Material's surface-related complications are major obstacles for the implantation of ventricular assist devices (VADs). Surface coating of a VAD is an effective way to minimize the complications.
• TiN and diamond-like carbon coatings are two inorganic coatings with good biocompatibility. It seems that TiN coatings have not been widely used for commercial VADs, and the major limitation of DLC coatings is the micro-cracks possibly formed on the surface of a metal substrate.
• The polymer of 2-methacryloyloxyethyl phosphorylcholine (MPC) is a biomimetic material with excellent haemocompatibility. However, this coating material is biodegradable, which suggests a limited life-time.
• Heparin as an anticoagulant is used on blood contacting surfaces. The release of the heparin from the coatings is controlled by whether the heparin is ionically or covalently bonded.
• Textured surfaces have been created on the blood contacting surfaces in order to achieve haemocompatibility via an in situ formed biological cell layer. Nano- and micro-fabrication techniques are expected to play important roles in the production of the textured or patterned surfaces.
• Endothelial cells or the like can also be seeded and grown on the blood contacting surfaces of a ventricular assist device. While the haemocompatibility of the endothelial cell layer is expected, it is challenging to generate a cell layer that is well attached to the substrate and maintain its biological functions. The endothelial cell lining strategy is still in its infancy and is far from final commercialisation.

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